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(54) APPARATUSES AND METHODS FOR CREATING AND TESTING PRE-FORMULATIONS AND SYSTEMS FOR SAME

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Related U.S. Application Data

(60) Provisional application No. 60/311,332, filed on Aug. 10, 2001.

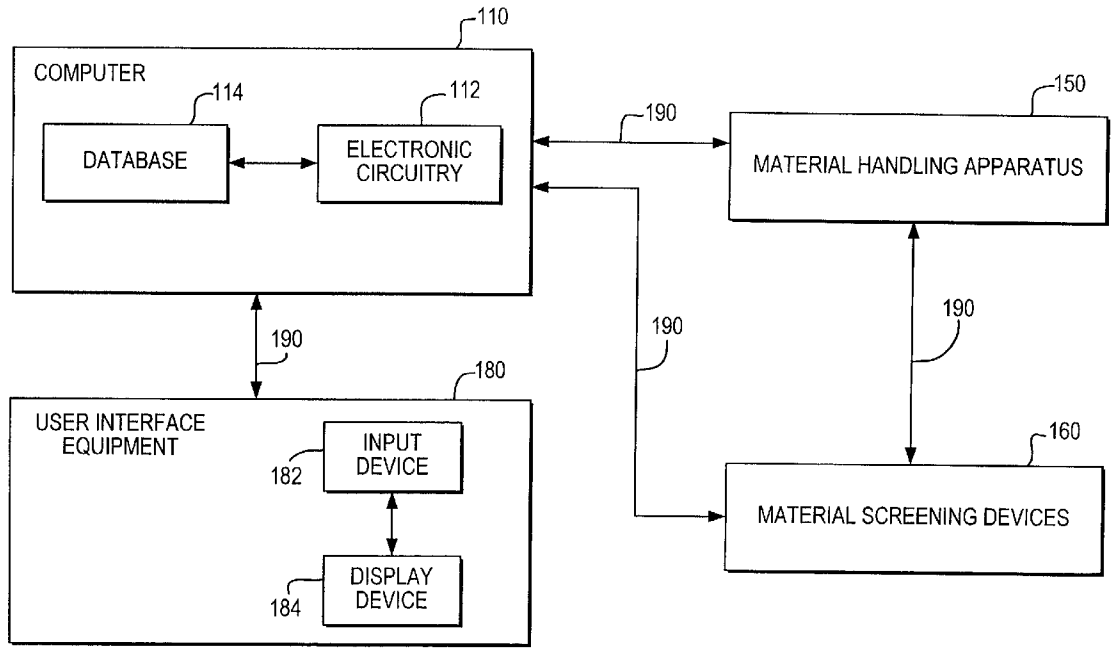
Publication Classification

(51) **Int. Cl.**[7] **G01N 21/47**; G01N 33/00

(52) **U.S. Cl.** **422/68.1**; 422/82.05

(57) ABSTRACT

The invention provides methods, apparatus, and systems for performing high-throughput preparation and screening of salts and polymorphs of drug candidates. The invention is directed towards enhancing the pre-formulation discovery process used for drug development. In particular, processes that determine suitable salts and processes that discover substantially every polymorph that can form from a particular drug candidate are provided. The processes are performed using several apparatuses that are specifically configured to carry-out various steps in a high-throughput characterization process. One such apparatus is configured for synthesizing a plurality of library members based on, for example, a library model generated by a computer system. Another apparatus may filter the synthesized solution to provide a substantially pure mixture that can be subjected to salt or polymorph testing. Yet another apparatus may be used to crystallize mixtures on a substrate such that the crystallized mixture can be screened by one or more screening devices.



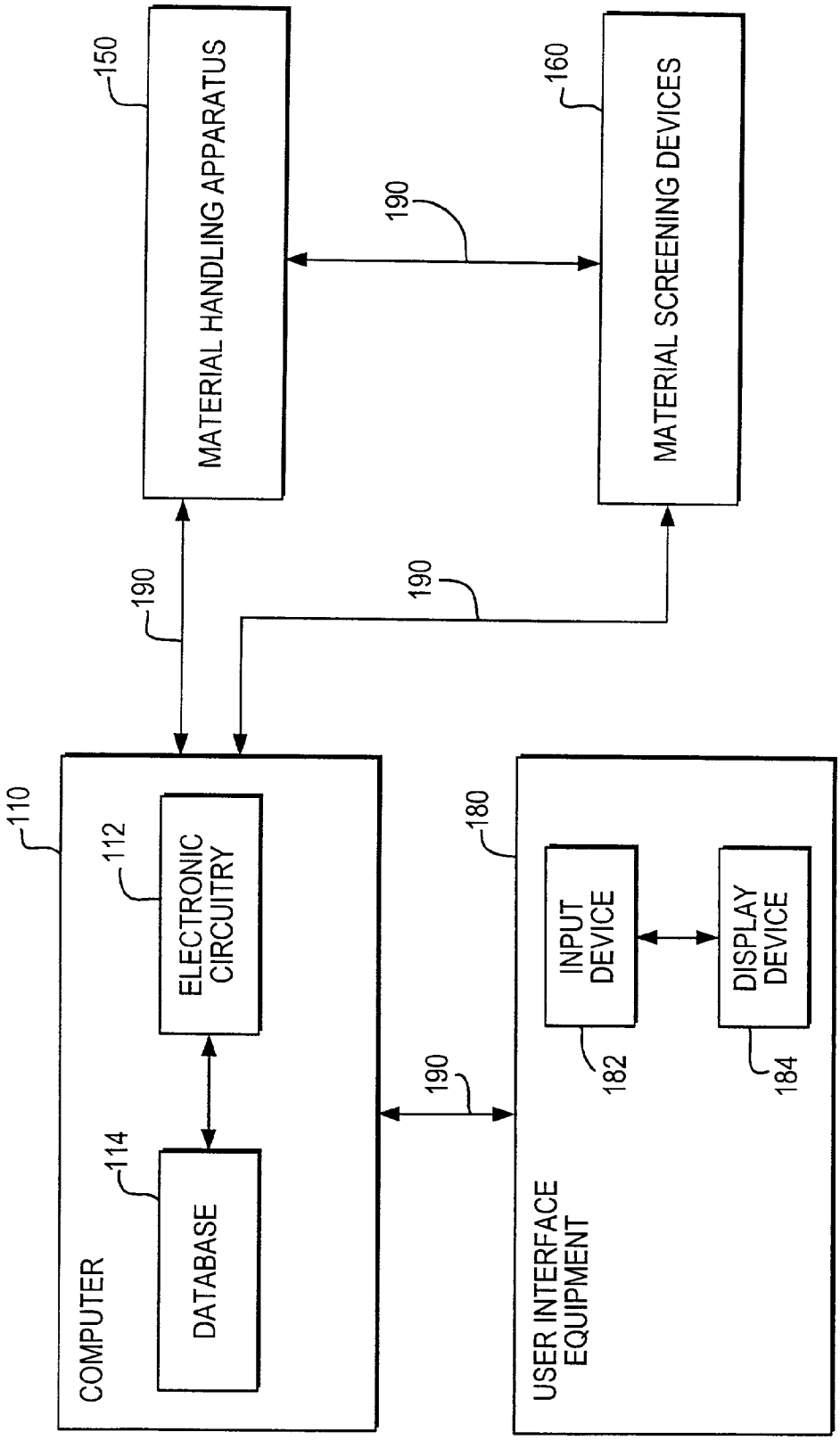

150
MATERIAL HANDLING APPARATUS
160
MATERIAL SCREENING DEVICES
190
190
190
110
COMPUTER
112
ELECTRONIC CIRCUITRY
114
DATABASE
190
180
USER INTERFACE EQUIPMENT
INPUT DEVICE
182
DISPLAY DEVICE
184

FIG.1

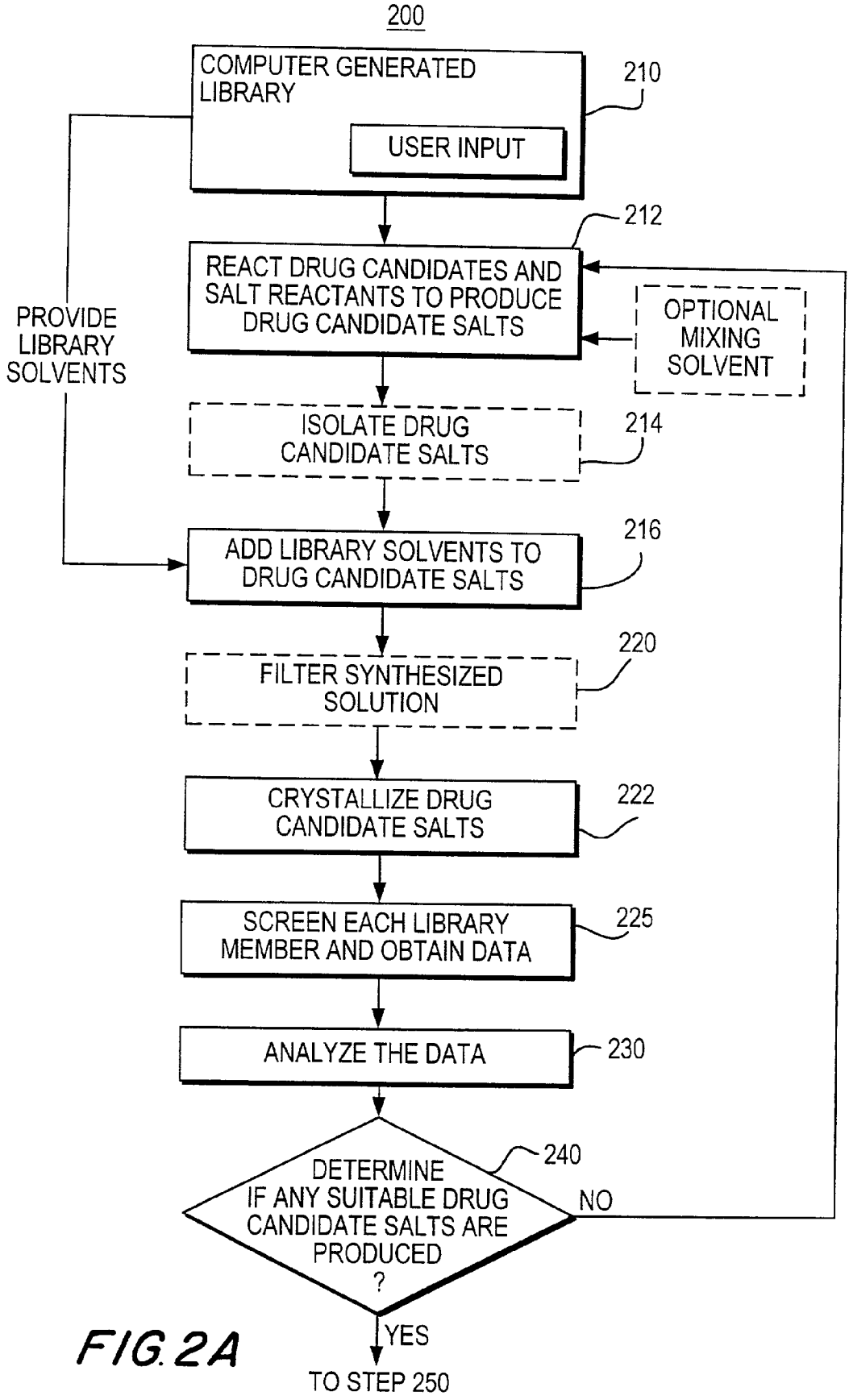

200
COMPUTER GENERATED LIBRARY
USER INPUT
210
212
REACT DRUG CANDIDATES AND SALT REACTANTS TO PRODUCE DRUG CANDIDATE SALTS
OPTIONAL MIXING SOLVENT
PROVIDE LIBRARY SOLVENTS
ISOLATE DRUG CANDIDATE SALTS
214
ADD LIBRARY SOLVENTS TO DRUG CANDIDATE SALTS
216
FILTER SYNTHESIZED SOLUTION
220
CRYSTALLIZE DRUG CANDIDATE SALTS
222
SCREEN EACH LIBRARY MEMBER AND OBTAIN DATA
225
ANALYZE THE DATA
230
DETERMINE IF ANY SUITABLE DRUG CANDIDATE SALTS ARE PRODUCED ?
240
NO
YES
TO STEP 250

FIG. 2A

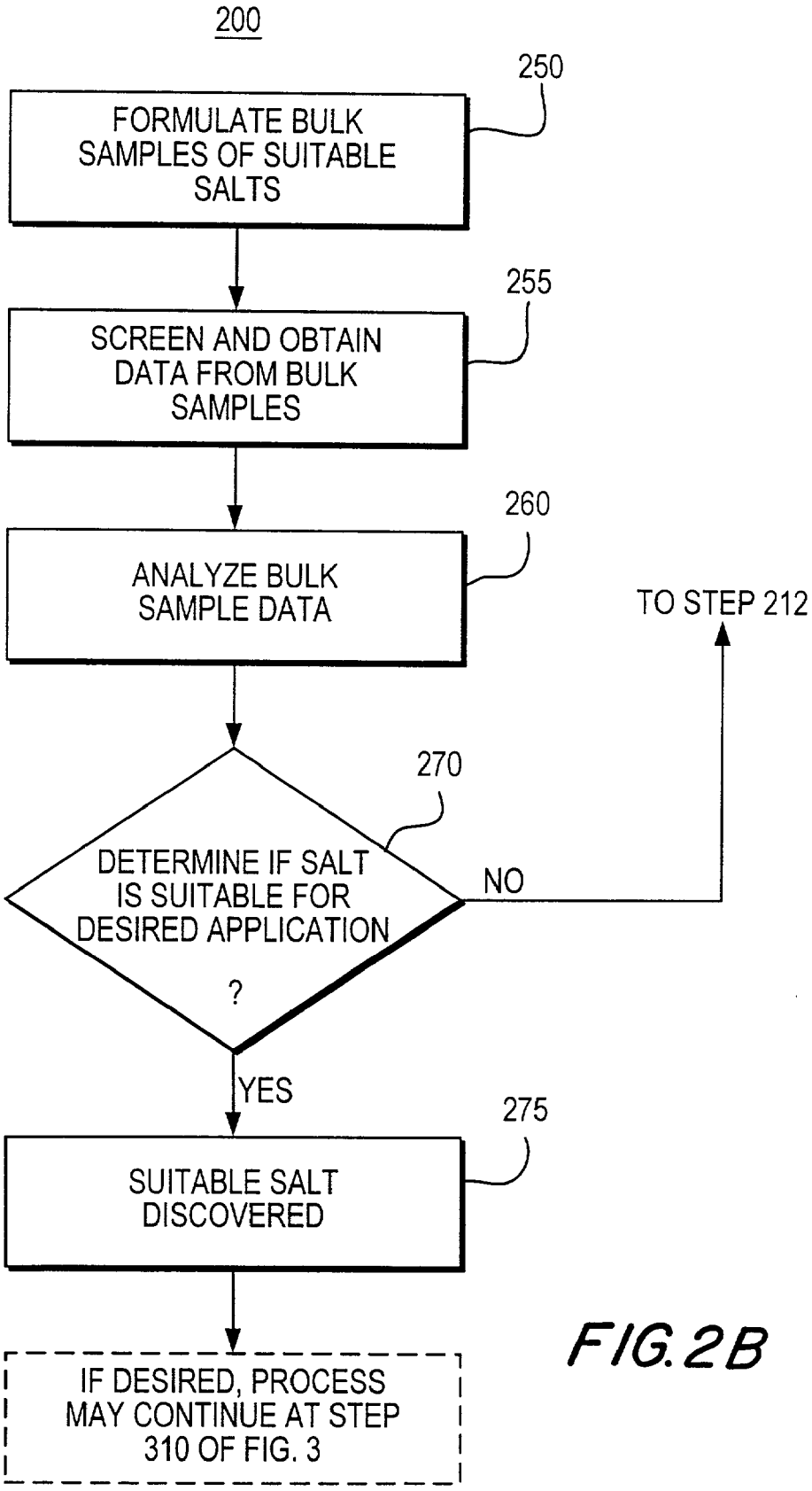

200
250
FORMULATE BULK SAMPLES OF SUITABLE SALTS
255
SCREEN AND OBTAIN DATA FROM BULK SAMPLES
260
ANALYZE BULK SAMPLE DATA
TO STEP 212
270
DETERMINE IF SALT IS SUITABLE FOR DESIRED APPLICATION ?
NO
YES
275
SUITABLE SALT DISCOVERED
IF DESIRED, PROCESS MAY CONTINUE AT STEP 310 OF FIG. 3

FIG. 2B

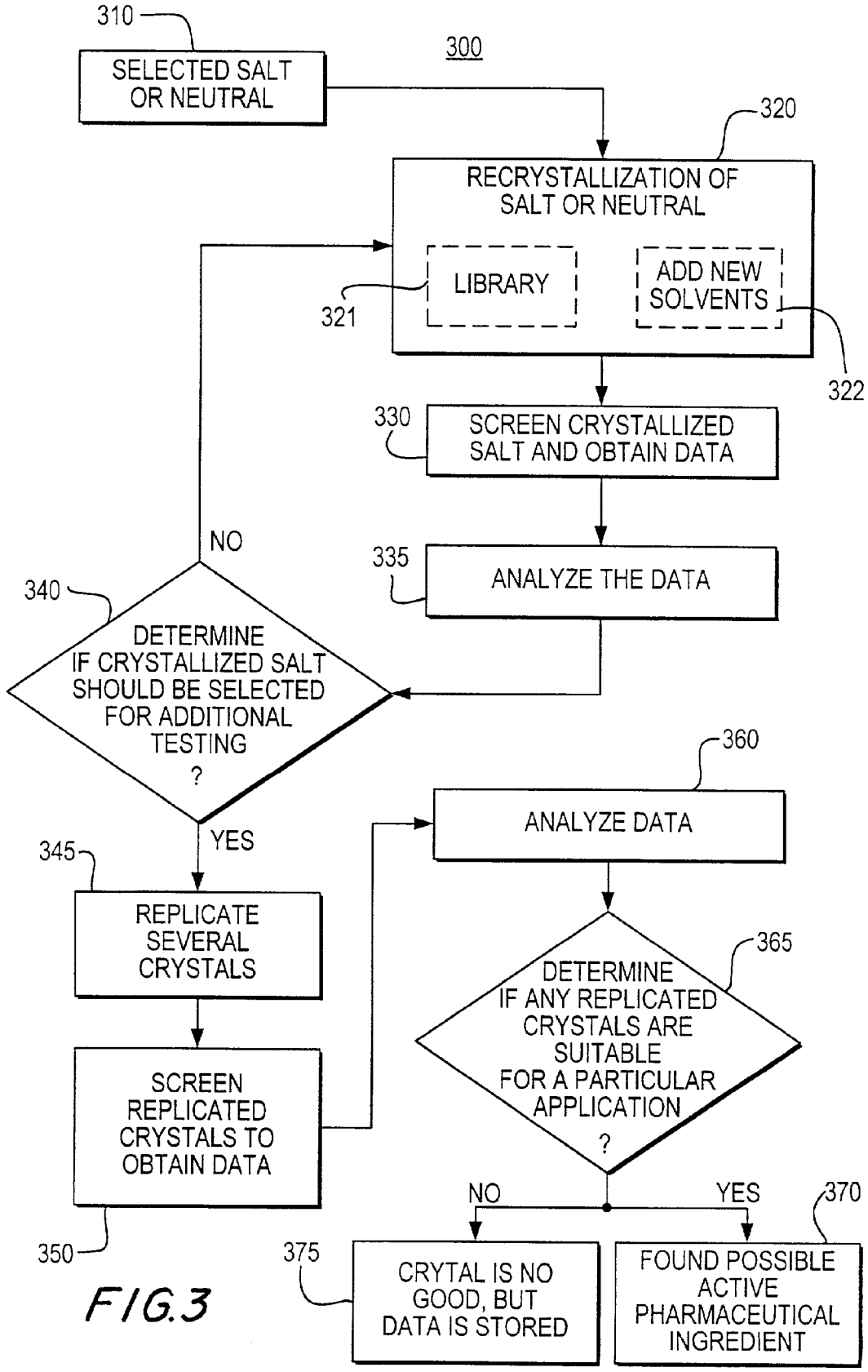

310
SELECTED SALT OR NEUTRAL
300
320
RECRYSTALLIZATION OF SALT OR NEUTRAL
LIBRARY
ADD NEW SOLVENTS
321
322
330
SCREEN CRYSTALLIZED SALT AND OBTAIN DATA
335
ANALYZE THE DATA
NO
340
DETERMINE IF CRYSTALLIZED SALT SHOULD BE SELECTED FOR ADDITIONAL TESTING ?
YES
345
REPLICATE SEVERAL CRYSTALS
SCREEN REPLICATED CRYSTALS TO OBTAIN DATA
350
360
ANALYZE DATA
365
DETERMINE IF ANY REPLICATED CRYSTALS ARE SUITABLE FOR A PARTICULAR APPLICATION ?
NO
YES
370
375
CRYTAL IS NO GOOD, BUT DATA IS STORED
FOUND POSSIBLE ACTIVE PHARMACEUTICAL INGREDIENT

FIG.3

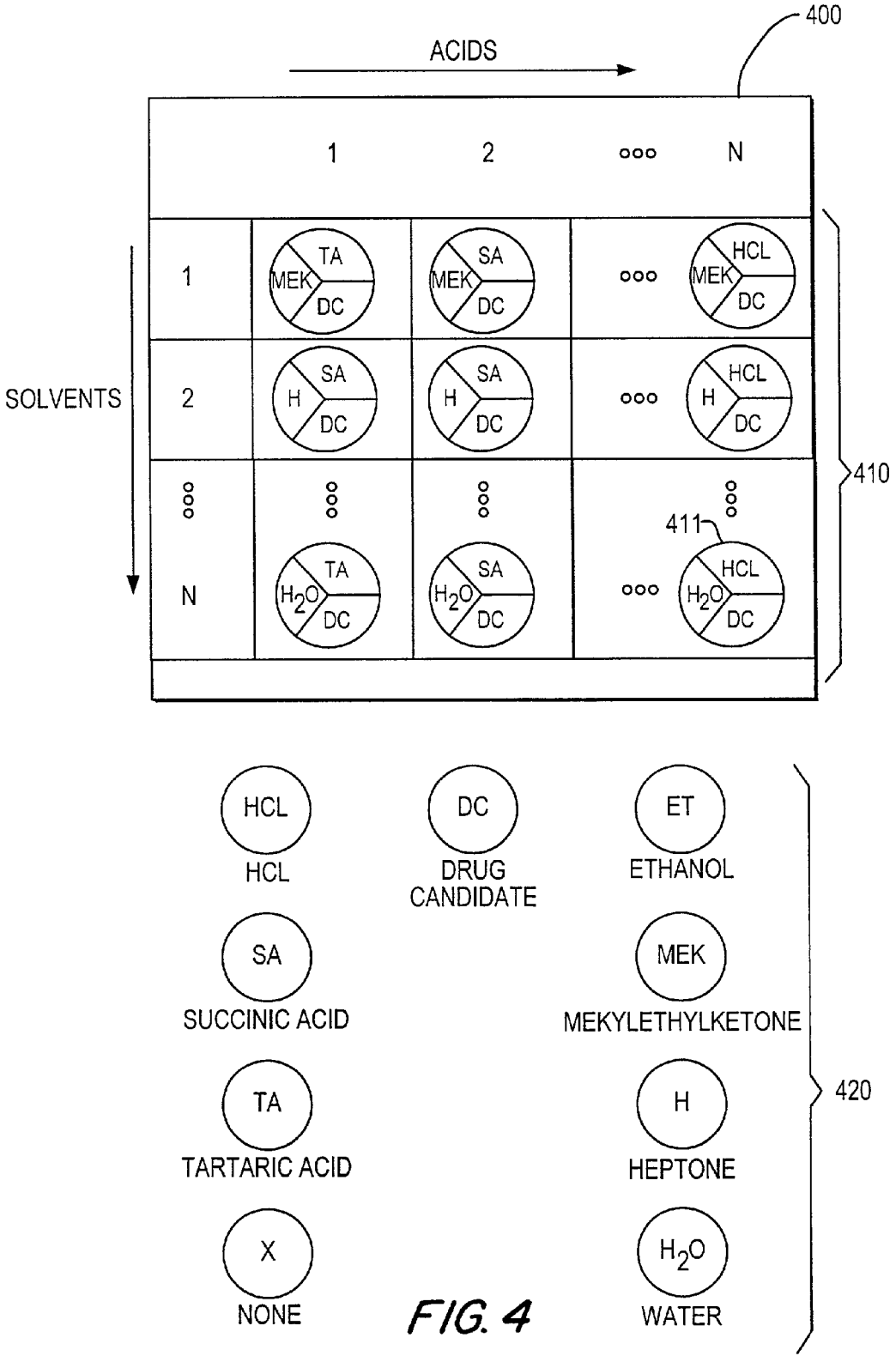

400
ACIDS
1
2
ooo
N
SOLVENTS
1
2
N
TA
MEK
DC
SA
MEK
DC
HCL
MEK
DC
SA
H
DC
SA
H
DC
HCL
H
DC
TA
H2O
DC
SA
H2O
DC
411
HCL
H2O
DC
410
HCL
HCL
DC
DRUG CANDIDATE
ET
ETHANOL
SA
SUCCINIC ACID
MEK
MEKYLETHYLKETONE
TA
TARTARIC ACID
H
HEPTONE
X
NONE
H2O
WATER
420

FIG. 4

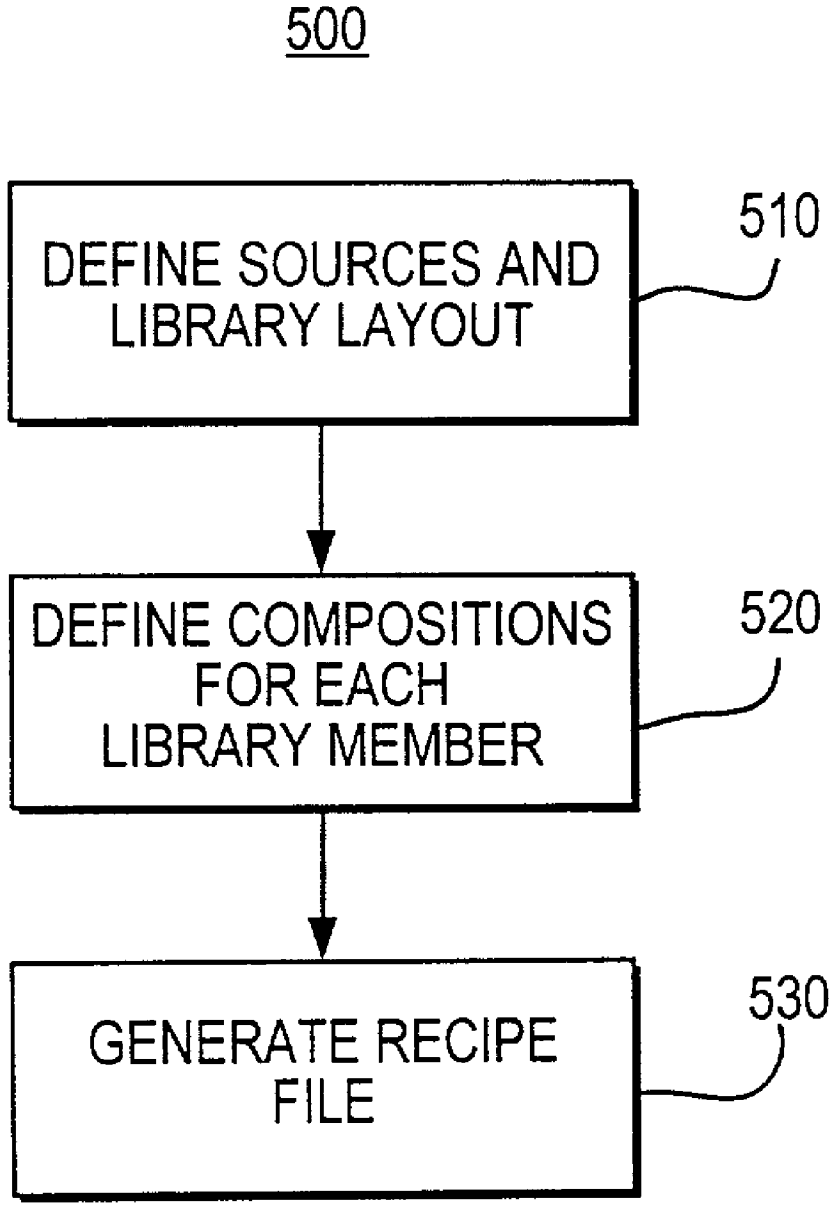

500
DEFINE SOURCES AND LIBRARY LAYOUT
510
DEFINE COMPOSITIONS FOR EACH LIBRARY MEMBER
520
GENERATE RECIPE FILE
530

FIG. 5

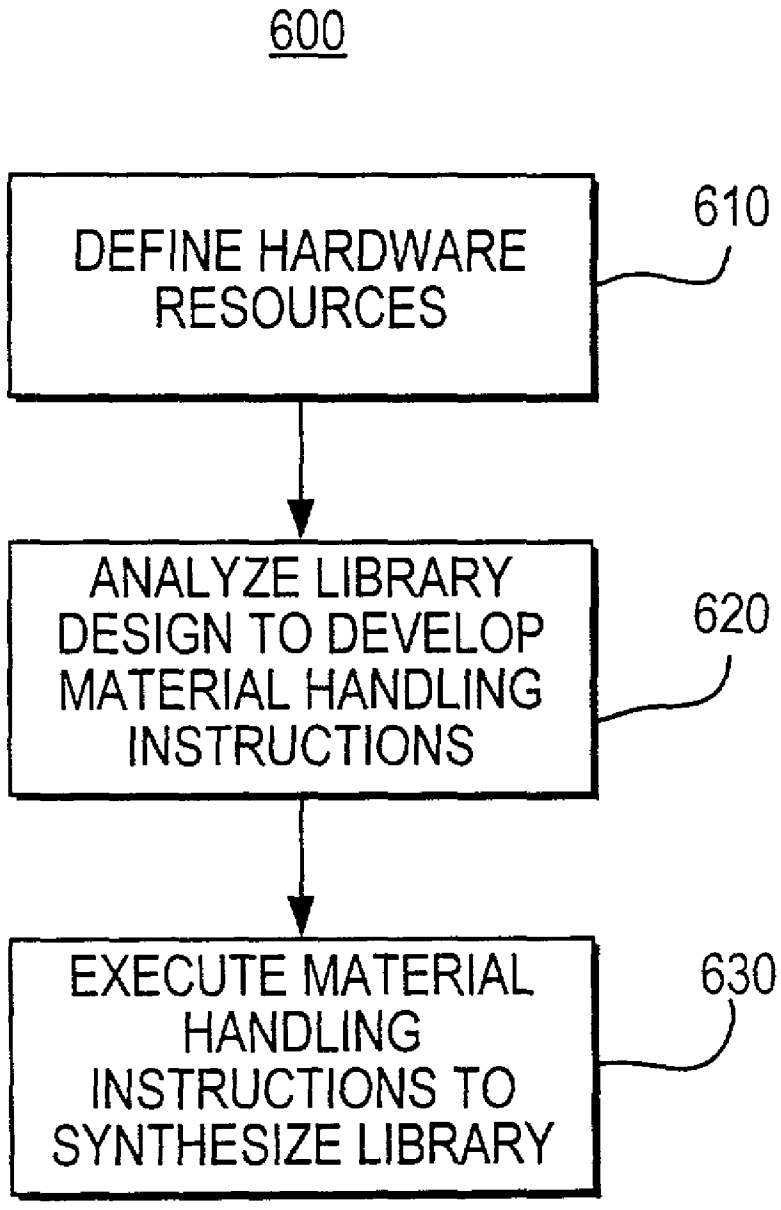

600
DEFINE HARDWARE RESOURCES
610
ANALYZE LIBRARY DESIGN TO DEVELOP MATERIAL HANDLING INSTRUCTIONS
620
EXECUTE MATERIAL HANDLING INSTRUCTIONS TO SYNTHESIZE LIBRARY
630

FIG. 6

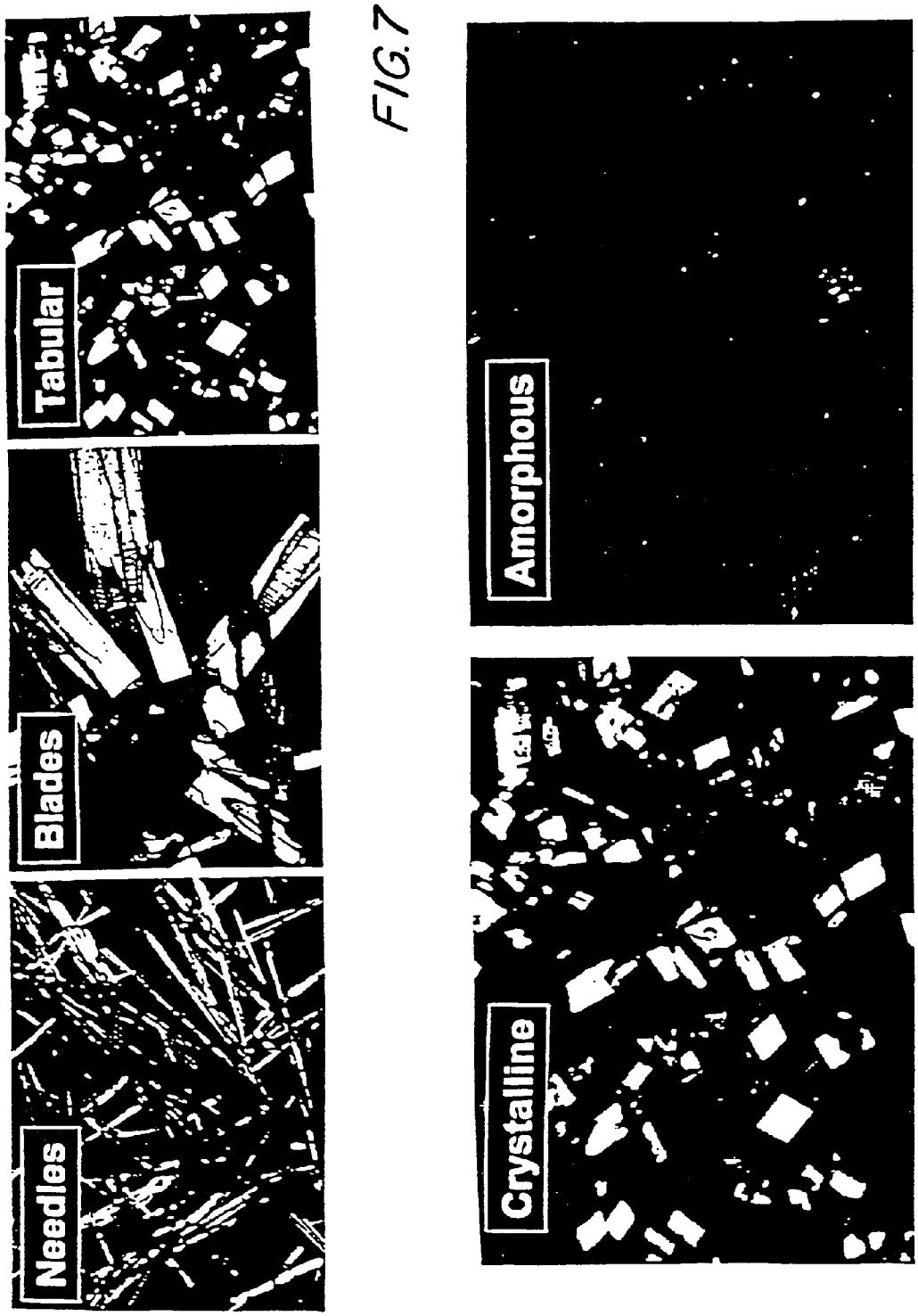


FIG.7

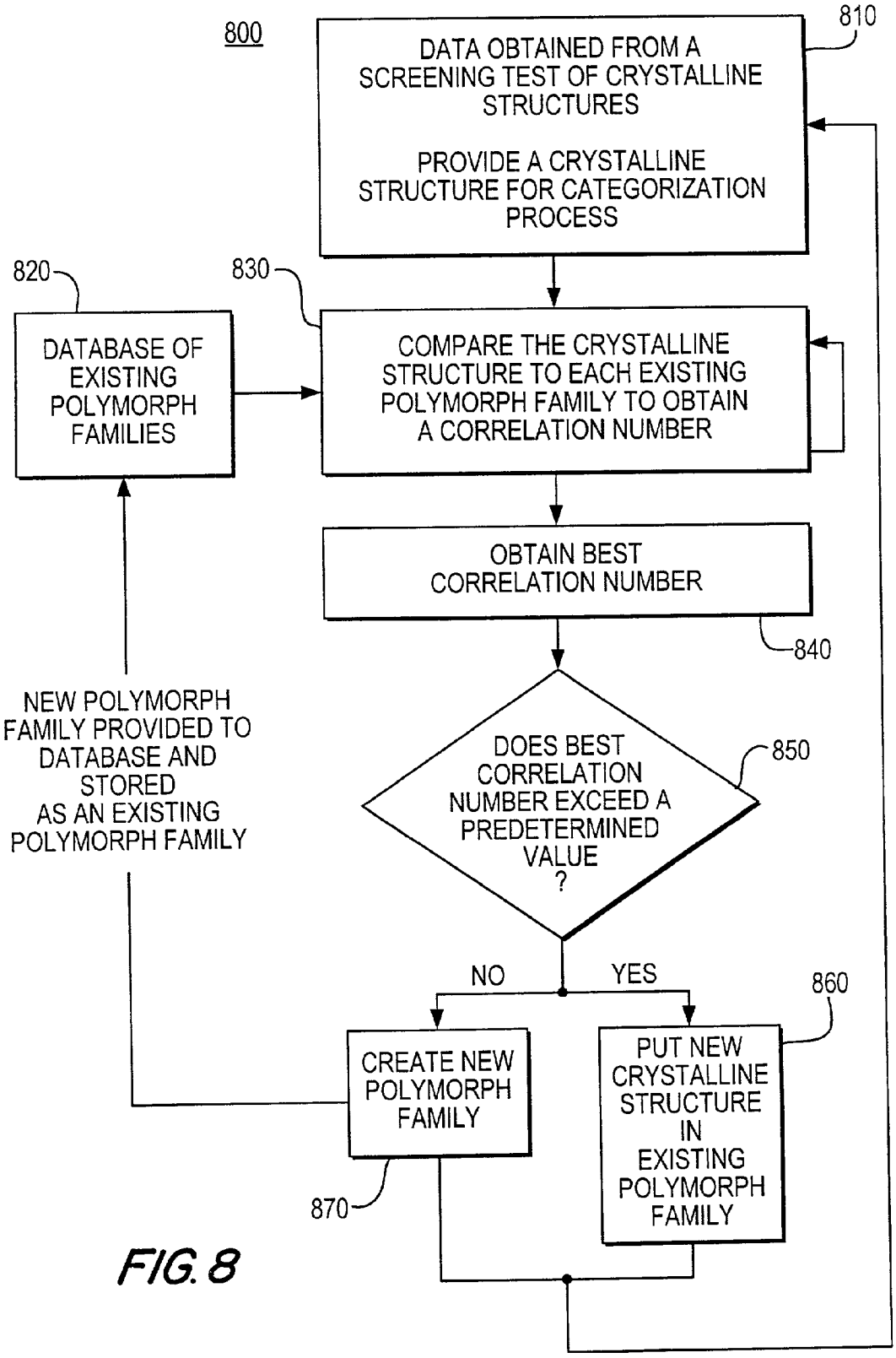

800
DATA OBTAINED FROM A SCREENING TEST OF CRYSTALLINE STRUCTURES
PROVIDE A CRYSTALLINE STRUCTURE FOR CATEGORIZATION PROCESS
810
820
DATABASE OF EXISTING POLYMORPH FAMILIES
830
COMPARE THE CRYSTALLINE STRUCTURE TO EACH EXISTING POLYMORPH FAMILY TO OBTAIN A CORRELATION NUMBER
OBTAIN BEST CORRELATION NUMBER
840
NEW POLYMORPH FAMILY PROVIDED TO DATABASE AND STORED AS AN EXISTING POLYMORPH FAMILY
DOES BEST CORRELATION NUMBER EXCEED A PREDETERMINED VALUE ?
850
NO
YES
860
CREATE NEW POLYMORPH FAMILY
870
PUT NEW CRYSTALLINE STRUCTURE IN EXISTING POLYMORPH FAMILY

FIG. 8

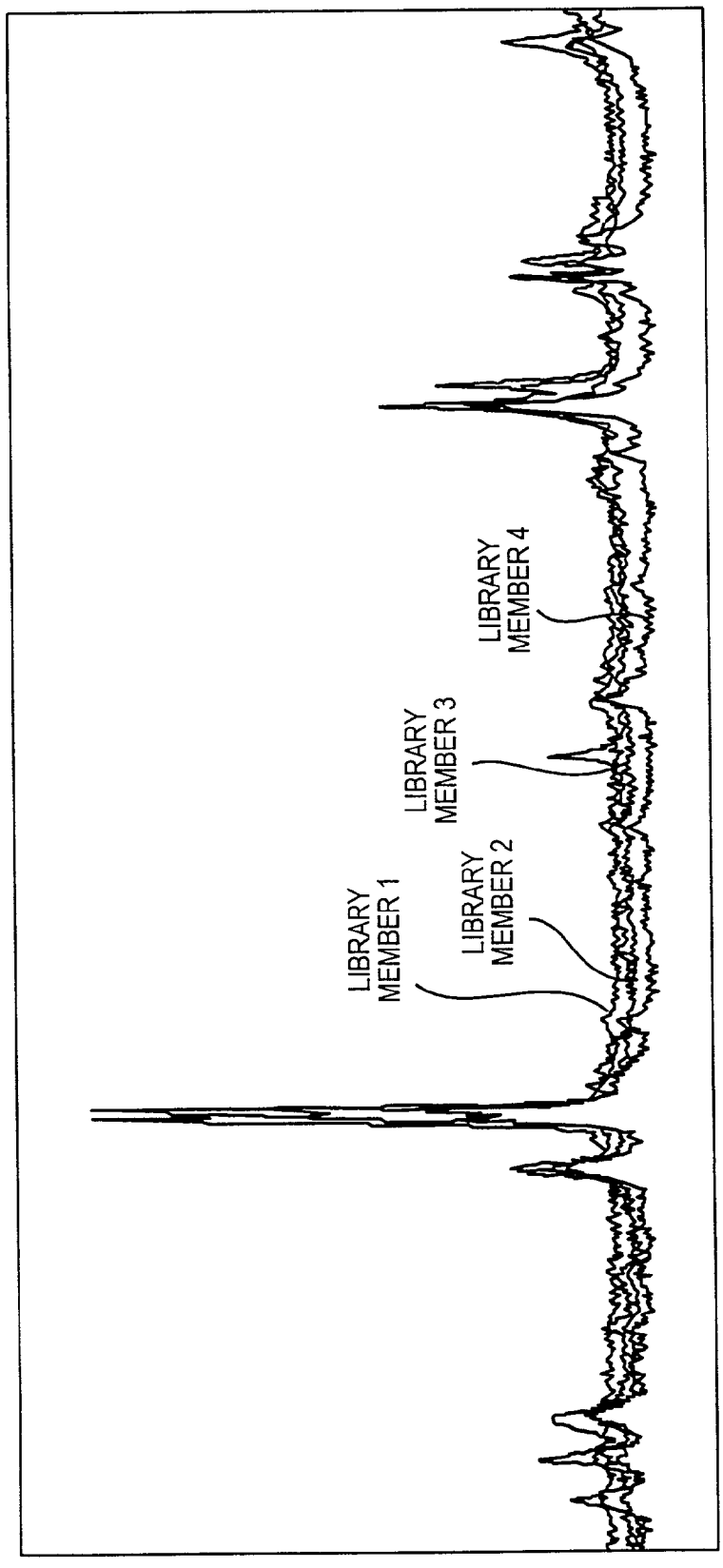

LIBRARY MEMBER 1
LIBRARY MEMBER 2
LIBRARY MEMBER 3
LIBRARY MEMBER 4
FREQUENCY cm-1
INTENSITY

FIG. 9

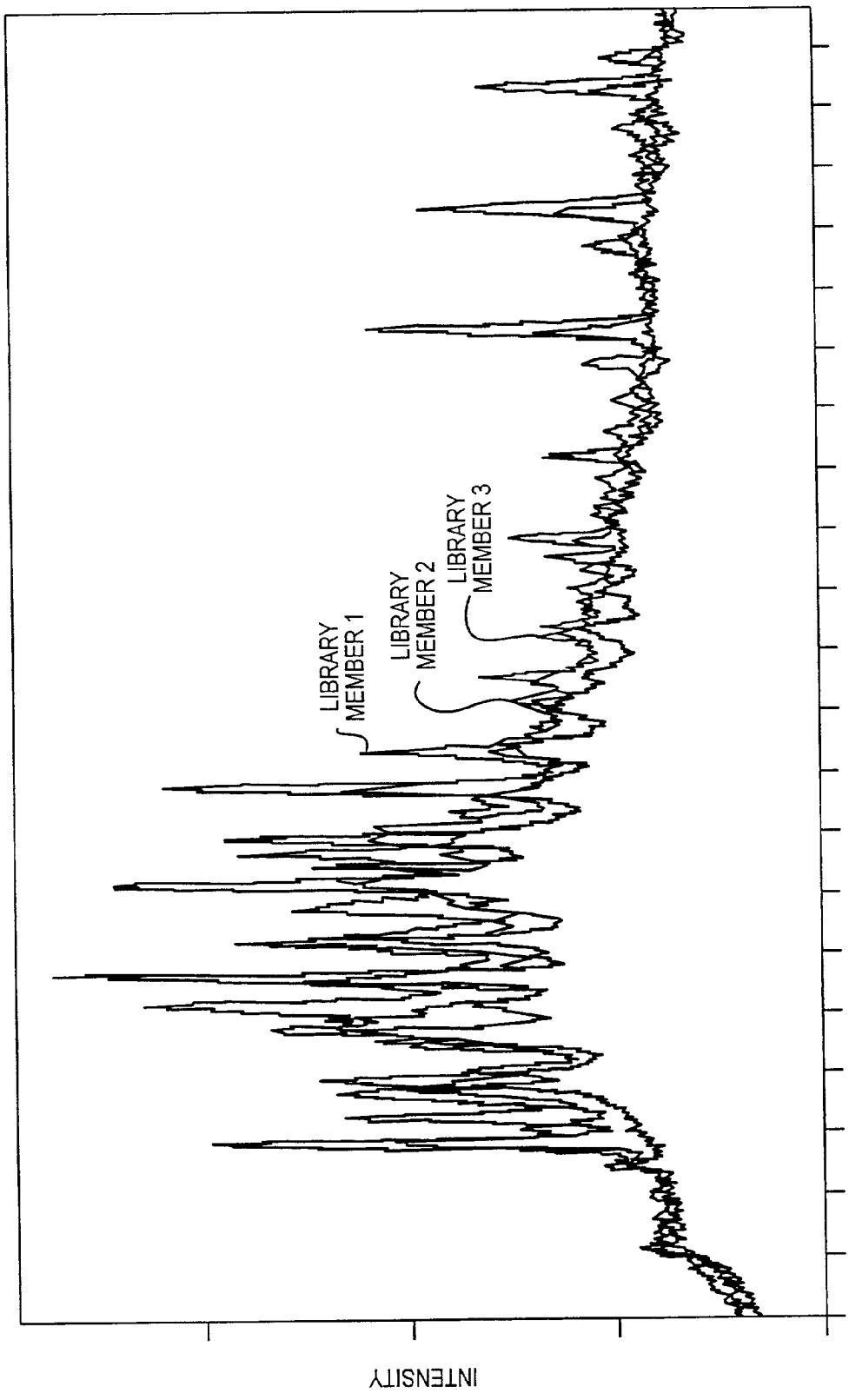

LIBRARY MEMBER 1
LIBRARY MEMBER 2
LIBRARY MEMBER 3
INTENSITY
2 - THETA (°)

FIG.10

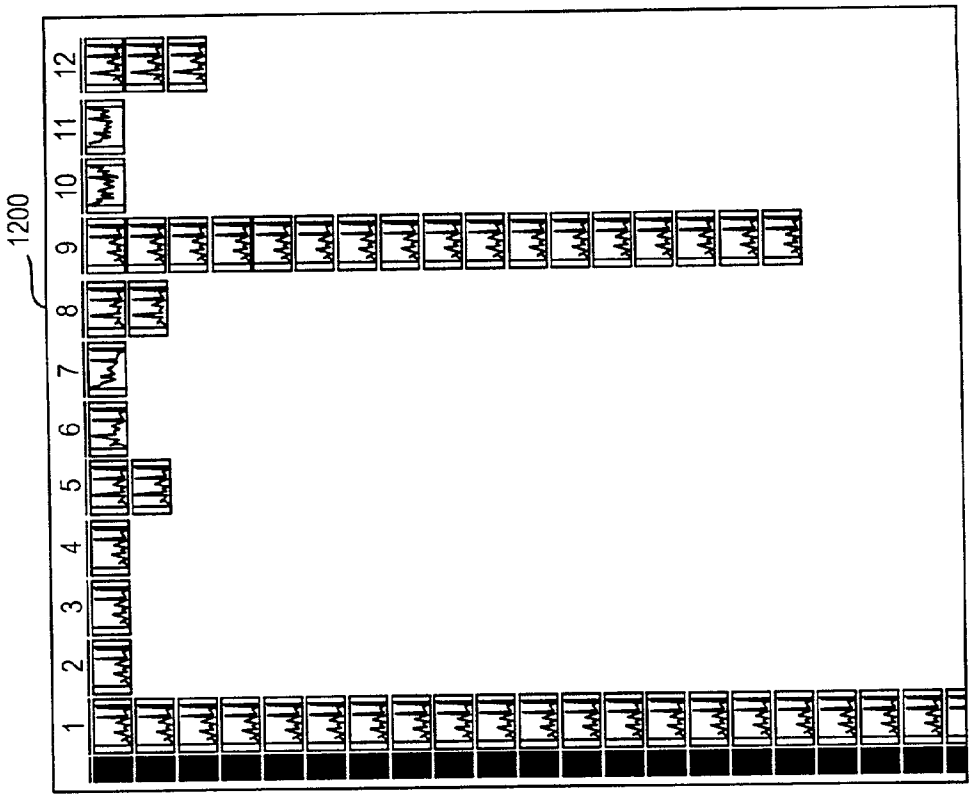

1200
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 12

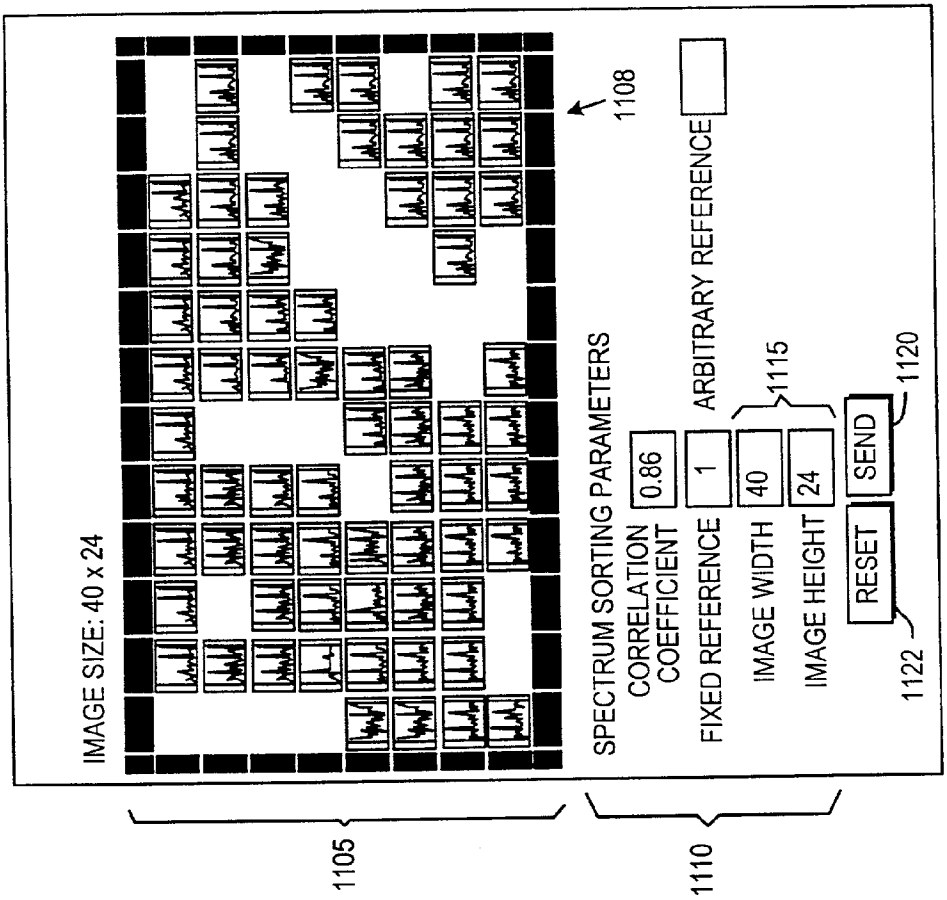

IMAGE SIZE: 40 x 24
1105
1110
SPECTRUM SORTING PARAMETERS
1108
CORRELATION COEFFICIENT
0.86
FIXED REFERENCE
1
ARBITRARY REFERENCE
IMAGE WIDTH
40
IMAGE HEIGHT
24
1115
RESET
SEND
1120
1122

FIG. 11

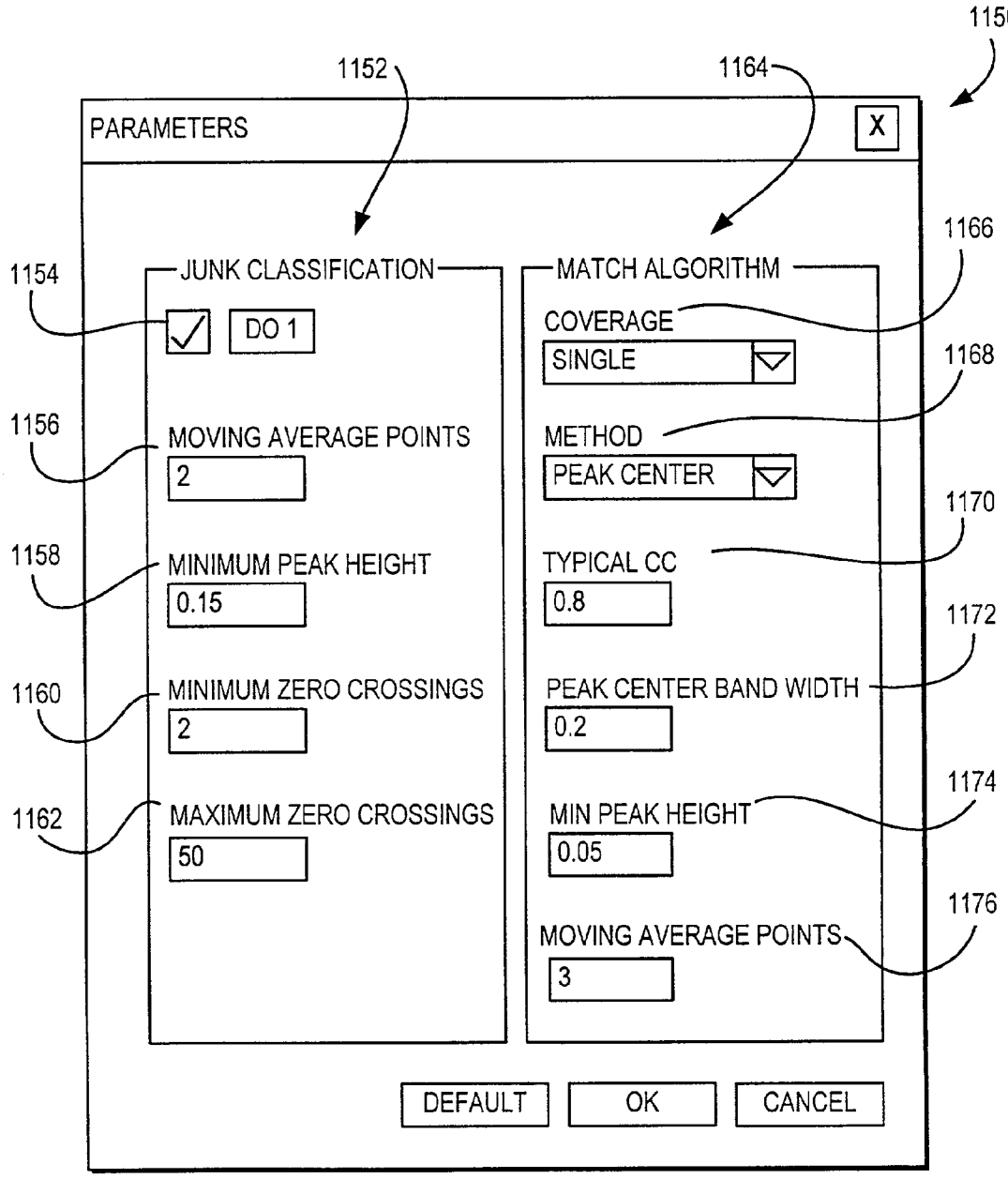
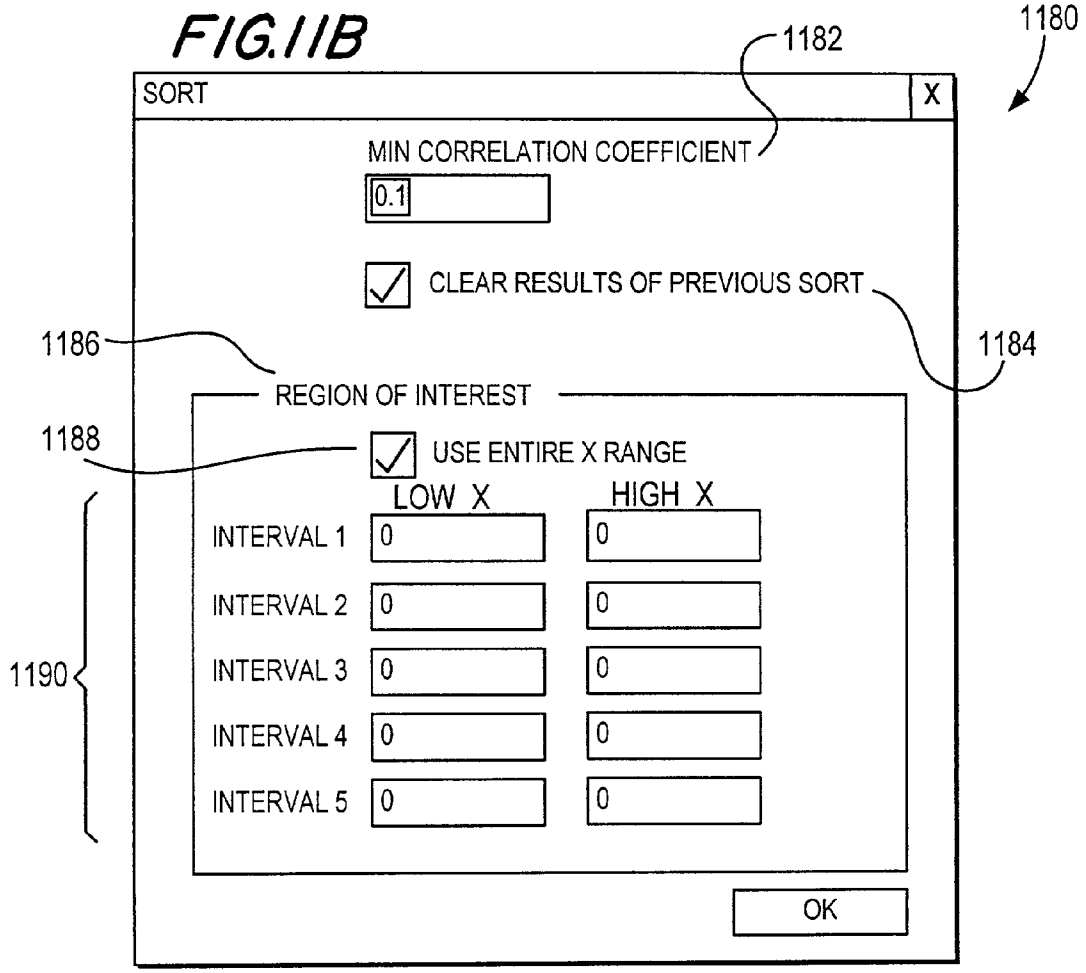

1150
1152
1164
PARAMETERS
X
1166
1154
JUNK CLASSIFICATION
MATCH ALGORITHM
DO 1
COVERAGE
SINGLE
1168
1156
MOVING AVERAGE POINTS
2
METHOD
PEAK CENTER
1170
1158
MINIMUM PEAK HEIGHT
0.15
TYPICAL CC
0.8
1172
1160
MINIMUM ZERO CROSSINGS
2
PEAK CENTER BAND WIDTH
0.2
1174
1162
MAXIMUM ZERO CROSSINGS
50
MIN PEAK HEIGHT
0.05
1176
MOVING AVERAGE POINTS
3
DEFAULT
OK
CANCEL

FIG. 11A

FIG.11B



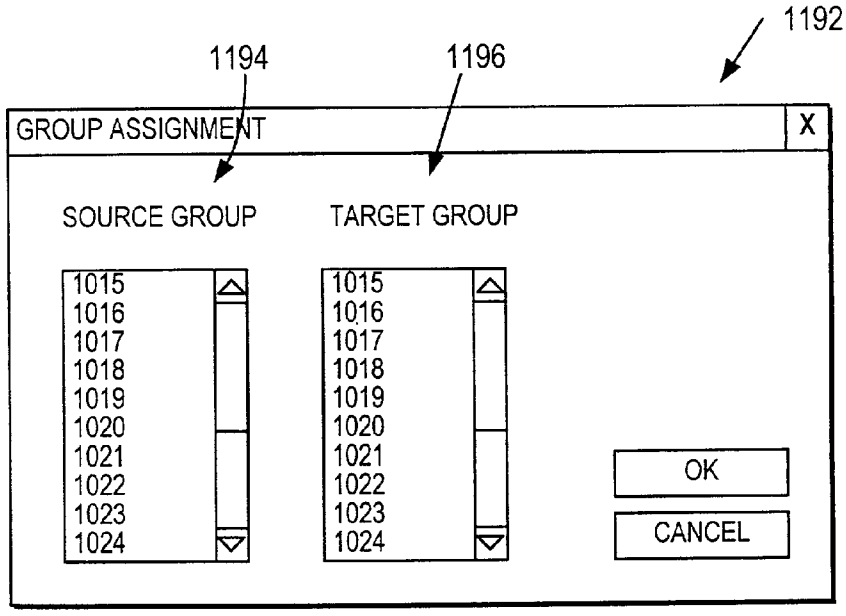


FIG. 11C

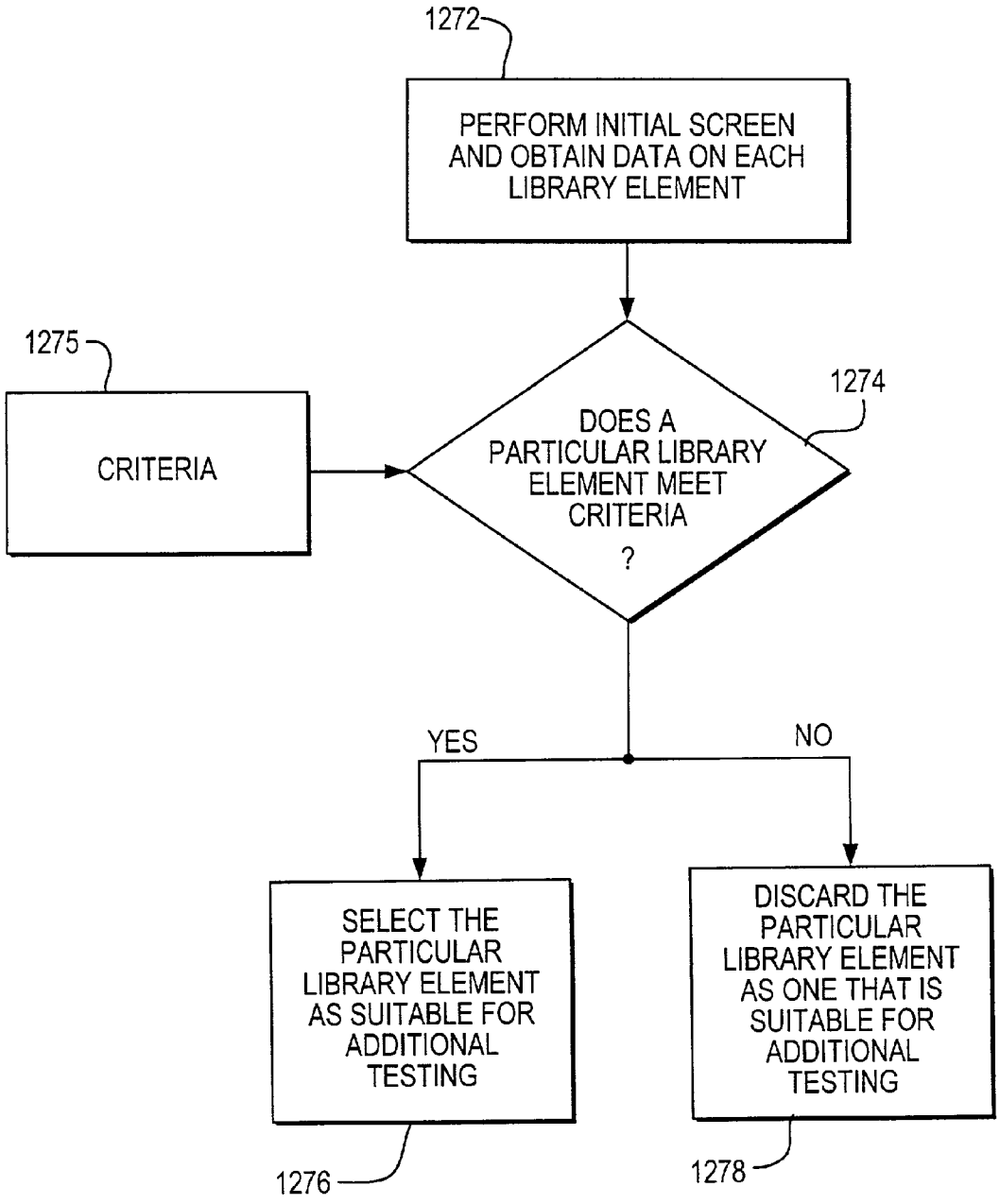

1272
PERFORM INITIAL SCREEN AND OBTAIN DATA ON EACH LIBRARY ELEMENT
1275
CRITERIA
1274
DOES A PARTICULAR LIBRARY ELEMENT MEET CRITERIA ?
YES
NO
SELECT THE PARTICULAR LIBRARY ELEMENT AS SUITABLE FOR ADDITIONAL TESTING
DISCARD THE PARTICULAR LIBRARY ELEMENT AS ONE THAT IS SUITABLE FOR ADDITIONAL TESTING
1276
1278

FIG. 12A

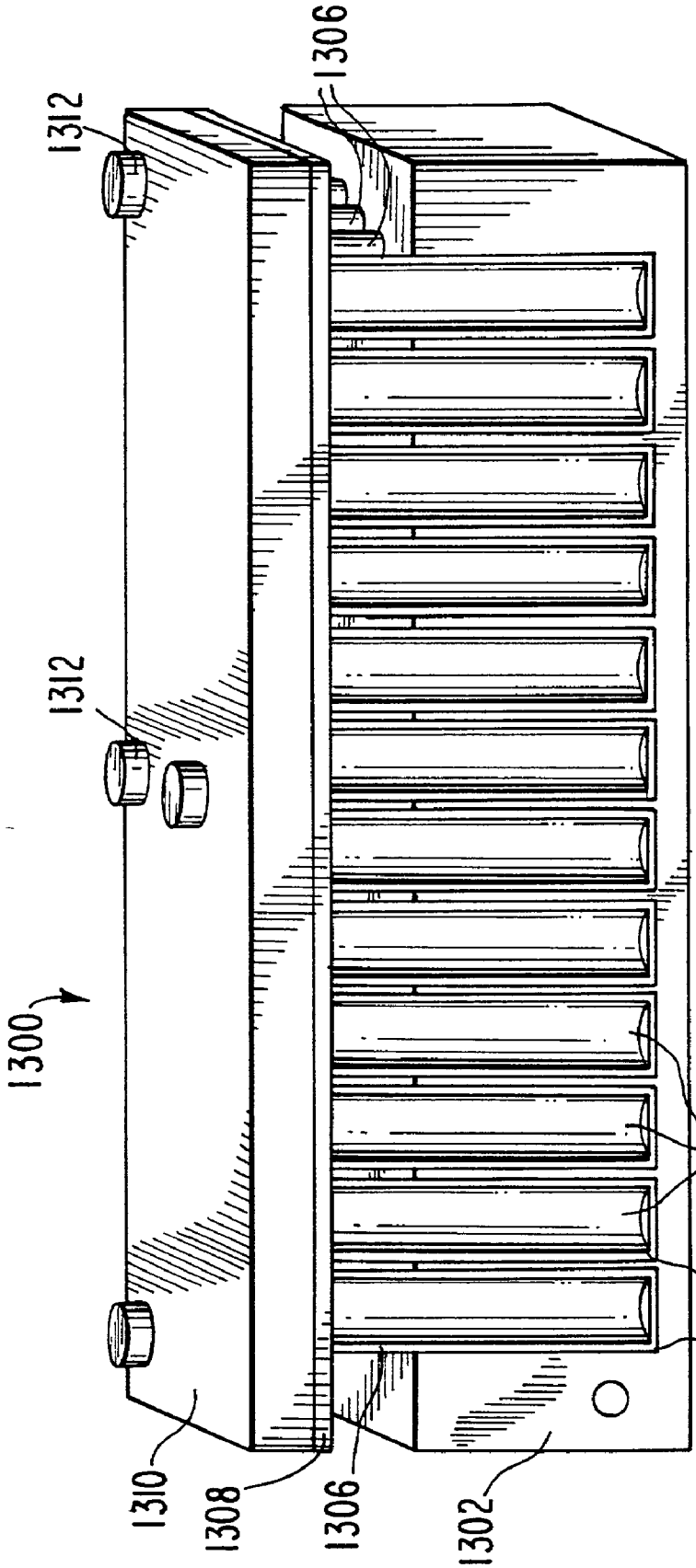


FIG.13

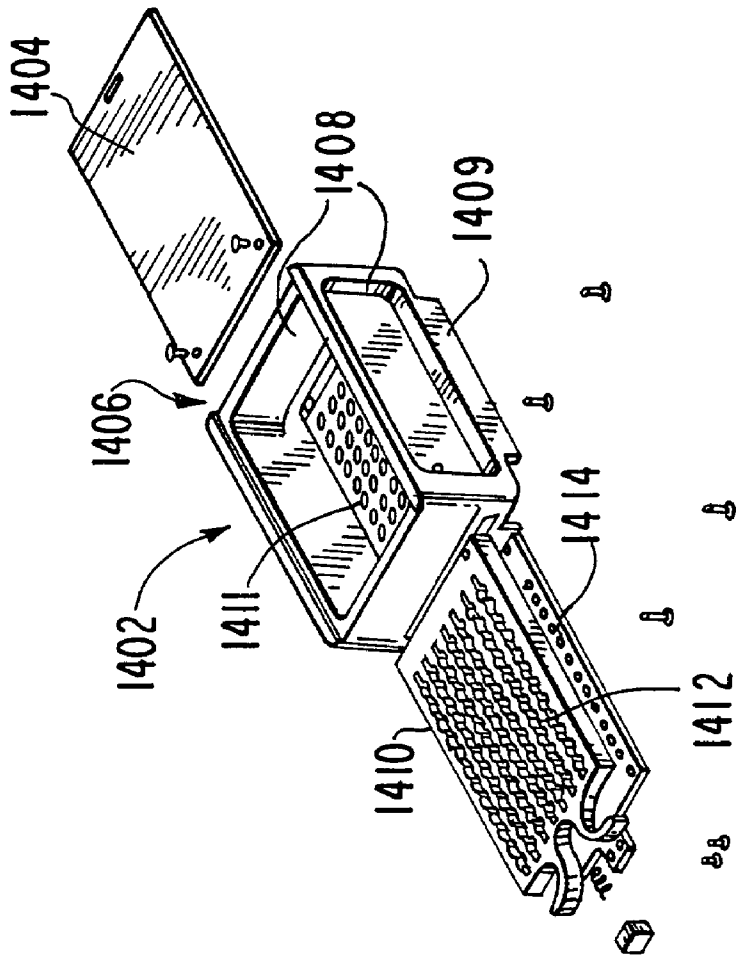


FIG. 14A

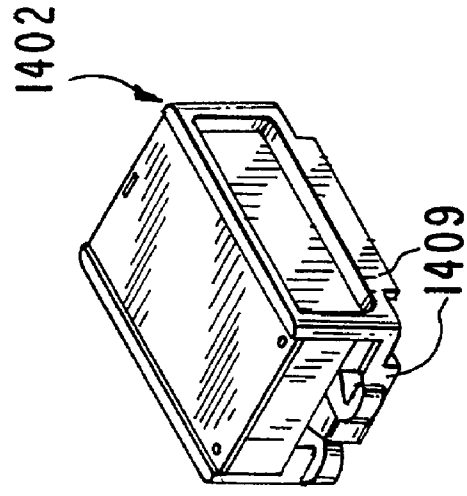


FIG. 14

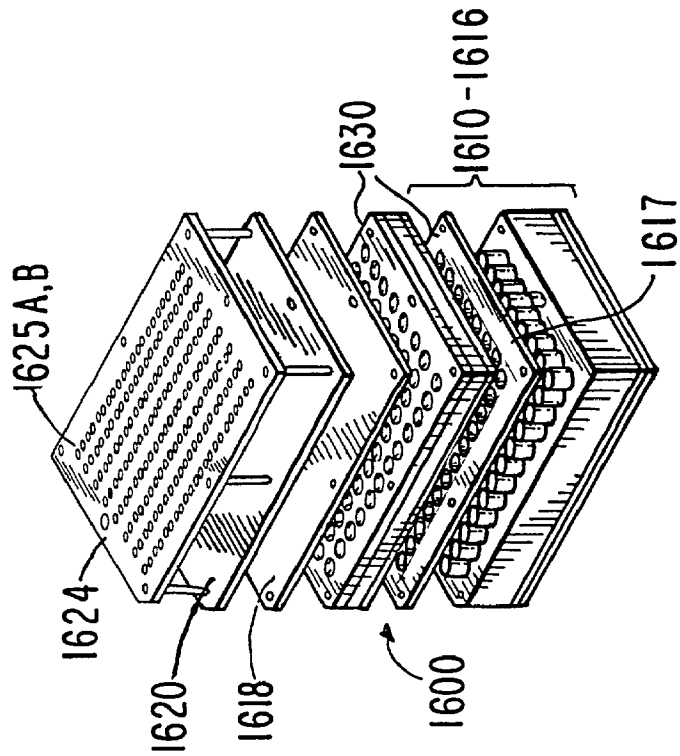

1625A,B
1624
1620
1618
1600
1630
1610-1616
1617

FIG. 16

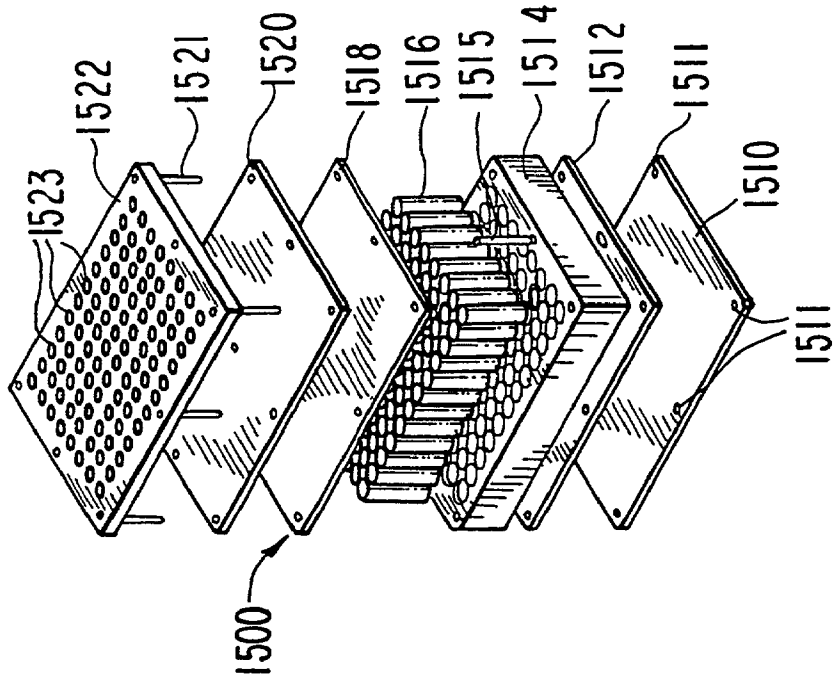

1500
1523
1522
1521
1520
1518
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1514
1512
1511
1510
1511

FIG. 15

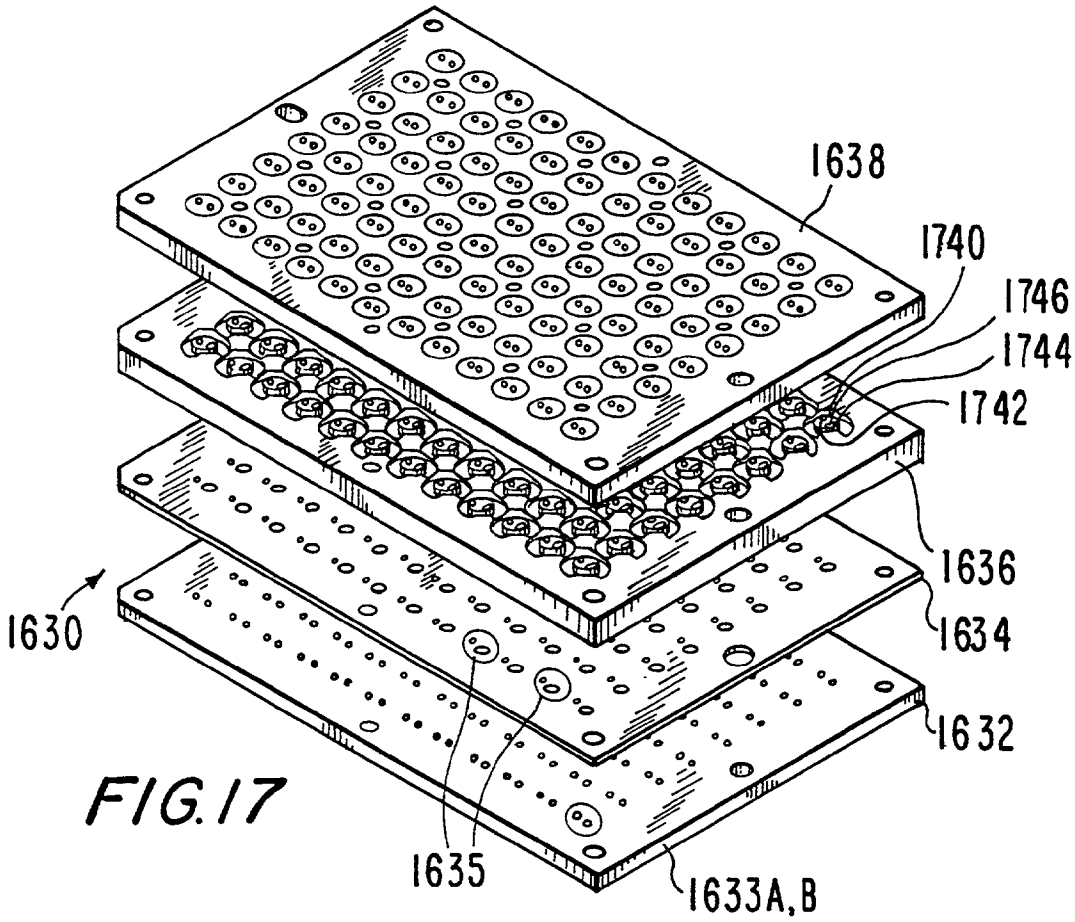

1638
1740
1746
1744
1742
1636
1634
1632
1630
1635
1633A,B

FIG. 17

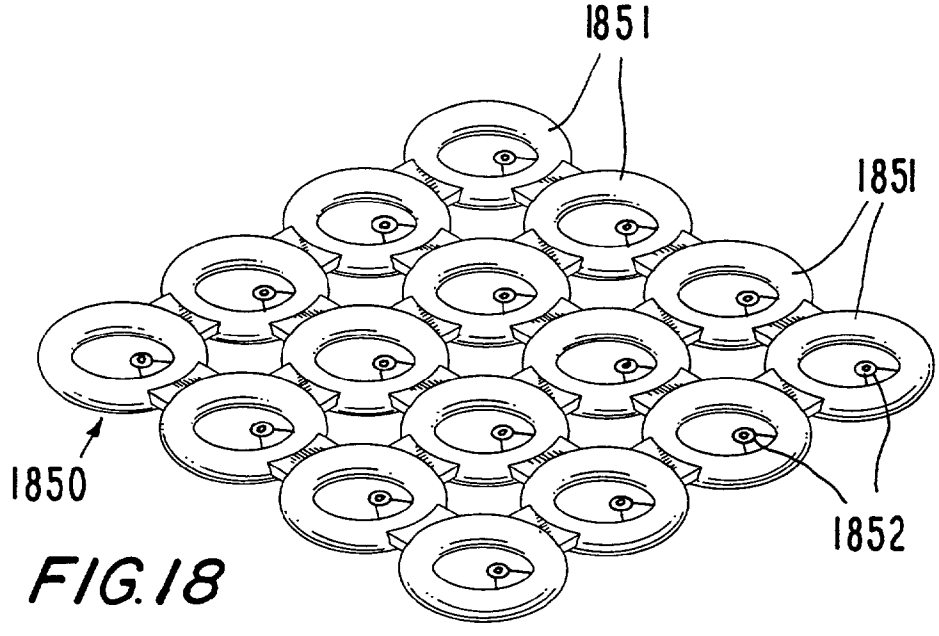

1851
1851
1850
1852

FIG. 18

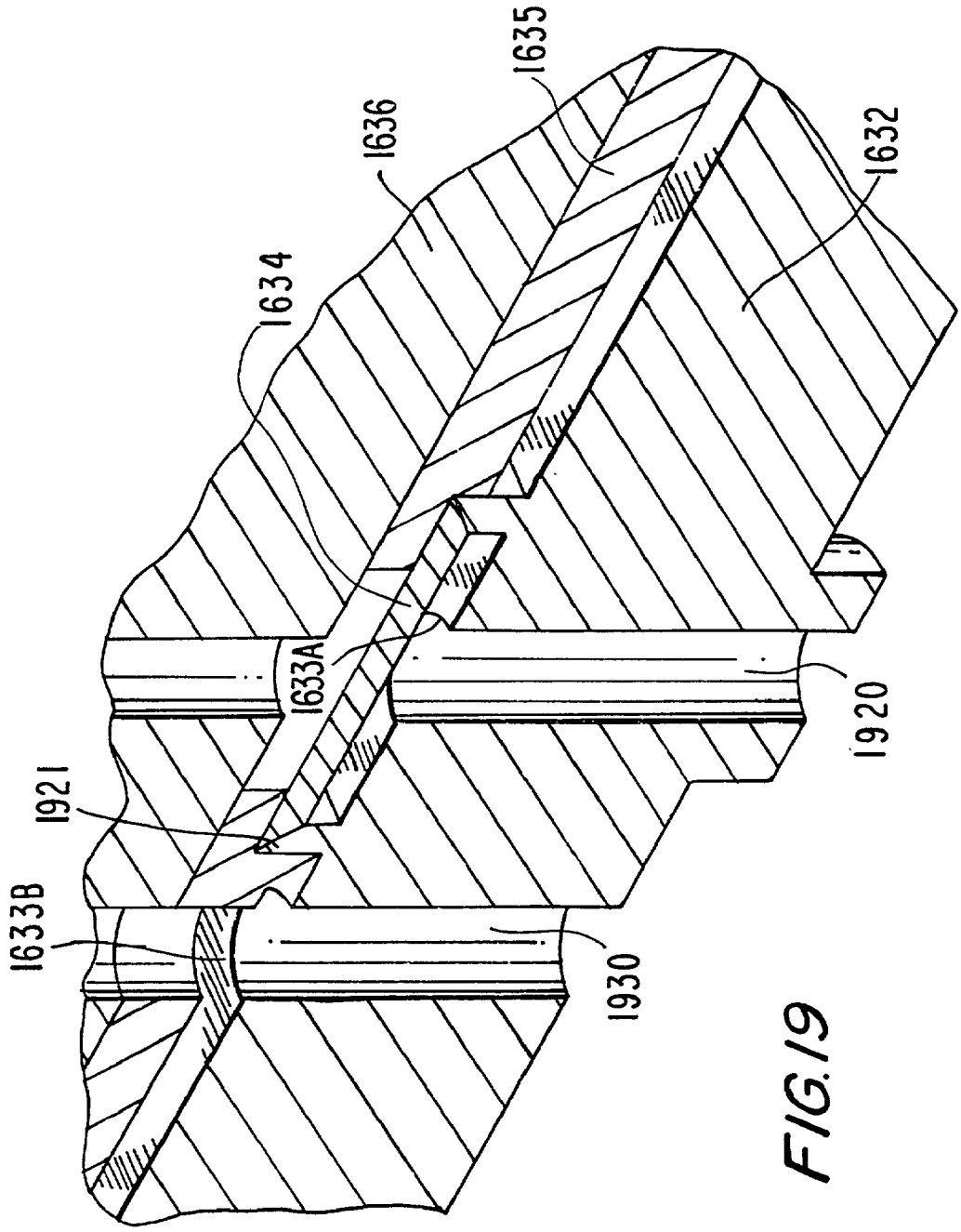


FIG. 19

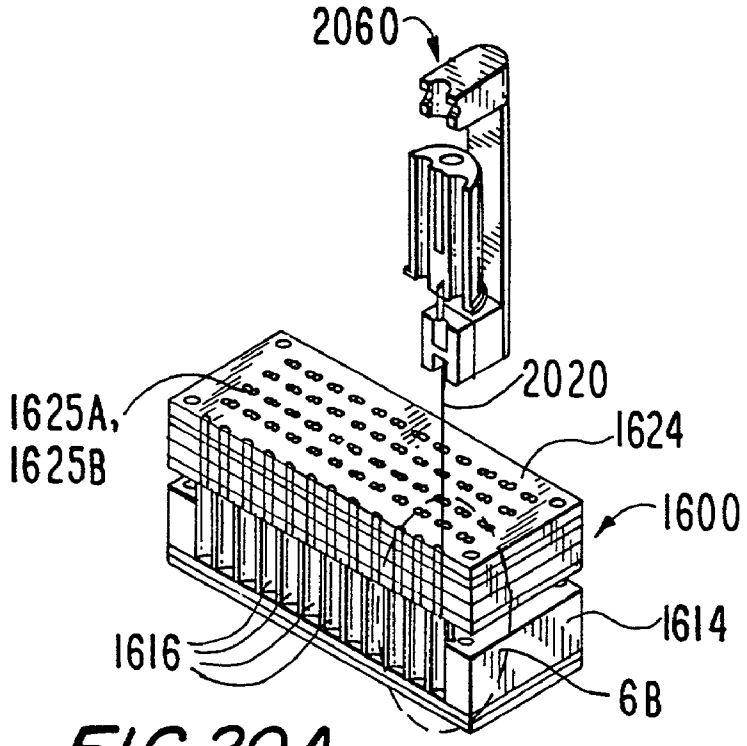


FIG. 20A

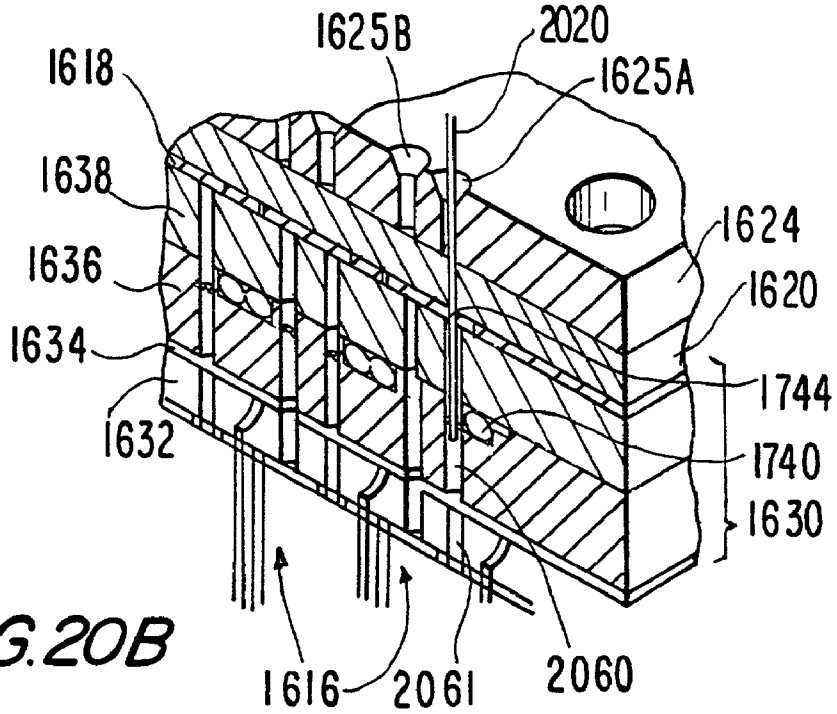


FIG. 20B

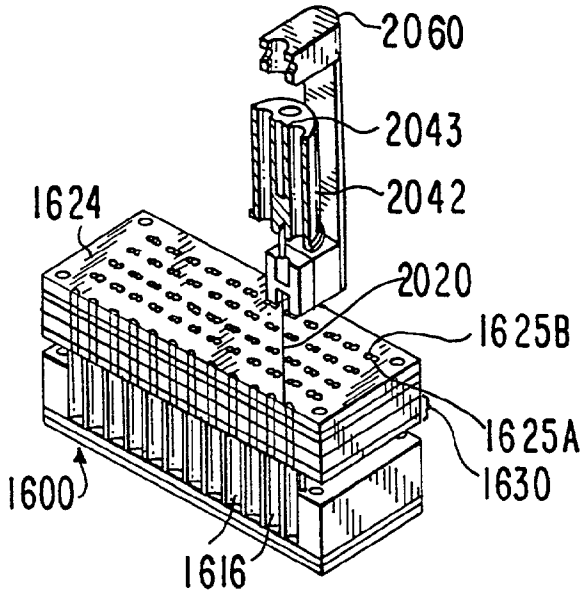


FIG. 20C

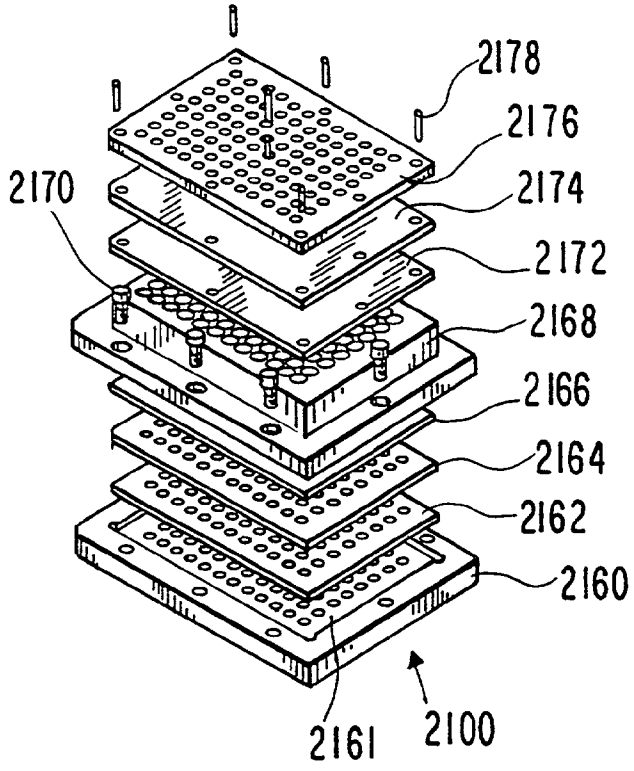


FIG. 21

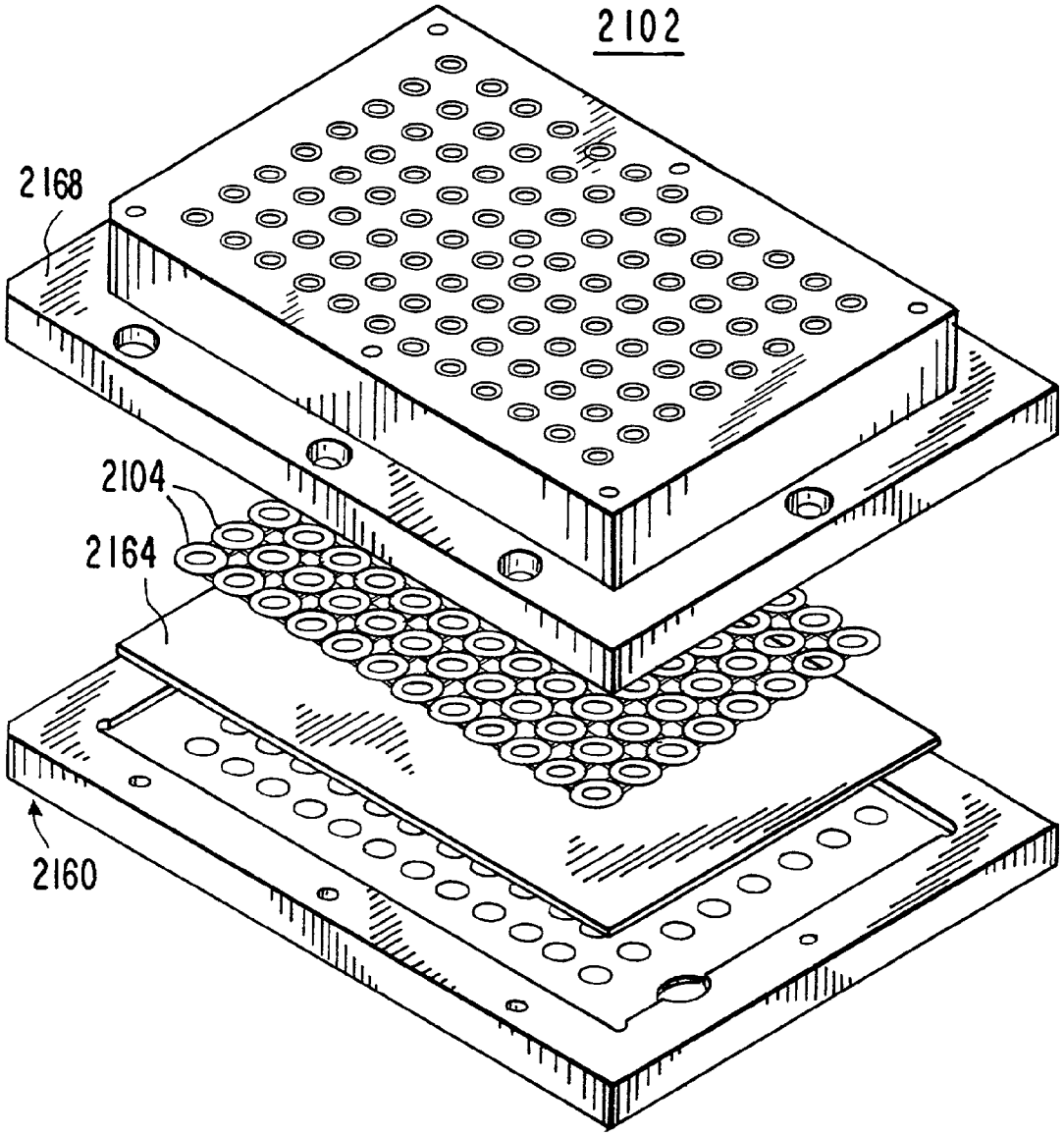


FIG. 21A

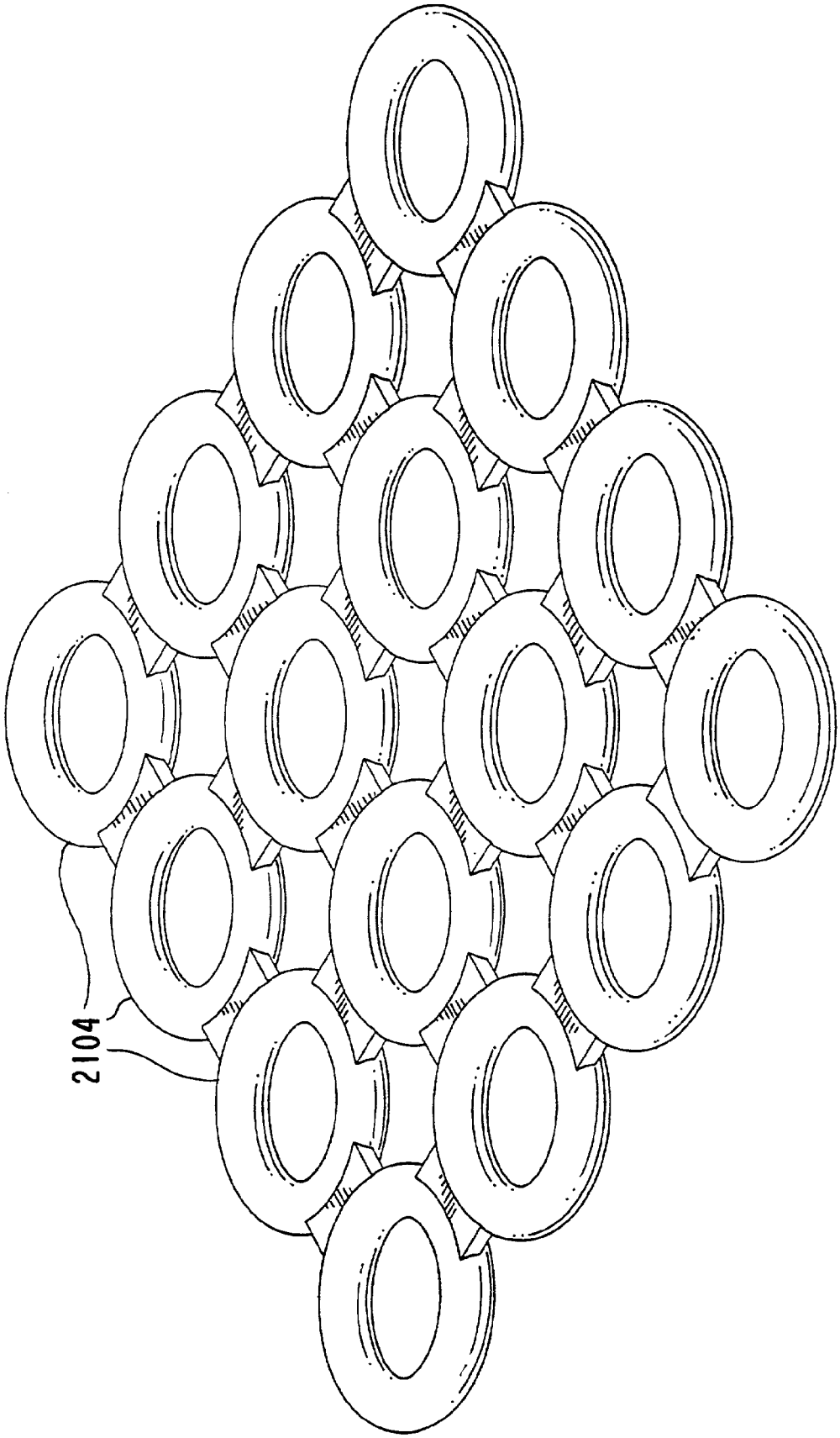


FIG. 21B

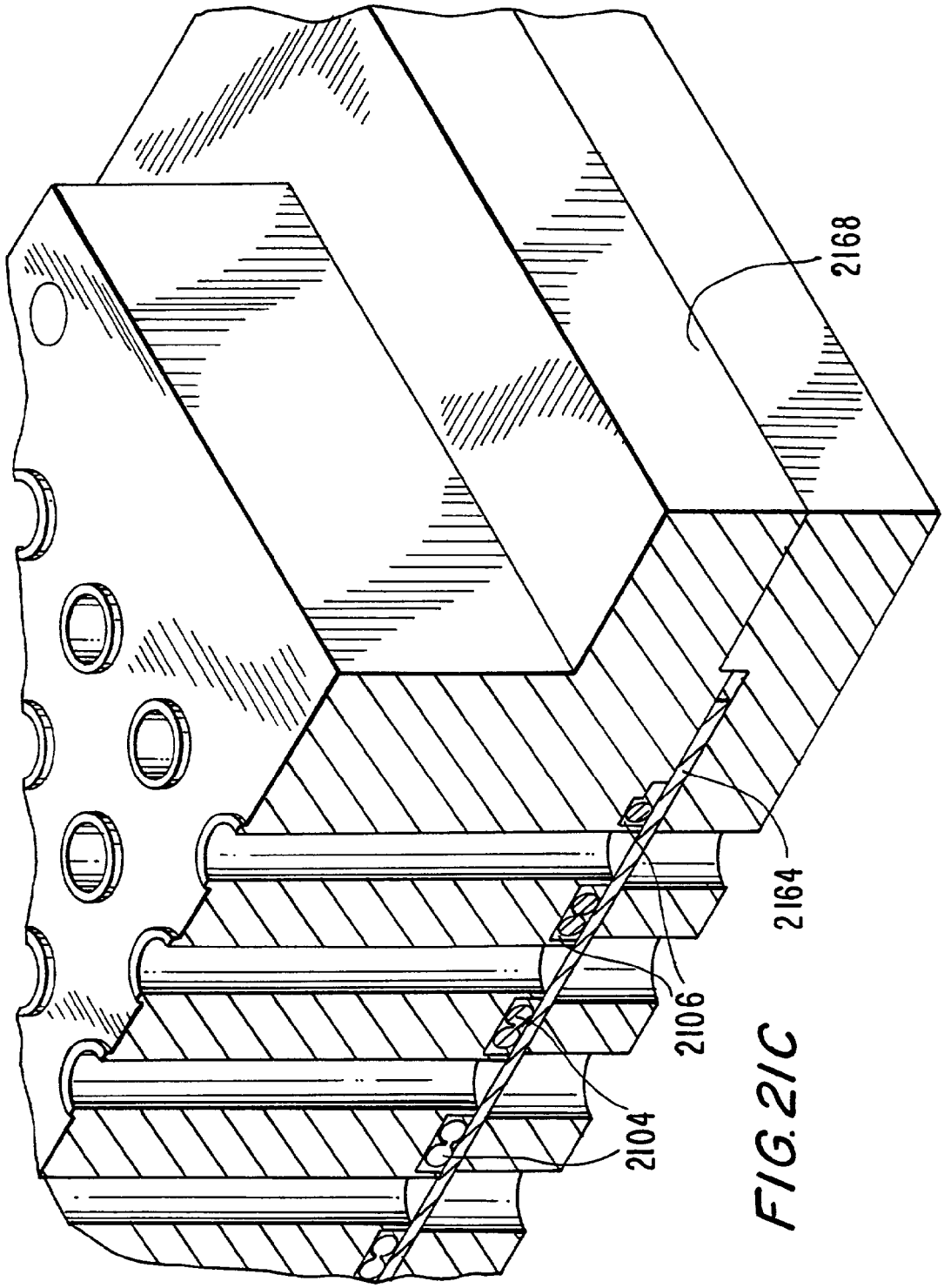


FIG. 21C

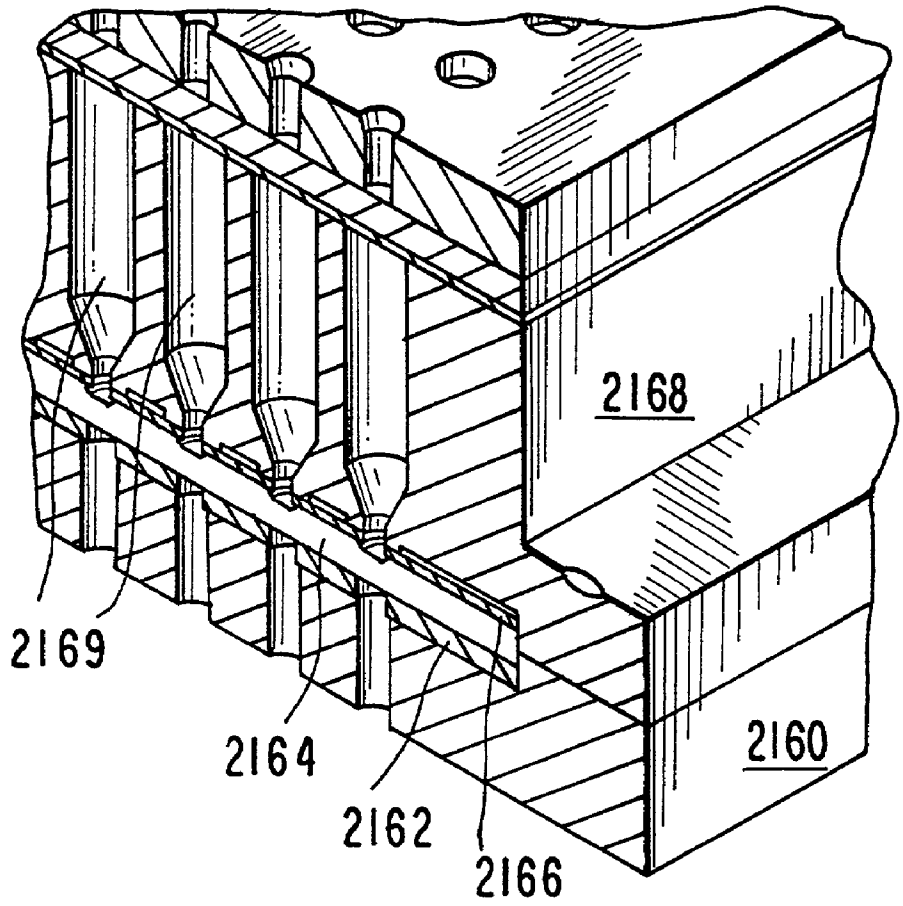


FIG. 22

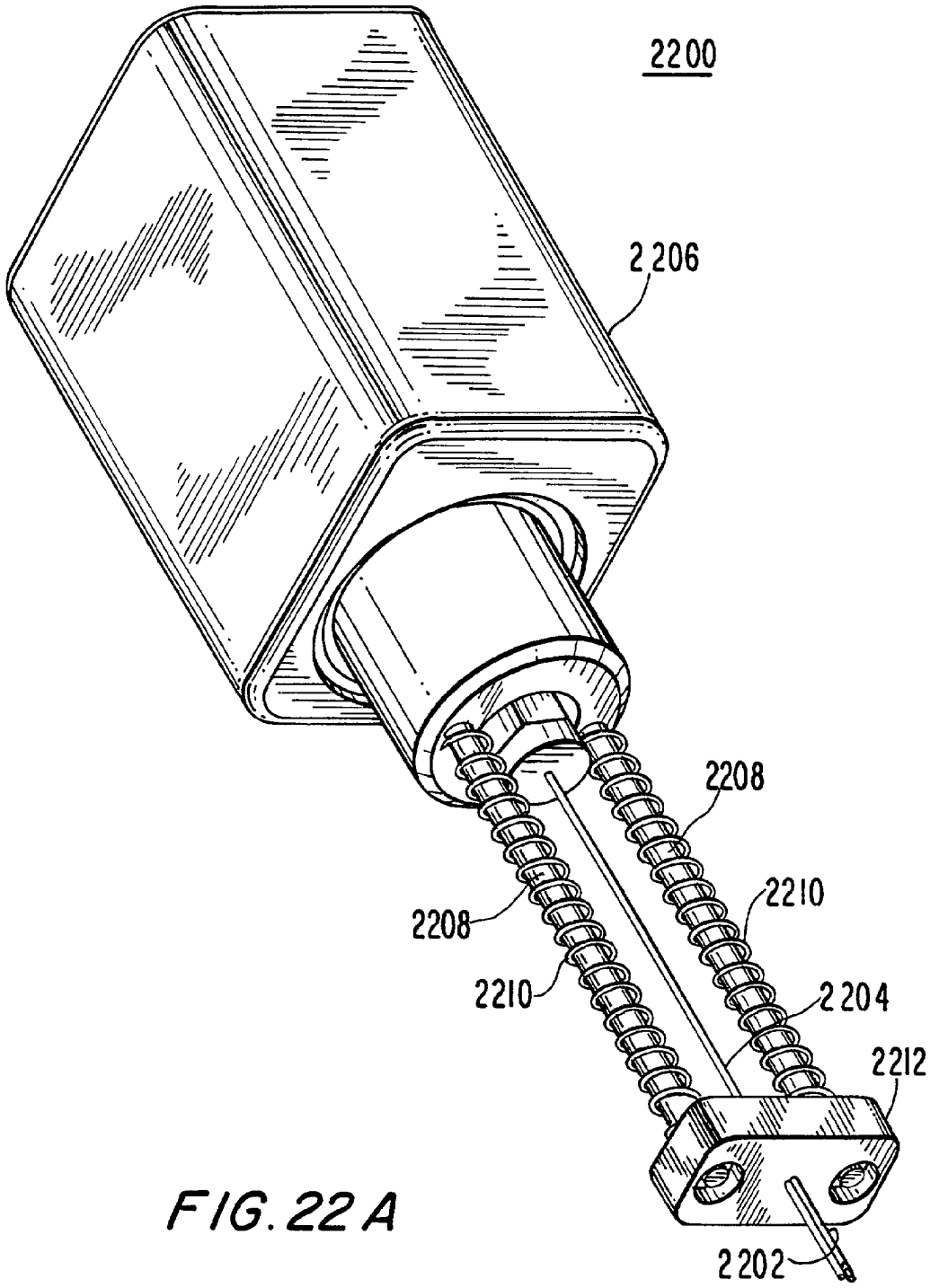


FIG. 22A

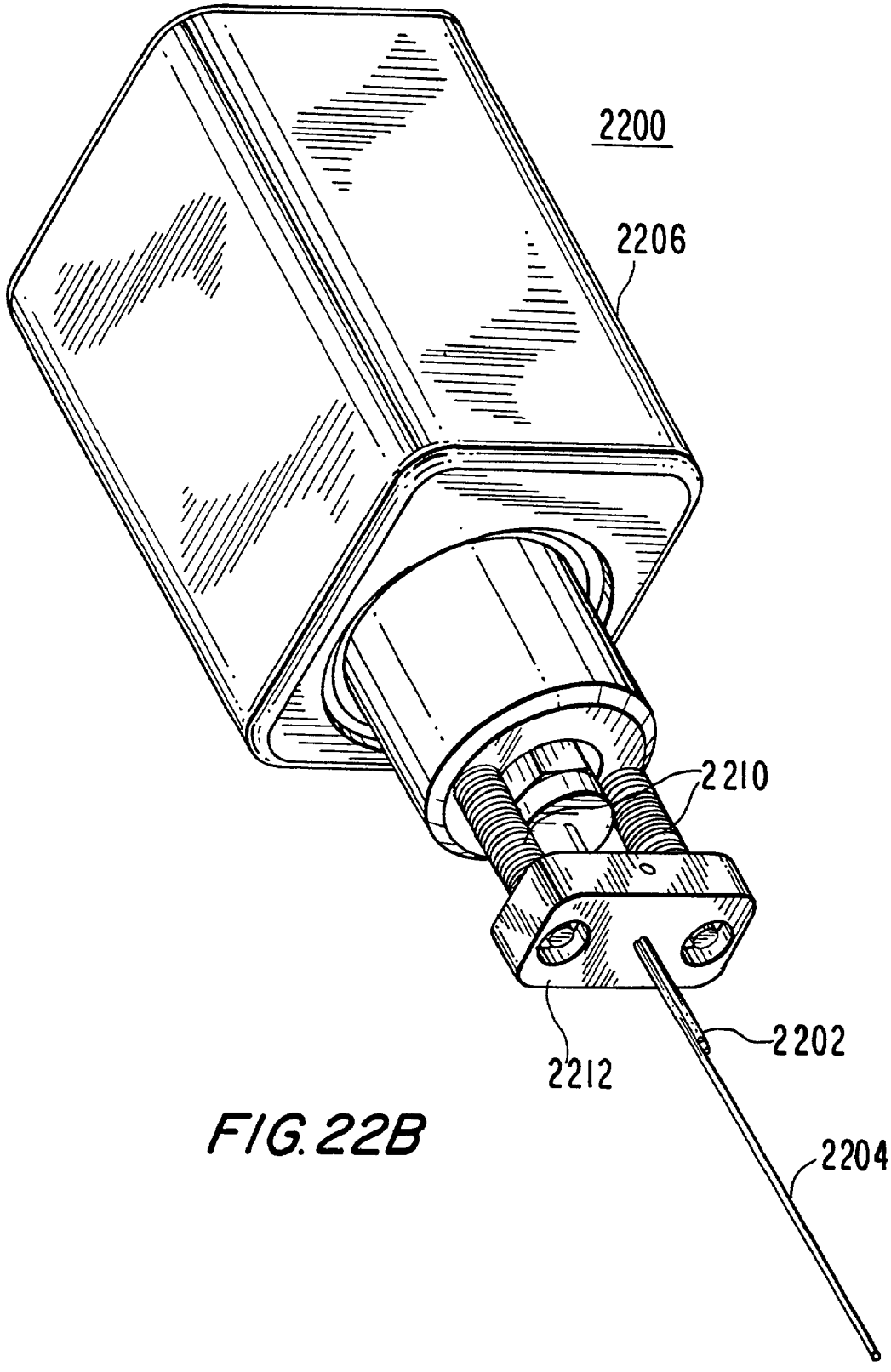


FIG. 22B

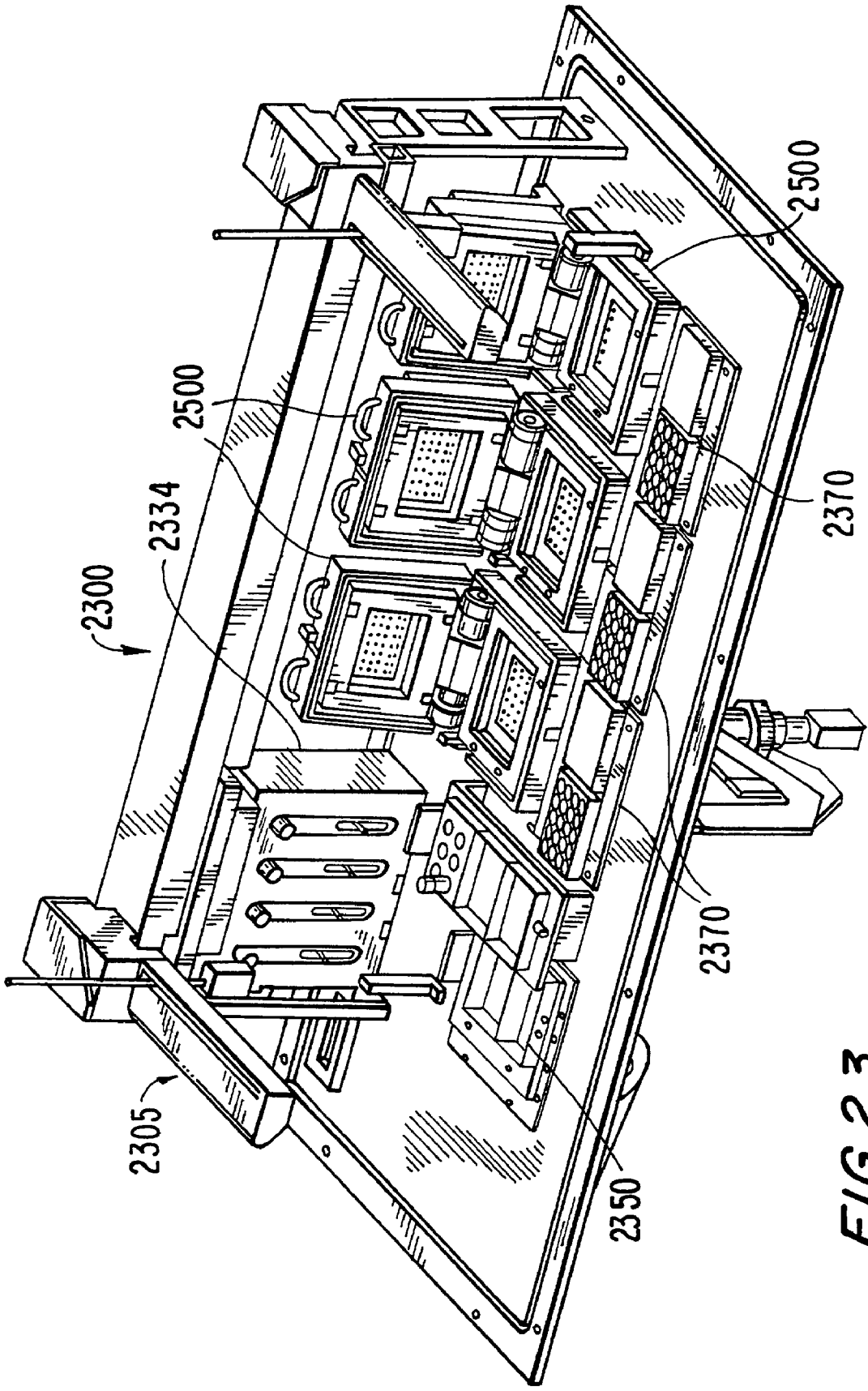


FIG.23

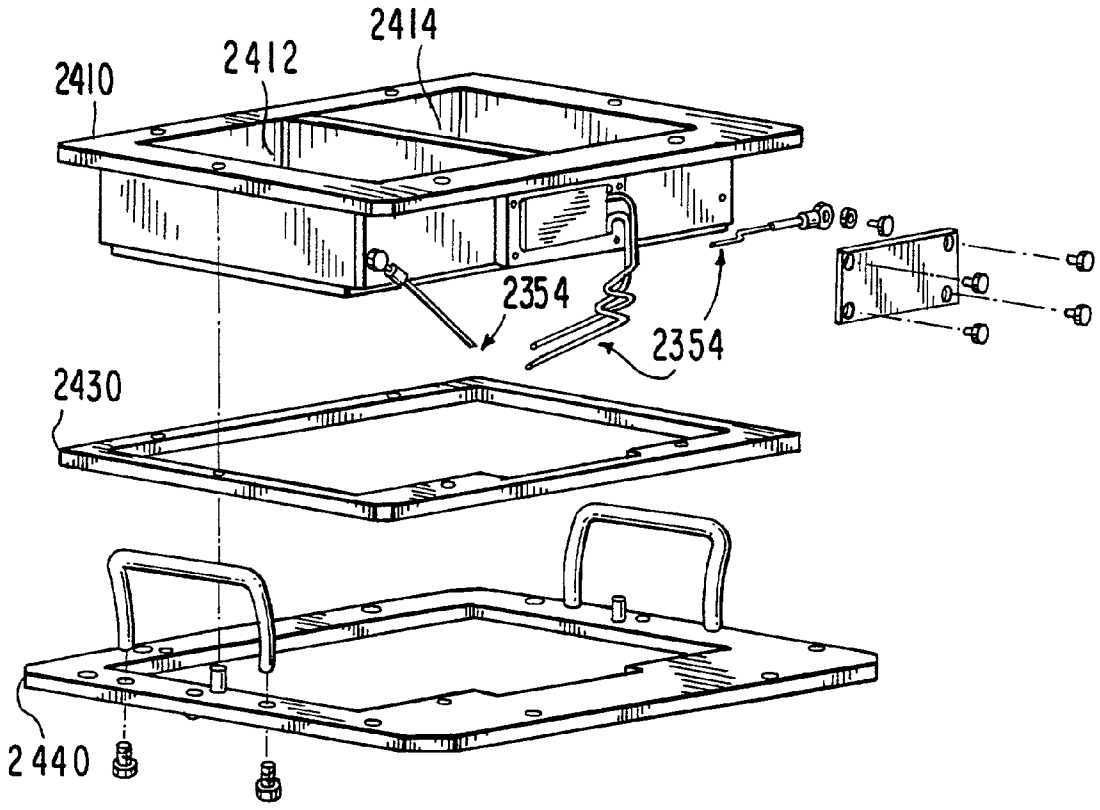


FIG. 24

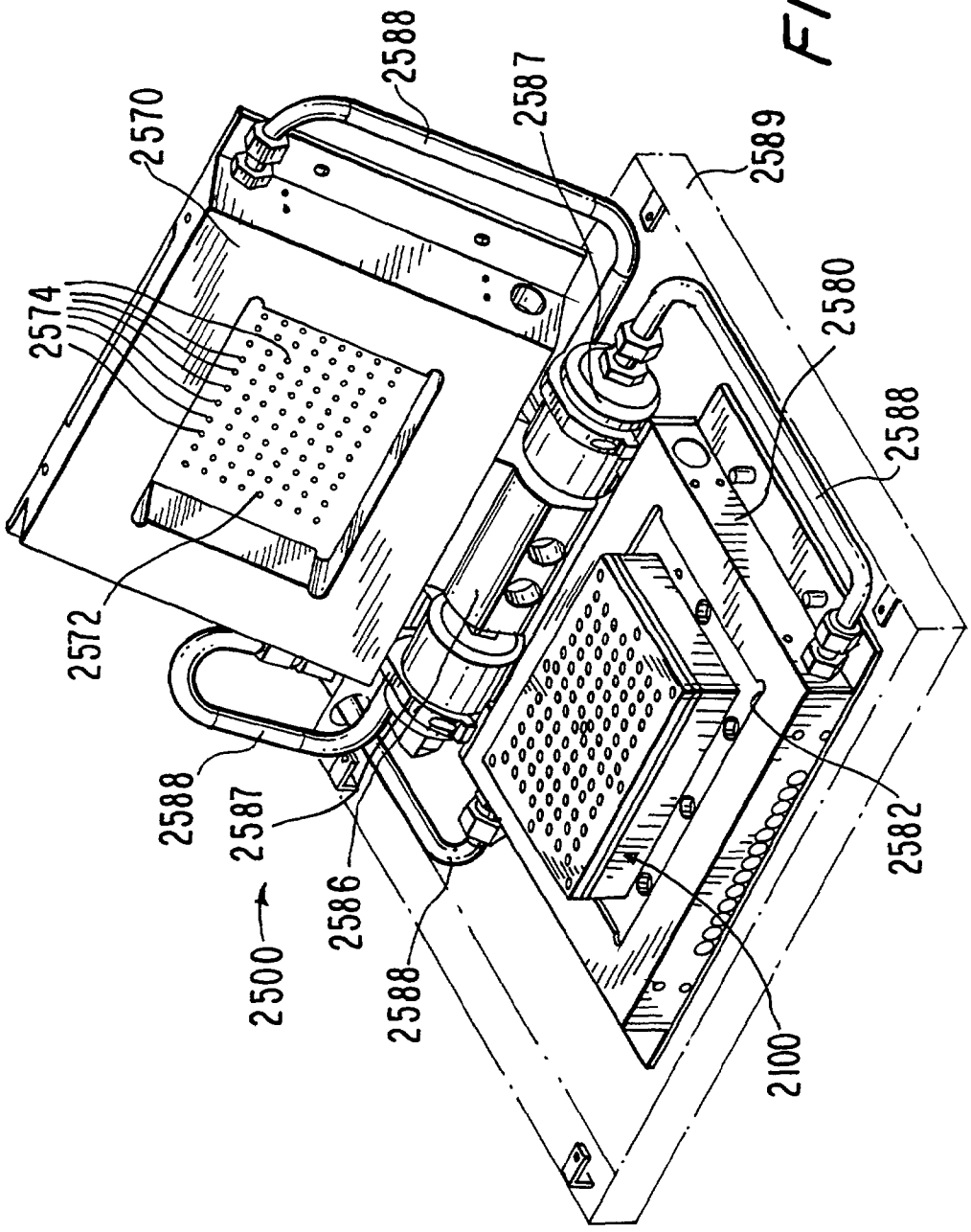

2588
2587
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2588
2572
2588
2587
2582
2586
2500
2588
2100

FIG. 25

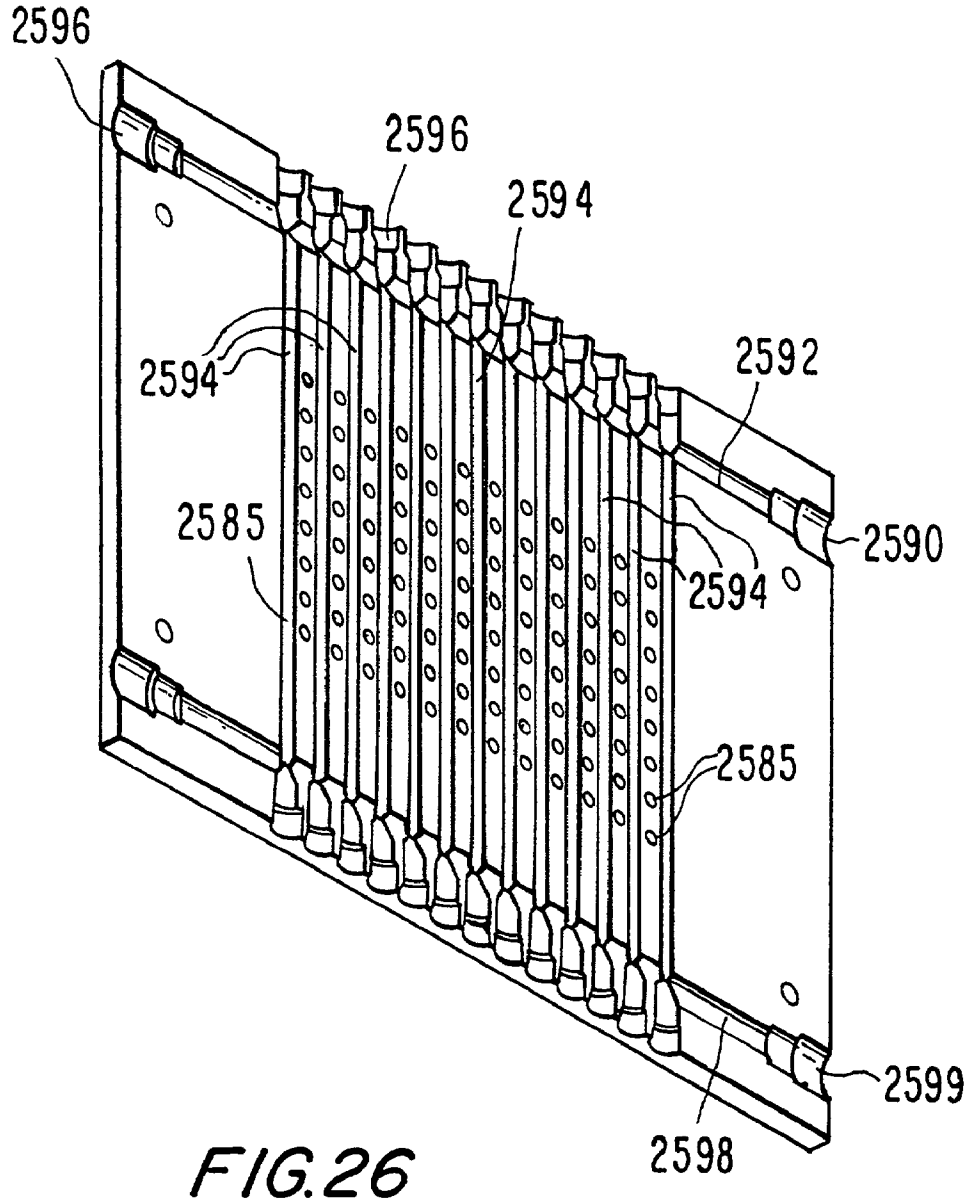


FIG. 26

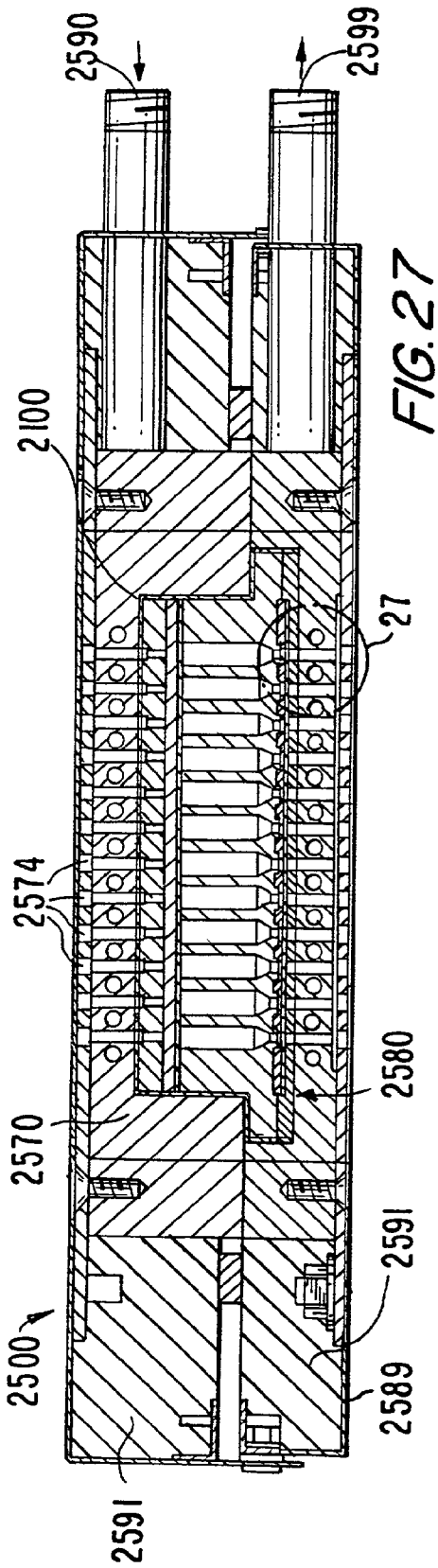


FIG. 27

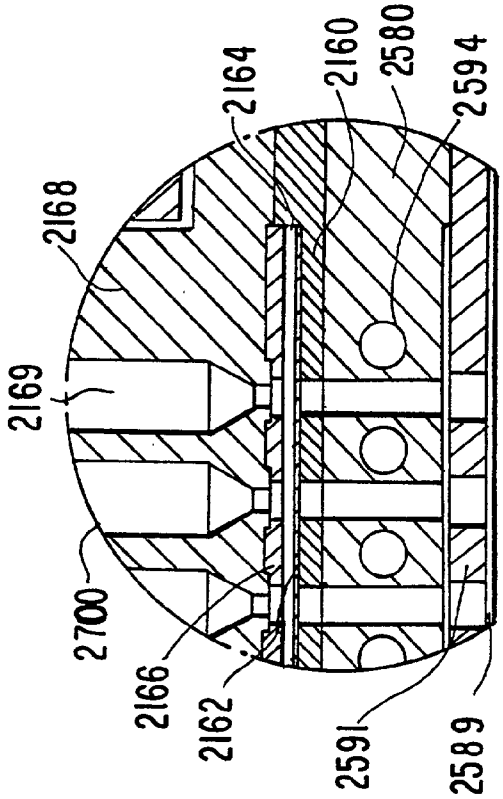


FIG. 27A

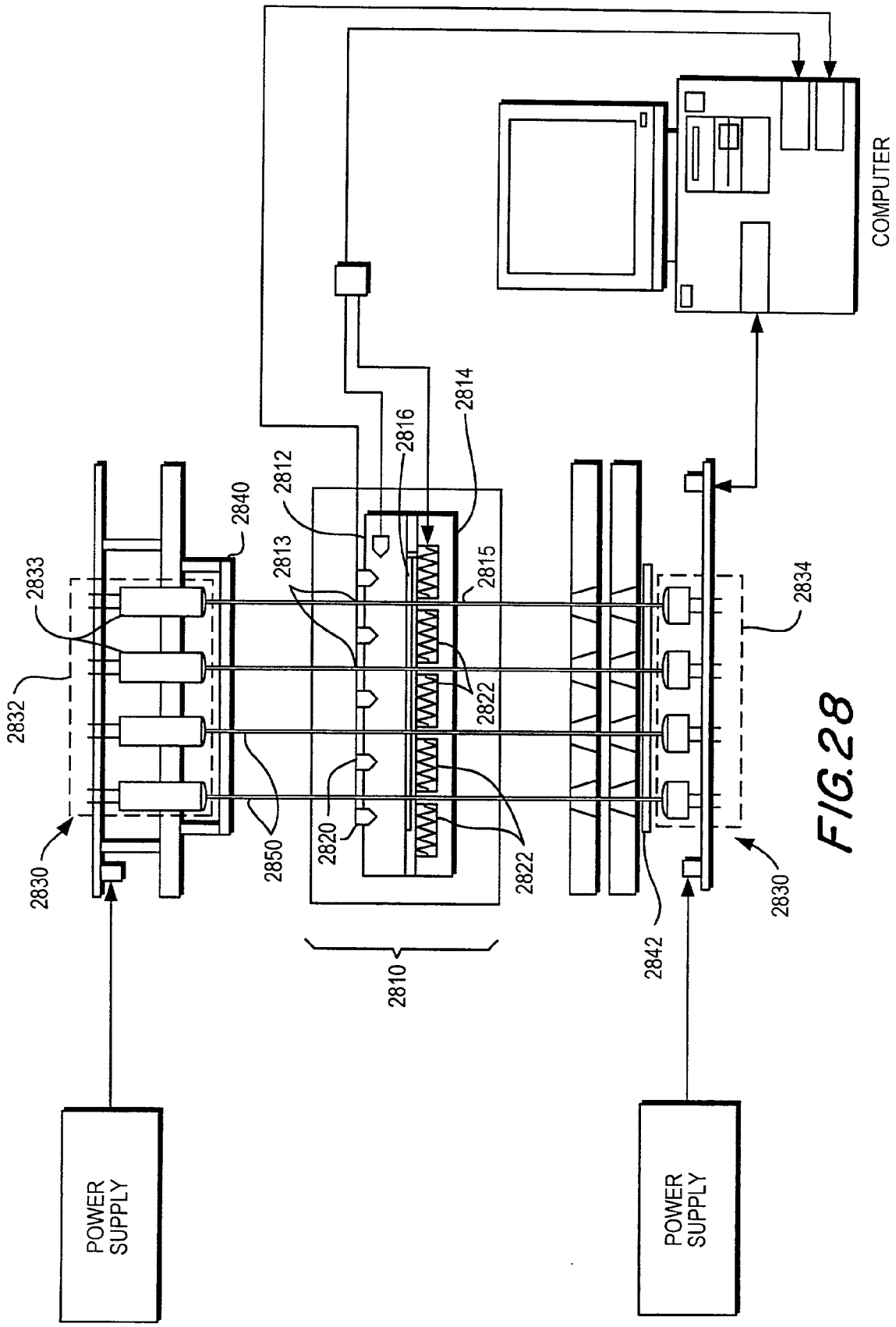

COMPUTER
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POWER SUPPLY
POWER SUPPLY

FIG.28

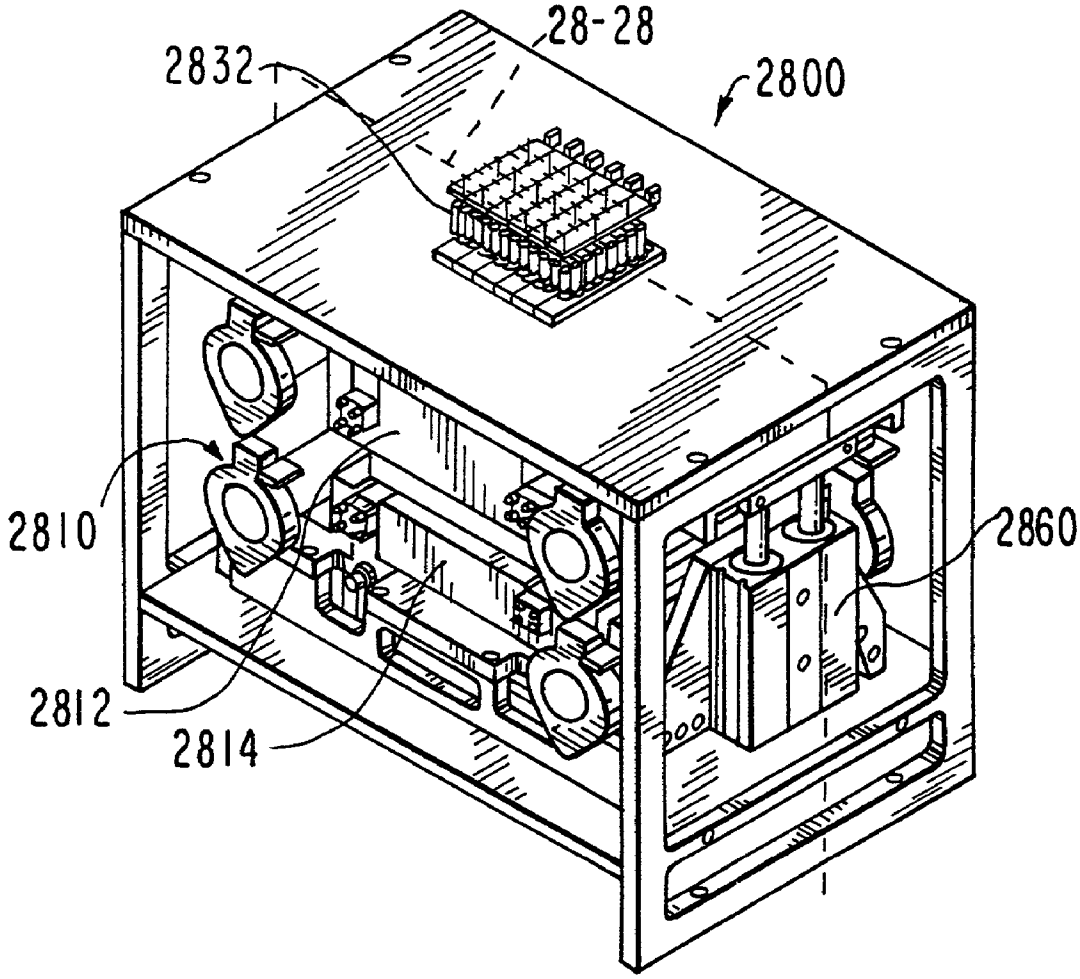


FIG. 28A

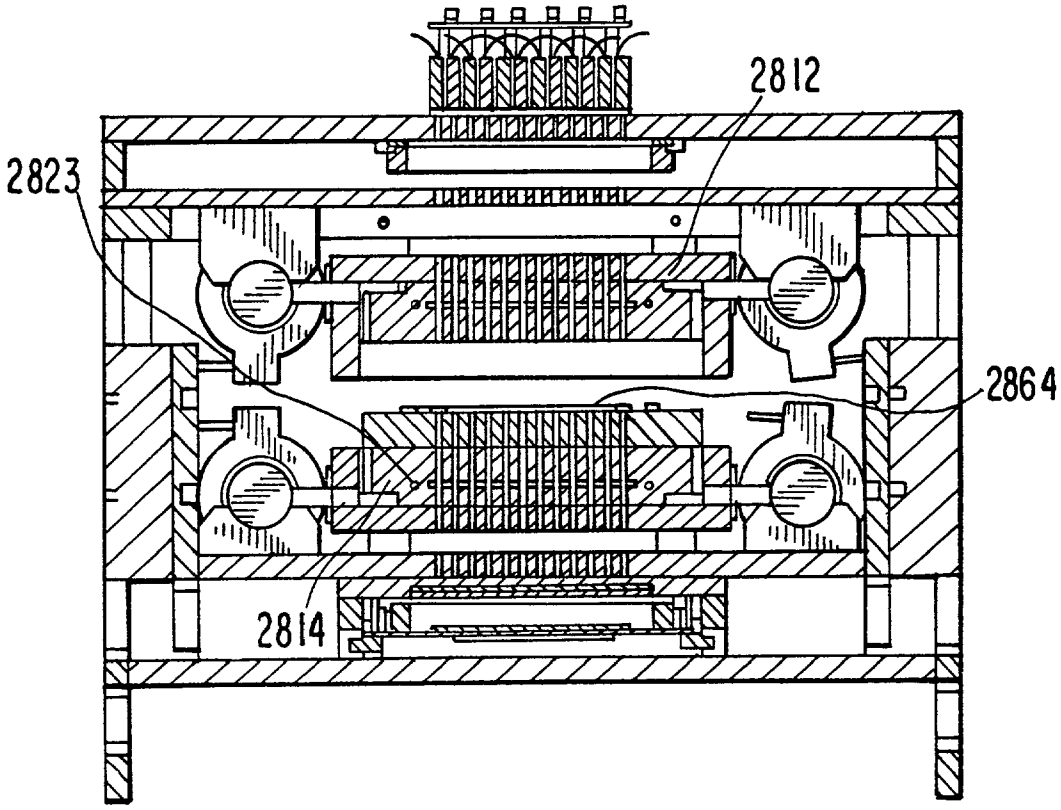


FIG. 28B

FIG. 29A

SOLVENT	CLASS	#	MW	n	V_m	MP	BP	ΔH_{vap}	δ	μ	logS	logP	pKa	ε	IE	pK_{a+}
TRIFLUOROACETIC ACID	ACID	1	114.02	1.48	77.0	-15	72	41	10.93	2.28	8.00	0.5	0.23	39	11.5	-8
FORMIC ACID	ACID	1	46.03	1.22	37.7	8	100	46.3	16.66	1.41	8.00	-0.540	3.75	51.1	11.33	-6
ACETIC ACID	ACID	1	60.05	1.04	57.7	15	115	51.6	14.26	1.74	8.00	-0.17	4.756	6.15	10.65	-6
PROPIONIC ACID	ACID	1	74.08	0.993	74.6	-20.7	141	55	12.97	1.75	8.00	0.33	4.88	3.3	10.44	-6
METHANOL	ALCHOHOL	2	32.04	0.791	40.5	-98	64.7	37.83	14.44	1.70	8.00	-0.77	15.5	32.63	10.84	-205
ETHANOL	ALCHOHOL	2	46.07	0.816	56.5	-114	78	42.46	13.01	1.69	8.00	-0.31	15.9	24.30	10.48	-2
TRIFLUOROETHANOL	ALCHOHOL	2	100.4	1.373	73.1	-43	78	43.97	11.65	1.9	8.00	0.41	12.4	26.5	11.49	-4
2-PROPANOL	ALCHOHOL	2	60.1	0.785	76.6	-89.5	82.4	45.48	11.59	1.66	8.00	0.05	18.0	18.3	10.17	-2
T-BUTANOL	ALCHOHOL	2	74.12	0.775	95.6	25	83	46.74	10.52	1.64	8.00	0.35	19.0	17.7	9.9	-2
1-PROPANOL	ALCHOHOL	2	60.10	0.804	74.8	-127	97	47.5	12.00	1.68	8.00	0.25	16.1	20.1	10.22	-2
2-BUTANOL	ALCHOHOL	2	74.12	0.808	91.7	-115	98	49.86	11.11	1.70	2.258	0.61	17.6	16.56	9.88	-2
1-BUTANOL	ALCHOHOL	2	74.12	0.810	91.5	-90	117.7	52.42	11.42	1.66	1.801	0.88	16.1	17.8	9.99	-2
2-METHOXYETHANOL	ALCHOHOL	2	76.09	0.965	78.8	-85	124	45.2	11.38	2.20	8.00	-0.77	14.8	17.2	10.13	-3
3-METHYL-1-BUTANOL	ALCHOHOL	2	88.15	0.809	109.0	-117	130	55.63	10.80	1.82	1.427	1.16	16.1	14.7	10	-2
2-ETHOXYTHETHANOL	ALCHOHOL	2	90.12	0.93	96.9	-90	135	48.23	10.62	2.08	8.00	-0.32	14.8	29.6	9.6	-2
1-PENTANOL	ALCHOHOL	2	88.15	0.811	108.7	-78	137	57.04	10.95	1.80	1.342	1.51	16.1	13.6	10.0	-2
1-OCTANOL	ALCHOHOL	2	130.23	0.827	157.5	-15	196	70.98	10.20	1.76	-0.268	2.97	16.1	10.3	10	-2
ETHYLENE GLYCOL	ALCHOHOL	2	62.07	1.113	55.8	-13	197	65.6	16.45	2.28	8.00	-1.360	15.1	37.3	10.55	-3
WATER	WATER	3	18.105	1.000	18.1	0	100	43.98	23.41	1.85	8.00	-1.38	15.74	80.37	12.621	-1.74
FORMAMIDE	AMIDE	4	45.04	1.134	39.7	2	210	60.15	18.63	3.70	8.00	-1.510	13.7	110	10.16	-0.48
N.N-DIMETHYLFOMAMIDE	ALKYLAMIDE	5	73.09	0.944	77.4	-61	153	47.45	11.78	3.82	8.00	-1.01	50.2	36.7	9.13	-0.3
N.N-DIMETHYLACETAMIDE	ALKYLAMIDE	5	87.12	0.937	93.0	-20	165	45.6	10.53	3.81	8.00	-0.770	25.8	37.78	9.2	-0.19
BUTYL AMINE	AMINE	6	73.14	0.740	98.8	-49	78	35.84	8.98	1.0	8.00	0.97	35	5.4	8.73	10.77
DIISOPROPYL AMINE	AMINE	6	101.19	0.722	140.2	-61	84	34.72	7.42	1.13	2.041	1.40	37.3	4.0	7.59	11.13
TRIETHYL AMINE	AMINE	6	101.19	0.726	139.4	-115	88.8	34.96	7.46	0.66	1.867	1.45	51	2.42	7.53	11.01
PYRIDINE	AMINE	6	79.10	0.978	80.9	-42	115	40.21	10.56	2.19	8.00	0.65	38.3	12.3	9.26	5.21
ETHYLENE DIAMINE	AMINE	6	60.01	0.899	66.8	9	118	45.01	12.34	1.99	8.00	-2.04	35	14.2	8.6	9.92
MORPHOLINE	AMINE	6	87.12	0.999	87.2	-6	129	42.40	10.46	1.5	8.00	-086	35	7.33	8.88	8.33
NITROMETNANE	NITRO	7	61.04	1.127	54.2	-29	101	38.36	12.58	3.46	2.061	-0.35	10.2	39.4	11.08	-12
NITROETHANE	NITRO	7	75.07	1.045	71.8	-90	114	41.6	11.41	3.65	1.672	0.18	10.9	28.0	10.92	-12
2-NITROPROPANE	NITRO	7	89.09	0.992	89.8	-93	120	41.3	10.16	3.73	1.230	0.93	11.4	26.74	10.74	-12
1-NITROPROPANE	NITRO	7	89.09	0.998	89.3	-108	132	43.39	10.47	3.66	1.176	0.87	8.5	24.70	10.78	-12
NITROBENZENE	NITRO	8	123.11	1.196	102.9	5	210	56.10	11.16	4.22	0.320	1.85	20	34.82	9.94	-10.7
ACETONE	KETONE	9	58.08	0.791	73.4	-94	56	31.27	9.68	2.88	8.00	-0.24	20	20.7	9.703	-7.2
2-BUTANONE	KETONE	9	72.11	0.805	89.6	-87	80	34.92	9.30	2.50	2.348	0.29	20.3	18.5	9.52	-7
METHYLISOPROPYL KETONE	KETONE	9	86.13	0.805	107.0	-92	94	36.87	8.77	2.8	1.778	0.84	21.5	10.37	9.31	-7
3-PENTANONE	KETONE	9	86.13	0.813	105.9	-40	102	38.68	9.04	2.82	1.682	0.99	20.3	17.0	9.31	-7
2-PENTANONE	KETONE	9	86.13	0.802	107.4	-78	105	38.46	8.95	2.70	1.637	0.91	21	15.4	9.38	-7
METHYLISOBUTYL KETONE	KETONE	9	100.16	0.801	125.0	-80	117	40.65	8.54	2.7	1.279	1.31	21	13.11	9.3	-7
CYCLOPENTANONE	KETONE	9	84.12	0.951	88.5	-51	130	42.77	10.43	3.13	0.963	0.63	19.4	13.58	9.26	-7
CYCLOHEXANONE	KETONE	9	98.15	0.947	103.6	-47	155	45.09	9.91	3.24	0.398	0.81	20.1	18.2	9.16	-7
ETHYLFORMATE	ESTER	10	74.08	0.917	80.8	-80	53	32.11	9.36	1.93	1.945	0.230	53	7.2	10.61	-6.5
METHYL ACETATE	ESTER	10	74.08	0.932	79.5	-98	58	32.5	9.50	1.72	2.386	0.18	23.3	6.68	10.25	-6.5

FIG. 29B

SOLVENT	CLASS	#	MW	n	V_m	MP	BP	ΔH_{vap}	δ	μ	logS	logP	pKa	ε	IE	pK_{a+}
ETHYL ACETATE	ESTER	10	88.11	0.902	97.7	-84	77	35.69	9.01	1.78	1.903	0.73	24.5	6.02	10.01	-6.5
ISOPROPYL ACETATE	ESTER	10	102.13	0.872	117.1	-73	89	37.2	8.42	1.8	1.490	1.02	23.3	6.3	9.99	-6.5
PROPYL ACETATE	ESTER	10	102.13	0.888	115.0	-95	102	39.77	8.80	1.78	1.276	1.24	22.8	6 002	10.04	-6 5
ISOBUTYL ACETATE	ESTER	10	116.16	0.868	133.8	-99	116	35.9	7.73	1.86	0.799	1.780	24	5.07	9 97	-6.5
BUTYL ACETATE	ESTER	10	115.16	0.882	131.7	-78	125	43.89	8.67	1.87	0.924	1.78	22.4	5 01	9.92	-6.5
ACETONITRILE	NITRILE	11	41.05	0.786	52.2	-48	81	33.4	11.90	3.92	8.00	-0 34	25	37.5	12 2	-11
PROPIONITRILE	NITRILE	11	55.08	0.772	71.3	-93	97	36.19	10.63	4.02	8.00	0.16	25.2	29.7	11.85	-11
BUTYRONITRILE	NITRILE	11	69.11	0.794	87.0	-112	116	39.41	10.07	3.82	0.519	0.53	25	20.7	11.2	-11
BENZONITRILE	NITRILE	12	103.12	1.01	102.1	-13	191	55.48	11.14	4.18	0.301	1.56	37.5	26.0	9.73	-10
DIMETHYL SULFOXIDE	SULFOXIDE	13	78.13	1.101	71.0	18	189	52.89	13.03	3.96	8 00	-1.35	24.5	46.45	9.1	-0.65
DIETHYL ETHER	ETHER	14	74.12	0.715	103.7	-116	34.6	27.37	7.58	1.15	1.781	0.89	53	4.335	9.51	-2.39
METHYL-T-BUTYL ETHER	ETHER	14	88.15	0.740	119.1	-109	56	30.04	7.44	1.2	1.708	1.24	53	5	9.48	-3 5
DIMETHOXYMETHANE	ETHER	14	76.09	0.852	89.3	-105	64	26.89	8.41	0.74	8.00	0.22	53	2.7	9.7	-3 5
TETRAHYDROFURAN	ETHER	14	72.11	0.889	81.1	-108	66	32.16	9.35	1.63	8.00	0.46	53	7.58	9.4	-2.08
ISOPROPLY ETHER	ETHER	14	102.17	0.725	140.9	-85.5	68	32.26	7.11	1.13	0.944	1.488	53	3.88	9 20	-3.5
1.2-DIMETHOXYETHANE	ETHER	14	90.12	0.867	103.9	-58	85	36.47	8.84	2.08	8.00	-0.21	53	7.3	9 3	-3.5
PROPYL ETHER	ETHER	14	102.18	0.736	138.8	-123	89	35.79	7.57	1.21	0.690	2.03	53	3.3	9.3	-3.5
1.4-DIOXANE	ETHER	14	88.11	1.034	85.2	11.8	101	38.66	10.07	0.00	8.00	-0.27	53	2.209	9.19	-2.92
1.2-DIETHOXYETHANE	ETHER	14	118.18	0.842	140.4	-74	121	43.27	8.33	0.00	1.923	0.66	53	3.90	9.2	-3.5
BUTYL ETHER	ETHER	14	130.23	0.764	170.5	-98	142	45 0	7.72	1.17	-0.523	3.21	53	3 08	9.28	-3.5
BENZENE	AROMATIC	15	78.12	0.874	89.4	5.5	80	33.93	9.17	0 00	0 253	2.13	40	2.284	9.244	-16
TOLUENE	AROMATIC	15	92.14	0.865	106.5	-93	110.6	38.06	8.94	0.36	-0.279	2.73	37	2.379	8.828	-14
O-XYLENE	AROMATIC	15	106.17	0.860	123.5	-24	140	43.45	8.91	0.62	-0.750	3.12	38	2.568	8.56	-13
CUMENE	AROMATIC	15	120.19	0.864	139.1	-96	153	45.15	8.56	0.79	-1.215	3.66	38	2.38	8.73	-14
ANISOLE	AROMATIC	15	108.14	0.995	108.7	-37.5	154	46.91	9.88	1.38	0.017	2.11	46.0	4.33	8.2	-6.2
MESITYLENE	AROMATIC	15	120.19	0.864	139.1	-45	163	47.51	8.80	0.00	-1.317	3.42	40	3.4	8.4	-10
TETRALIN	AROMATIC	15	132.2	0.973	135.9	-35	207	55.23	9.63	0.60	-1.328	3.49	38	2.76	8.46	-13
PENTANES	HC	16	72.15	0.626	115.3	-130	36	26.75	7.09	0.00	-1.420	3.39	50	1.844	10.28	-20
HEXANES	HC	16	86.18	0.659	130.8	-95	69	31.73	7.31	0.00	-2.022	3.9	50	1.890	10.13	-20
CYCLOHEXANE	HC	16	84.16	0.779	108.0	6.5	80.7	33.12	8.23	0.00	-1.260	3.44	52	2.023	9.88	-20
HEPTANE	HC	16	100.20	0.684	146.5	-91	98	36.66	7.47	0.00	-2.469	4.397	50	1 925	9.93	-20
ISOOCATANE	HC	16	114.23	0.692	165.1	-107	98	35.24	6.89	0.1	-2.613	4.09	50	1 94	9.89	-20
METHYLCYCLOHEXANE	HC	16	98.19	0.77	127.5	-126	101	35.44	7.86	0.1	-1.854	3.61	50	2.02	9.64	-20
OCTANE	HC	16	114.23	0.703	162.5	-57	126	41.53	7.58	0.00	-3.180	5.18	50	1.95	9.8	-20
DECANE	HC	16	142.29	0.73	194.9	-30	174	51.9	7.78	0.00	-4.284	5.01	50	1.99	9.65	-20
DECALIN	HC	16	132.21	0896	147.6	-125	190	49.4	8.72	0.00	-3.051	4.20	50	2.18	9.35	-20
HEXAFLUOROBENZENE	ARYL HALIDE	17	186.06	1.612	115.4	-4	80	35.82	8.31	0.00	-0.469	2.55	60	2.03	9.89	-22
FLUOROBENZENE	ARYL HALIDE	17	96.10	1.024	93.8	-42	85	34.68	9.06	1.60	0.188	2.27	39	5.42	9.2	-16
A.A.A-TRIFLUOROTOLUENE	ARYL HALIDE	17	146.11	1.199	121.9	-29	102	37.67	8.31	2.86	-0.854	3.01	34.1	9.2	9.685	-17
OCTAFLUOROTOLUENE	ARYL HALIDE	17	236.06	1.666	141.7	-66	104	41.6	8.12	0.2	-1.921	3.96	60	2.1	10.2	-23
CHLOROBENZENE	ARYL HALIDE	17	112.56	1.107	101.7	-45	132	41.0	9.52	1.69	-0.303	2.84	37.5	5.708	9.07	-16
BROMOBENZENE	ARYL HALIDE	17	157.01	1.491	105.3	-31	156	44.54	9.77	1.70	-0.351	2.99	34.3	5.4	9.00	-15
1.2-DICHLOROBENZENE	ARYL HALIDE	17	147.00	1.306	112.6	-17	180	50.21	10.07	2.50	-0.807	3.43	32	7.75	9.06	-17

SOLVENT	CLASS	#	MW	n	V_m	MP	BP	ΔH_{vap}	δ	μ	logS	logP	pKa	ε	IE	pK_{a+}
1.1-DICHLOROETHENE	CHC	18	94.93	1.213	78.3	-122	31	26.74	8.61	1.34	0.352	2.13	38	4.6	9.81	-22
DICHLOROMETHANE	CHC	18	84.93	1.325	64.1	-97	40	29	9.94	1.60	1.115	1.25	30	9.08	11.33	-22
CHLOROFORM	CHC	18	119.38	1.492	80.0	-63	61	31.4	9.29	1.01	0.900	1.97	18	4.806	11.37	-22
1.1.1-TRICHLOROETHANE	CHC	18	133.40	1.338	99.7	-35	75	32.62	8.50	1.78	0.173	2.48	41	7.252	11	-22
1.2-DICHLOROETHANE	CHC	18	98.96	1.256	78.8	-35	83	35.22	9.97	0.00	0.930	1.48	35	10.3	11.07	-22
TRICHLOROETHENE	CHC	18	131.39	1.463	89.8	-85	87	34.52	9.25	0.77	0.041	2.42	26	3.42	9.46	-22
1.1.2-TRICHLOROETHANE	CHC	18	133.40	1.435	93.0	-37	112	40.28	9.86	1.25	0.645	1.89	23	9.4	11.0	-22
1.1.2.2-TETRACHLOROETHANE	CHC	18	167.85	1.586	105.8	-43	147	45.72	9.88	0.00	0.471	2.39	20	8.5	11.1	-22
CARBON TETRACHLORIDE	PCC	19	153.82	1.594	96.5	-23	76	32.54	8.63	0.00	-0.101	2.83	60	2.238	11.47	-22
TETRACHLOROETHYLENE	PCC	19	165.82	1.623	102.2	-22	121	39.72	9.33	0.00	-0.699	3.4	60	2.5	9.326	-22
PERFLUOROHEXANE	PFC	20	338.05	1.669	202.5	-87	59	31.02	5.80	0.00	-5.000	6.02	60	1.75	13.0	-25
PERFLUOROHEPTANE	PFC	20	388.05	1.745	222.4	-78	83	36.34	6.03	0.00	-6.000	6.99	50	1.8	12.9	-25
PERFLUOROOCTANE	PFC	20	438.06	1.766	248.1	-25	103	41.16	6.11	0.00	-7	7.95	60	1.8	12.8	-25
PERFLUORODECALIN	PFC	20	462.08	1.908	242.2	-10	142	44.51	6.44	0.00	-7	7.80	60	1.9	12.4	-25

FIG. 29C

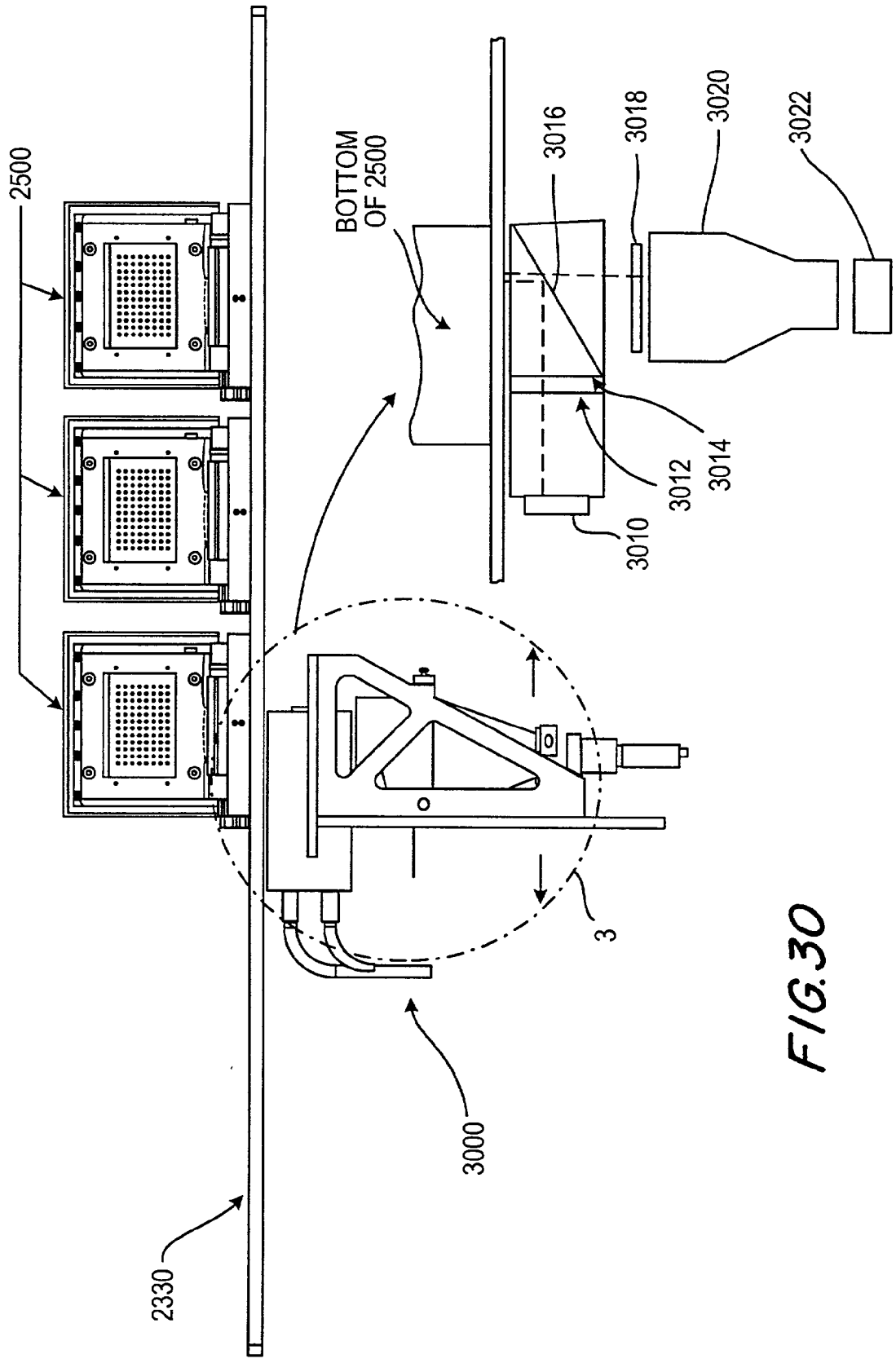

2500
BOTTOM OF 2500
3016
3018
3020
3022
3012
3014
3010
3
3000
2330

FIG.30

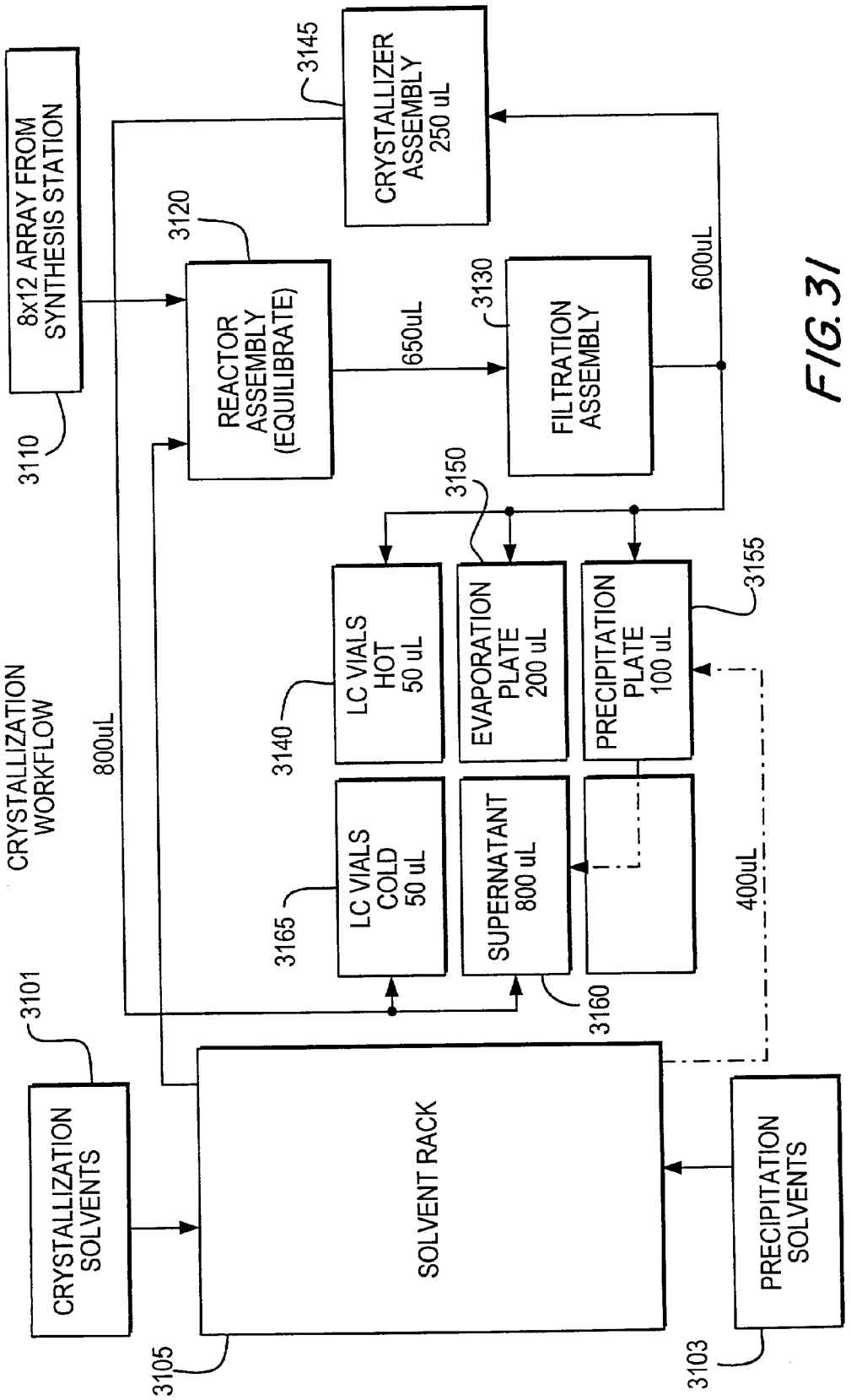

CRYSTALLIZATION WORKFLOW
8x12 ARRAY FROM SYNTHESIS STATION
3110
REACTOR ASSEMBLY (EQUILIBRATE)
3120
650uL
FILTRATION ASSEMBLY
3130
600uL
CRYSTALLIZER ASSEMBLY 250 uL
3145
3150
LC VIALS HOT 50 uL
3140
EVAPORATION PLATE 200 uL
PRECIPITATION PLATE 100 uL
3155
800uL
LC VIALS COLD 50 uL
3165
SUPERNATANT 800 uL
3160
400uL
3101
CRYSTALLIZATION SOLVENTS
SOLVENT RACK
3105
PRECIPITATION SOLVENTS
3103

FIG. 31

APPARATUSES AND METHODS FOR CREATING AND TESTING PRE-FORMULATIONS AND SYSTEMS FOR SAME

CROSS-REFERENCE TO A RELATED PATENT APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/311,332, filed Aug. 10, 2001, the disclosure of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to the field of research for pre-formulations or polymorphs. More particularly, the present invention is directed toward apparatus and methods for performing parallel synthesis and screening of salts and polymorphic forms of drug candidates.

BACKGROUND OF THE INVENTION

[0003] Combinatorial chemistry has revolutionized the process of drug discovery. See, for example, 29 *Ace. Chem. Res.* 1-170 (1996); 97 *Chem. Rev.* 349-509 (1997); S. Borman, *Chem. Eng. News* 43-62 (Feb. 24, 1997); A. M. Thayer, *Chem. Eng. News* 57-64 (Feb. 12, 1996); N. Terret, 1 *Drug Discovery Today* 402 (1996)). Although combinatorial chemistry has to a great extent eliminated the bottleneck in drug discovery, other S bottlenecks have emerged in getting a drug to market. One such bottleneck is the selection of salts of active pharmaceutical ingredients in such drugs. Another is the identification of polymorphs and pseudo-polymorphs of drug candidates.

[0004] A salt of a compound often has characteristics that are desirable for a drug candidate, including increased water solubility and a higher melting point than the compound itself. Further, different salts of a drug candidate may have disparate and discrete physical properties from one another. For instance, different salts of a compound may have different melting points or solubilities, or may crystallize in different forms and/or under different conditions. Traditional salt selection for a drug candidate requires mixing (e.g., sometimes referred to as synthesizing or formulating) a number of different salts of a compound, recrystallizing the salts under a number of different conditions to generate a crystalline form, and then characterizing the salt. This process is time consuming because it has to be reiterated a number of times to identify salts with desirable characteristics.

[0005] Not only do different salts of a drug candidate have different properties, different polymorphs of the salt or of the neutral compound may also have different physical characteristics. As is known in the pharmaceutical industry, the polymorphic state of an active pharmaceutical ingredient can change the biological profile of the drug. An industry journal published an entire special issue on this topic, *Organic Process Research & Development* (Vol. 4, No. 5, 2000 and in particular pp. 370-435), with the issue pointing out, inter alia, that polymorphism and crystallization issues affect many industries as well as pharmaceutical compounds, including explosives, color chemicals and food additives.

[0006] Traditional polymorph characterization requires recrystallizing a neutral drug candidate or a drug candidate salt, characterizing the crystals, and comparing the crystals to known forms to identify polymorphs. These steps must be reiterated a large number of times in order to identify all of the polymorphs of a given neutral compound or drug candidate salt. Thus, although characterization of polymorphs is advantageous and, in some cases, necessary, the traditional methods of identifying and isolating polymorphs can be tedious. Crystallizing new polymorphs often requires hundreds to thousands of experiments that analyze the effects of varying critical parameters such as temperature, solvent and solvent mixtures, mixing time, cooling rates, stirring rates, and concentrations and methods and process for precipitation, cooling, evaporation, slurry, and thermo-cycling.

[0007] One reference in the special issue of *Organic Process Research & Development* discloses the use of a certain technique for the screening of potential salts of pharmaceutically active compounds. Bastin et al. "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities", *Organic Process Research & Development* 2000, 4, 427-435, incorporated herein by reference. The paper discloses a library design for an array of different salts in different solvents. While this reference discloses a start at speeding up the pre-formulation process, it fails to follow through with screening in parallel or with high throughput research into crystallographic polymorphs.

[0008] In addition, several published patent applications in the area of high throughput or combinatorial materials science disclose a process in which the materials created in the process can be screened on the same plate in which they are synthesized. For example, WO 99/59716 discloses and claims creating solids on a removable reactor base plate and then performing X-RAY analysis of the solids. WO 01/34290 and WO 01/34291 reportedly relate to a "work station" that employs an array that can be transferred between preparing, screening and characterization stations without requiring sample handling, preparation or transfer steps. WO 96/11878 also discloses parallel crystallization and screening of materials on a substrate.

[0009] WO 01/51919 also reportedly relates to a high throughput method for formation, identification and analysis of diverse solid-forms; however, the methods in this application are extremely broad and vague, such that the publication serves merely to identify many problems without providing a solution beyond suggesting high throughput methods. Other publications reportedly disclose methods of analyzing polymorphs. For instance, WO 01/82659 reports a method of using X-ray diffraction to screen polymorphs. The publication reports that one can compare the X-ray diffraction pattern acquired for a polymorph and compare it with the X-ray diffraction patterns of known polymorphs of a compound. However, the publication does not disclose methods for rapidly generating the polymorph samples or for using the polymorph comparisons in drug discovery.

[0010] Given the rapid process of drug discovery in the pharmaceutical industry through combinatorial chemistry, a need generally exists in industry for a combinatorial or high throughput method and apparatus for the research, discovery and development of polymorphs formed by drug candidates. However, despite the cited work, a process for the systematic high throughput research of pre-formulations has not been directly disclosed.

SUMMARY OF THE INVENTION

[0011] The present invention addresses this problem by providing a universal system that addresses the need to characterize drug candidates. The system provides, inter alia, generation of libraries, salt selection, polymorph characterization, and other high throughput methods for identifying and characterizing physical properties of drug candidates, using a variety of reacting and screening options.

[0012] Specifically, the invention provides methods, systems and apparatus for performing combinatorial or high throughput preparing, screening and characterization of drug candidate salts and/or crystalline structures (e.g., polymorphs) of drug candidates. These methods, systems and apparatus decrease the time needed to find a suitable form of active ingredient for formulation and allow for additional forms of active pharmaceutical ingredients to be discovered, which may allow for additional patent coverage, a decreased risk of unwanted polymorphs appearing in later stages of pharmaceutical development or of competitors discovering a related form. In addition, the novel apparatus and methods disclosed herein allow for multiple different drug candidates to be formulated, crystallized and characterized in parallel, thereby creating a high throughput methodology for pharmaceutical research organizations and others.

[0013] In one aspect, the invention provides a workflow that enhances the process of identifying and characterizing potential active pharmaceutical ingredients (API) from a drug candidate. In one embodiment of the invention, salts of a drug candidate of interest are formulated using high throughput and/or combinatorial methods. The drug candidate salts are then screened to determine a variety of parameters or properties, which may include, without limitation, solubility, partition coefficient (log P), crystallinity, hygroscopicity, Raman spectral pattern, X-ray diffraction (XRD) pattern and melting point. The data obtained from the screening are then analyzed to identify suitable drug candidate salts. In a preferred embodiment, the formulation, screening and analysis are automated. Further, the workflow may be performed using the apparatus described herein. In another embodiment, the analysis is performed as the data are generated so that suitable salts may be rapidly identified. The workflow may be terminated after a suitable salt is selected. In a preferred embodiment, the suitable salt is then subjected to polymorph formulation, characterization and analysis.

[0014] In another aspect, the invention uses high throughput and combinatorial methods to crystallize, characterize and analyze polymorphs and/or pseudo-polymorphs of a drug candidate of interest. Generating and analyzing polymorphs may follow directly after salt selection or may be performed using an existing drug candidate. The drug candidate may be a neutral, acidic or basic compound, or may be a drug candidate salt. In one embodiment, the drug candidate is recrystallized under a variety of conditions using high throughput and/or combinatorial methods. The drug candidate crystals are then screened to determine a number of characteristics of the crystal, including, without limitation, solubility, log P, crystallinity, melting point, hygroscopicity, crystal morphology and birefringence, as well as X-ray diffraction, infrared (IR), Near IR and Raman spectroscopy, among others. The data obtained from the screening are then analyzed to identify the crystalline structures of the recrystallized drug candidate. Polymorphs of a recrystallized drug candidate may then be categorized according to the crystalline structure of the polymorph. In a preferred embodiment, polymorph recrystallization, screening and analysis are automated, and may be performed with the apparatus described herein. In another preferred embodiment, the analysis is performed as the data are generated so that different polymorphs and the conditions that produced them may be rapidly identified.

[0015] The invention further provides a method for selecting solvents for salt selection or polymorph generation. The invention further provides apparatus for high throughput salt preparation, recrystallization, solubility analysis, Raman and X-ray diffraction spectral analysis, and melting point determinations. The invention also provides hardware and software for controlling the salt selection and polymorph characterization methods of the invention and provides systems for automated high throughput operation of these methods.

[0016] Thus, one aspect of the invention is directed toward a high throughput method for preparing and characterizing different salts of a drug candidate. In one embodiment, a library is provided having a plurality of library members, wherein each library member comprises at least one drug candidate, and reacting in parallel each of the library members with an acid, base or salt to form different salts (e.g., complex salts or neutrals) of at least one drug candidate. In one embodiment, each library member may further comprise a solvent. In a preferred embodiment, the first library is comprised of at least eight members in regions on a first substrate, wherein the at least eight members comprises at least one drug candidate in an amount of between 0.05 and 50 mg of sample, reacting in parallel each of the at least eight members with an acid, base or salt to form different salts of at least one drug candidate. In another preferred embodiment, the drug candidate is present in an amount of less than 10 mg. In a further embodiment, the salts are produced as crystals in glass microtiter plates by cooling, evaporation, precipitation, slurry, or solvent gradients of aliquots of hot solutions.

[0017] In one embodiment, the drug candidate salts form crystalline structures. The drug candidate salt crystals and the supernatant or mother liquor may be left together or may be separated from each other after the salt reaction step, such that the crystals reside on the substrate, typically in regions so that the crystals can be screened individually. The method further provides for screening the crystals to identify new forms while said crystals reside on the substrate, as well as screening the supernatant or mother liquor for solubility of one or more drug candidate salts in each of the different solvents or solvent mixtures.

[0018] In general, salts are screened for at least two properties using various tests such as, for example, birefringence, melting point, solubility, hygroscopicity, Raman spectroscopy pattern, crystal morphology, X-ray powder diffraction pattern, infrared, near infrared or any other suitable test. In another embodiment, the salts are screened for at least three properties, four properties or five properties. In one embodiment, the salts are screened for at least birefringence, melting point, solubility, Raman spectroscopy pattern and X-ray powder diffraction pattern.

[0019] Another aspect of the invention is polymorph identification and/or characterization of a selected drug candi-

date. The drug candidate may be a neutral, acidic or basic compound or may be a salt of a drug candidate. In one embodiment, a library is provided and may include a plurality of members that each contain at least one drug candidate and at least one solvent. The library members are subjected to crystallizing conditions in parallel for each of the plurality of members on a substrate in different solvents or solvent mixtures. Each of the members are then screened to identify and/or characterize different crystalline structures of at least one drug candidate. In one embodiment, the library comprises at least eight members in an amount from 0.05 to 50 mg each, preferably less than 20 mg each. In a further embodiment, the polymorphs are produced in glass microtiter plates or other optically transmissive substrate by cooling, evaporation, precipitation by an anti-solvent, slurry, or solvent gradients of aliquots of hot solutions. In another embodiment, the polymorph characterization may be performed with a drug candidate or drug candidate salt without previously having performed salt selection.

[0020] In a further embodiment, the crystalline structures comprising the crystals and the supernatant or mother liquor is separated from each other after the recrystallization step such that the crystals reside on a substrate, typically in regions so that the crystals can be screened individually or in parallel. The method further provides for screening the crystals for at least crystallinity while the crystals reside on the substrate, as well as screening the supernatant or mother liquor for solubility of the one or more drug candidates in the different solvents or solvent mixtures. Other screening tests can be selected from a variety of tests, but a sufficient number of tests are performed to make a determination of the number of polymorphs and/or to identify polymorphs or salts thereof that may be suitable for drug formulation.

[0021] The crystals may be screened for any physical property that would help identify a polymorph. In general, at least two properties are screened. The properties may be birefringence, melting point, solubility, hygroscopicity, IR spectroscopy, Near IR spectroscopy, Raman spectroscopy, crystal morphology, X-Ray powder diffraction pattern or any other suitable screening method. In another embodiment, the crystals are screened for at least three properties, four properties or five properties to identify and characterize polymorphs. In one embodiment, the crystals are screened for at least birefringence, melting point, solubility, Raman pattern and X-ray powder diffraction pattern.

[0022] In one embodiment, crystals may be screened to identify and characterize polymorphs by optically imaging glass microtiter plates or another optically transmissive substrate that contains crystals of drug candidates or salts thereof. Two different optical scanning techniques can be used: transmission and reflection. Optical transmission occurs when an optical signal passes through an array of material samples. Optical reflection occurs when the optical signal is reflected by the material sample. Either one of these scanning techniques determine whether there are crystalline solids as well as determine the characteristics (size or habit) of any crystals. In one embodiment, the crystals may be optically imaged between polarization filters to measure birefringence, (e.g., to assess crystallinity).

[0023] In another embodiment, the crystals are analyzed by birefringence measurements before and after removal of a supernatant or mother liquor to detect unstable solvates or hydrates of drug candidates or salts thereof. In a further embodiment, individual wells or regions of the optically transmissive substrate may be imaged under magnification (with and without crossed polarization plates) to determine crystal habit and size. In yet another embodiment, scattered light measurements can be used to determine if there is a crystalline structure. In another embodiment, the crystalline structures may be characterized by their spectral properties, including, without limitation, Raman, IR, Near IR or X-ray diffraction spectroscopy to characterize the crystals formed on glass microtiter plates or other substrate. Preferred embodiments include Raman and/or X-ray diffraction spectroscopy. The invention also provides methods of using software to analyze the spectral data to identify polymorphs and/or solvates or hydrates contained in the arrays. In one embodiment, the optical imaging measurements (e.g., birefringence or crystal morphology), and the spectral measurements (e.g., Raman and X-ray diffraction) are made on the same samples without transfer of material from the substrate.

[0024] In another embodiment, the crystalline structures are formed on a glass substrate and/or in an apparatus that has an optical pathway to the regions or vessels so that optical measurements can be made while the crystalline structure is formed (sometimes referred to herein "in situ" measurements). The crystalline structures may be characterized by their optical or spectral properties, including, without limitation, birefringence, Raman spectral pattern, IR pattern, Near IR pattern, and/or light scattering. In some embodiments, the apparatus described herein can be used for these in situ measurements.

[0025] In another aspect, the melting temperature of the crystals may be determined. The method involves the steps of heating glass microtiter plates or other substrate comprising drug candidates crystallized under different crystallization conditions while making birefringence, scattering, other optical measurements to determine melting points, and/or other phase transitions including but not limited to loss of molecules of solvent or water from solvated crystals. In a preferred embodiment, the melting point of the crystals is determined using a parallel melting point apparatus.

[0026] In another aspect, the invention is directed toward making multiple copies of the arrays by "daughtering" from a parent set of solutions. Thus, in one embodiment, the invention is directed toward a method for testing drug candidates using daughter libraries, comprising forming a library comprised of a plurality members in regions on a first substrate, wherein each of the members comprises at least one drug candidate and a different solvent or solvent mixture, daughtering the members to a plurality of second substrates to form a plurality of daughter libraries; and subjecting the daughter libraries to different crystallization conditions, such as different crystallization methods (e.g., solvent evaporation and precipitation) and/or different crystallization parameters (e.g., different temperatures or different rates of cooling). In another embodiment, daughter libraries are constructed so that sets of identical crystals can be used in destructive measurements (e.g., melting point, hygroscopicity). In another embodiment, daughter libraries are constructed to archive libraries.

[0027] The various assemblies and computer software of this invention may be combined into a flexible workflow to

identify and characterize polymorphs. Similarly, the invention also provides a flexible workflow to identify and characterize different drug candidate salts.

[0028] In another aspect, this invention is directed toward a solvent array, wherein the solvent array is chosen to achieve a degree of diversity based on an analysis of solvent parameters. Physical and chemical properties or other characteristics of the solvents are used to group the solvents into sets based upon similarities of their physical properties or characteristics. The number of physical or chemical properties or characteristics and the number of groups into which the solvents and solvent mixtures are clustered determines the type and degree of diversity in the solvent array for a given experiment or assay. The diverse solvent arrays may be used in the salt selection and polymorph generation methods described herein. The invention is also directed toward software to implement the use of solvent arrays in the methods and systems of the invention.

[0029] In another aspect, the invention is directed toward an apparatus that may be used for preparing an array of salts or crystals for screening. The apparatus comprises at least two different assemblies, but preferably three different assemblies, preferably with interchangeable parts between the different assemblies. In one embodiment, the apparatus comprises at least two assemblies, one for solubilizing drug candidates for recrystallization and/or synthesizing salts of drug candidates (the reactor assembly) and one for crystallizing the compounds (the crystallization assembly). In another embodiment, the apparatus comprises three assemblies, including a reactor assembly, a filtering assembly and a crystallizing assembly. Futher, one or more of the assemblies are provided separately (e.g., the filtering assembly).

[0030] In one aspect, the reactor assembly may include a reactor base having an array of a plurality of receptacles. Each of the receptacles may be isolated from each other to prevent cross-communication of materials contained therein. In one embodiment, the reactor base comprises thermal sensors embedded in the reactor base and a thermal block that surrounds the reactor base. The temperature of the thermal block may be computer controlled. The reactor assembly may be used in conjunction with a dispensing assembly that dispenses at least one object (e.g., ball or stirring flea) into a plurality of receptacles located in the reactor base.

[0031] In another aspect, the filtering assembly includes a reactor base comprising an array of a plurality of receptacles and a filtration subassembly. The filtration subassembly includes a plurality of pairs of holes, where each pair of holes is associated with a receptacle in the reactor base. One hole may be used for filtering a liquid before it is deposited into the associated receptacle. The other hole may be used to provide access to the associated receptacle without having to pass through a filter. Each pair of holes may isolated from each other to prevent cross-communication of fluid or vapor among other pairs of holes. Isolation may be accomplished using o-rings that are provided in the filtration subassembly. In particular, the o-rings may be constructed to include a large o-ring and a small o-ring. The large o-ring may surround each pair of holes to provide inter-pair isolation. The small o-ring may surround one of the holes in the pair to provide inter-hole isolation.

[0032] In another aspect, the crystallization assembly includes a reactor that comprises an optically transmissive substrate. The reactor may include a plurality of through-holes that correspond to regions on the substrate. The through-holes may be sealed such that each through-hole is isolated. In one embodiment, after the crystals form on the substrate, the substrate can be removed and subjected to screening test.

[0033] In another aspect, the invention is directed toward an apparatus that can determine the melting point of a crystal or other solid. In one embodiment, the melting point apparatus includes a thermal chamber and an image scanning device. An optically transmissive substrate supporting an array of materials (e.g., crystals) may be contained within the thermal chamber. The thermal chamber may heat the substrate at a predetermined rate (e.g., 1° C. per minute) to gradually heat the crystals on the substrate. As the substrate heats up, the image scanning device provides an optical signal to each material sample on the substrate and determines whether the crystal, if any, melts or changes phase, or whether the crystal changes composition (i.e., loss of water or solvent molecules).

[0034] The image scanning device may use birefringence imaging, light scattering, or other optical scanning techniques to determine when a crystal on the substrate melts. Birefringence imaging may be accomplished using an array of light emitters, polarizer filters and light detectors. In a preferred embodiment, the image scanning device is computer controlled. In addition, the computer may also control the rate in which the temperature of the thermal chamber is increased. Thus, the combination of temperature and birefringence imaging enables the present invention to accurately detect the temperature at which each crystal melts or changes phase, or whether the crystal changes composition.

[0035] In another aspect, the invention is directed toward hardware and software for controlling various apparatuses associated with the invention. The hardware and software may control the dispensing of liquid into the reactor assembly, filtering assembly and/or crystallization assembly. For example, the present invention may be able to control an automated pipette system to dispense materials into a reactor assembly. In one embodiment, the hardware and software can be integrated with library design software.

[0036] Moreover, this invention is directed toward hardware and software for characterizing and analyzing one or more physical properties of the crystals obtained during the polymorph characterization or salt selection methods of the invention. In one embodiment, the software groups the crystals into families of compounds based upon similarities in one or more of their physical properties. The physical properties that are used to group the crystals into families may be defined by the user and/or may be obtained from previous characterization experiments. Further, the different polymorphs or salts may be grouped into families based upon their similarity to one another for one or more physical properties of interest within a user-defined deviation. Different families may be defined by the user based on the same or on different deviations. The software enables quick analysis of data obtained from screening experiments and provides for a high throughput methods.

[0037] Physical properties that may be used to sort polymorphs into families include, without limitation, crystal shape, melting point and spectral properties of crystals. In a preferred embodiment, the physical property that is used to

sort polymorphs into families is a spectrum of the crystals obtained during the polymorph characterization. In one embodiment, the spectra may be obtained by Raman, infrared (IR), near-IR or X-ray diffraction spectroscopy, wherein the software sorts spectra into polymorph families, and in some embodiments this sorting is based on pattern matching. Thus, different polymorphs are grouped into families based upon their spectral similarities to one another within a user-defined variation, with different families being defined by the user.

[0038] In another aspect, the invention is directed toward a system for making and characterizing salts from at least one drug candidate. In one embodiment, the system may include a computer that controls dispensing, heating, and screening of the materials. The computer may control robotic equipment to dispense the drug candidate and one or more acids or bases into the receptacles to provide the mixture. Once the mixture is in a reactor assembly, a temperature-controlled housing that houses the reactor assembly may subject the reactor assembly to a predetermined temperature to promote dissolution of the drug candidate contained within the mixture.

[0039] Another aspect this invention is directed toward a system that tests a drug candidate in high throughput mode to make and characterize polymorphs. In one embodiment, the system includes a reactor assembly configured to contain a plurality of mixtures. The system may also include a crystallization assembly that is configured to contain crystallized compounds on a substrate. In addition, the system may include a temperature-controlled housing that is configured to contain an assembly such as, for example, a reactor assembly, filtration assembly, or a crystallization assembly and subject the assembly to a predetermined temperature. The system may also include a computer that controls the temperature-controlled housing and obtains data from the screening devices. The computer analyzes the data to determine if any polymorphs have formed and categorizes the polymorph into the appropriate family.

[0040] A further understanding of the nature and advantages of the present invention may be realized by reference to the remaining portions of the specification and the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] The above and other objects and advantages of the invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

[0042] **FIG. 1** shows an illustrative pre-formulation discovery tool system that is in accordance with the principles of the present invention;

[0043] **FIGS. 2A and 2B** show an illustrative flow diagram of salt selection process that is in accordance with the principles of the present invention;

[0044] **FIG. 3** shows an illustrative flow diagram of polymorph testing that is in accordance with the principles of the present invention;

[0045] **FIG. 4** shows an illustrative library that can be modeled in accordance with the principles of the present invention;

[0046] **FIG. 5** shows an illustrative flow diagram of a library design process in accordance with the principles of the present invention;

[0047] **FIG. 6** shows an illustrative flow diagram that generates a recipe file that enables automatic control of hardware to synthesize a library in accordance with the principles of the present invention;

[0048] **FIG. 7** shows several different crystalline structures that can be detected with birefringence testing in accordance with the principles of the present invention;

[0049] **FIG. 8** shows an illustrative flow diagram for categorizing samples according to data obtained in screening tests in accordance with the principles of the present invention;

[0050] **FIG. 9** shows a graphical representation of spectral data obtained from a Raman screening device in accordance with the principles of the present invention;

[0051] **FIG. 10** shows a graphical representation of spectral data obtained from a X-ray screening device in accordance with the principles of the present invention;

[0052] **FIG. 11** shows an interactive display screen that includes several spectral data graphs of crystalline structures discovered in an array of materials in accordance with the principles of the present invention;

[0053] **FIG. 11A** shows an illustrative display screen that enables a user to define parameters used for correlating data in accordance with the principles of the present invention;

[0054] **FIG. 11B** shows an illustrative display screen that enables a user to define parameters for preforming the correlation of data in accordance with the principles of the present invention;

[0055] **FIG. 11C** shows an illustrative display screen that enables a user associate data with particular polymorph families in accordance with the principles of the present invention.

[0056] **FIG. 12** shows an illustrative display screen that shows the spectral graphs of **FIG. 11** in categories in accordance with the principles of the present invention;

[0057] **FIG. 12A** shows a flow chart of a process that determines if a material sample should be selected for additional testing in accordance with the principles of the present invention;

[0058] **FIG. 13** shows a cross-sectional view of a reactor assembly in accordance with the principles of the present invention;

[0059] **FIG. 14** shows both a three-dimension view and an exploded three-dimensional view of a ball dispensing assembly in accordance with the principles of the present invention;

[0060] **FIG. 15** shows an exploded view of a reactor assembly in accordance with the principles of the present invention;

[0061] **FIG. 16** shows an exploded view of a filtration assembly in accordance with the principles of the present invention;

[0062] **FIG. 17** shows an exploded view of a filter subassembly of **FIG. 16** in accordance with the principles of the present invention;

[0063] **FIG. 18** shows an embodiment of o-ring sheets that may be used in the filter subassembly of **FIG. 17** in accordance with the principles of the present invention;

[0064] **FIG. 19** shows an embodiment of filter disk that can be used in conjunction with the filter assembly of **FIG. 16** in accordance with the principles of the present invention;

[0065] **FIGS. 20A and 20B** show how a mixture is filtered using the filter assembly of **FIG. 16** in accordance with the principles of the present invention;

[0066] **FIG. 20C** shows how a filtrate is extracted from the filter assembly of **FIG. 16** in accordance with the principles of the present invention;

[0067] **FIG. 21** illustrates an exploded view of a crystallization assembly in accordance with the principles of the present invention;

[0068] **FIG. 21A** illustrates an exploded view of an alternative embodiment of a crystallization assembly in accordance with the principles of the present invention;

[0069] **FIG. 21B** illustrates a two-dimensional array of o-rings that are used in conjunction with the crystallization assembly of **FIG. 21A** in accordance with the principles of the present invention;

[0070] **FIG. 21C** illustrates a partial cross-sectional view of the crystallization assembly of **FIG. 21A** which in accordance with the principles of the present invention;

[0071] **FIG. 22** illustrates a partial cross-sectional view of crystallization assembly of **FIG. 21** that is in accordance with the principles of the present invention;

[0072] **FIG. 22A** shows an venting needle assembly in an expanded position in accordance with the principles of the present invention;

[0073] **FIG. 22B** show a venting needle assembly in a compressed position in accordance with the principles of the present invention;

[0074] **FIG. 23** shows a process platform that has a liquid handling robot that can dispense and aspirate fluid from assemblies positioned on the platform in accordance with the principles of the present invention;

[0075] **FIG. 24** shows perspective top and bottom views of a temperature-controlled housing in accordance with the principles of the present invention;

[0076] **FIG. 25** shows a thermal control chamber in accordance with the principles of the present invention;

[0077] **FIG. 26** shows a three dimensional view of fluid channels of the temperature-controlled housing of **FIG. 25** in accordance with the principles of the present invention;

[0078] **FIG. 27** shows a cross-sectional view of the temperature-controlled housing that includes a crystallization assembly contained within the housing in accordance with the principles of the present invention;

[0079] **FIG. 28** shows an apparatus that simultaneously performs melting point and birefringence or light scattering testing in accordance with the principles of the present invention;

[0080] **FIG. 28A** shows an isometric view of the apparatus of **FIG. 28** in accordance with the principles of the present invention;

[0081] **FIG. 28B** shows a cross-sectional view taken along the line **28-28** of the apparatus in **FIG. 28A** in accordance with the principles of the present invention;

[0082] **FIGS. 29A, 29B** and **29**C show Table 3, which lists solvents useful for a process of this invention, including certain physical properties of the solvents that may be used in solvent selection that is in accordance with the principles of the present invention;

[0083] **FIG. 30** shows an apparatus for performing in-situ measurement in accordance with the principles of the present invention; and

[0084] **FIG. 31** shows an exemplary crystallization workflow using the methods and apparatus of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0085] Scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art with the supplemental definitions found herein, which are not intended to be contrary to the generally accepted definitions. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0086] As discussed herein, an active pharmaceutical ingredient (API) is a specific compound (a salt or a neutral compound) that has been approved by the government for use in a pharmaceutical, e.g., it is safe and effective for a particular indication.

[0087] A drug candidate is a precursor to an API. A drug candidate may have shown efficacy under various assays for activity or safety under various toxicity assays. As used herein, a drug candidate is any compound of interest for which pre-formulation testing is desired to determine which form of the compound can or should be prepared. Pre-formulation testing can include salt selection and/or polymorph characterization and analysis. The methodology or process described in this patent application may be performed on API's and drug candidates. And, as those of skill in the art will appreciate, the exact API or drug candidate is not critical to this invention, but is typically a small molecule (as opposed to a protein) or a salt thereof. The term drug candidate, as used herein, refers to a neutral compound or a salt thereof, unless otherwise specified.

[0088] A polymorph of a compound, as used herein, is a crystal of a compound that is able to crystallize in more than one form. Thus, polymorphs of a compound refer to different crystalline forms of the compound. A polymorph may also be a pseudo-polymorph, which is a crystal of a compound that contains solvent or water molecules (i.e., solvates and hydrates, respectively) and thus differs from a crystal lacking solvent or water molecules. As used herein, the term

polymorph refers to both polymorphs or pseudo-polymorphs, unless otherwise specified.

[0089] A "crystalline structure," as used herein, comprises a crystal and a supernatant (or mother liquor) formed when a solution crystallizes.

[0090] The term "solvent" refers to a liquid that is used to dissolve a drug candidate in the methods described herein. The term "solvent" is also intended to include mixtures of solvents (i.e., two or more different liquids that may or may not be miscible).

[0091] The term "salt reactant" refers to acids, bases and salts that are used to produce drug candidate salts. A "salt reactant" may be defined functionally as a substance that provides an ion (either a cation or an anion) that forms a salt with a drug candidate. Generally, a "salt reactant" is added in stoichiometric amounts to drug candidate, e.g., an approximately equal number of salt ions of the salt reactant are added as there are acidic or basic moieties on the compound of interest.

[0092] A "salt" is defined as a compound comprising anions and cations; that is, there is a proton transfer between the drug candidate and the acid or base. As used herein, a salt complex is a co-crystal of a drug candidate and a acid or base; that is, there is no proton transfer between the drug candidate and the acid or base. Unless indicated otherwise, the term "salt" as used herein includes both salts and salt complexes.

[0093] The term "crystallization" or "crystallize" refers to the process by which crystals form from a liquid solvent, generating a supernatant (sometimes referred to as a mother liquor) above the crystals. Crystallization also refers to a process in which crystals form from melts or sublimation. As used herein, a "crystal" is a solid in which the molecules are held together in a regular repeating internal arrangement.

[0094] As used herein, the term "precipitation" or "precipitate" refers to a process by which a solid is generated by addition of an anti-solvent to a drug candidate mixture. The solid may be in either crystalline or amorphous form.

[0095] The terms "recrystallization" and "recrystallize" are intended to mean crystallization of the drug candidate compounds from a solution, without intending to mean that the drug candidate compounds were crystals prior to being dissolved, unless otherwise indicated.

[0096] The term "library" as used herein refers to a plurality of experiments, samples or members, wherein the experiments, samples or members may or may not be physically associated. Thus, a library refers to members on a single substrate, on multiple substrates or on a portion of a substrate. In general, each member will have some data associated with it, which may include, e.g., drug candidate, salt form, solvent identity, spectral data, melting point, solubility, etc.

[0097] For purposes of the present invention, the term drug candidate is used generically to represent material compounds that are being developed and tested in a process. Further, as used herein, the terms "drug candidate" or "drug candidate compound" are synonymous with the term "compound", unless otherwise indicated.

[0098] The present invention systematically enhances the efficiency of the pre-formulation process of drug development. In particular, the pre-formulation process is implemented as a process that generates, characterizes and analyzes material compositions. This process can be performed in accordance with the present invention by using illustrative pre-formulation discovery tool system **100** shown in **FIG. 1**. Pre-formulation system **100** may include computer **110**, material handling apparatus **150**, material screening device **160**, and user interface equipment **180**. Pre-formulation system **100** may include multiple material handling apparatuses **150** and multiple material screening devices **160**. Only one each of material handling device **150** and material screening device **160**, however, is illustrated in **FIG. 1** to avoid complicating the drawing. Computer **110** is illustrated to be connected to apparatus **150**, device **160**, and user interface equipment via communication paths **190**. In addition, apparatus **150** and device **160** are also connected by communication path **190**.

[0099] Computer **110** controls a process that is implemented to perform the pre-formulation process in accordance with the principles of the present invention. Several processes can be implemented in pre-formulation system **100**. For example, a process may be used for creating, analyzing and selecting salts for a particular drug product. Other processes may be implemented to generate, characterize and analyze different crystalline structures (e.g., polymorphs) of a compound. Comprehensive processes may involve a process that starts with library design of solvents and ends with identification of a suitable active pharmaceutical ingredient. Such a comprehensive process may, for example, combine a salt selection process with a polymorph process to pre-formulate a desired ingredient. While there are several possible processes that can be developed and used with pre-formulation system **110**, the present invention illustrates two such embodiments in **FIGS. 2 and 3**.

[0100] Computer **110** may include electronic circuitry **112** (e.g., hard-drive, processing memory communications buses, etc.) that handles transmission of data to, from, and/or between apparatus **150**, device **160**, and user interface equipment **180**. Electronic circuitry **112** may enable computer **110** to perform processes by controlling, for example, apparatus **150** and device **160**. Computer **110** may initiate processes by responding to user input from user interface equipment **180**. Computer **110** may also provide information to the user at user interface equipment **180** with respect to data acquired during operation of the process.

[0101] Electronic circuitry **112** may store, retrieve, and distribute information from database **114**. Database **114** stores information that enables a process to be created and also provides a basis for performing analysis on a material composition. For example, database **114** may store information such as method steps, library designs, results of prior processes, results of processes in progress, publicly available data, library compositions, record sets, polymorph family data, and other suitable pre-formulation data. Database **114** can also store information on material properties of drug candidates and solvents, such as molecular weight, density, boiling point, etc. Other stored information can include recipe files, reagents, solvents, compounds, salts, crystals, polymorphs, all known characteristics and properties of such materials and any other information suitable for a pre-formulation process. Database **114** may be updated with new information. The new information may be derived

from data obtained from a currently active process or by downloading data via user interface equipment **180**.

[**0102**] Computer **110** can run software programs that assist control and operation of a process. Software programs may be used to automate pre-determined portions of the process. For example, software may automate control apparatus **150** in preparing library compositions. An illustrative example of such software is Impressionist™ software sold by Symyx Technology, Inc. of Santa Clara, Calif. Impressionist™ is described in WO 00/67086, published Nov. 9, 2000, which hereby incorporated by reference in its entirety. Other software programs may provide a comprehensive computer generated library that provide the process with a template for preparing various material compositions. A computer generated library advantageously eliminates the time consuming task of manually determining all the permutations and combinations of materials that can be compared under a given set of constraints. An illustrative example of library design software is sold as Library Studio® of Symyx Technologies, Inc. of Santa Clara, Calif. Library Studio® is described in WO 00/23921, published Apr. 27, 2000, which hereby incorporated by reference in its entirety. Persons skilled in the art will appreciate that several software programs may be implemented on computer **110**. For example, Epoch™ software sold by Symyx Technologies, Inc. of Santa Clara, Calif., may be used to control and acquire data from instruments such as apparatus **150** and screening device **160**. Epoch™ is described in WO 01/79949, published Oct. 25, 2001, which hereby incorporated by reference in its entirety.

[**0103**] Material handling apparatus **150** may provide assemblies that prepare, filter, and/or crystalize salts or polymorphs of a particular drug candidate in accordance with the principles of the present invention. Material handling apparatus **150** may be controlled by computer **110** to automatically mix specific quantities of material (e.g., drug candidates, reagents, etc.) to form a material composition. The materials may be mixed in accordance with library designs produced by computer **110** (e.g., with library design software). When the materials are mixed, they may be analyzed by material screening device **160** to determine various properties such as solubility, crystallinity, melting point temperature, etc.

[**0104**] If desired, material handling apparatus **150** may also be controlled by computer **110** to automate a crystallization process. For example, computer **110** may instruct apparatus **150** to subject its resident material compositions to a precipitation process that causes crystallization. After the crystallization process is complete, the material compositions are tested for at least for crystallinity by screening device **160**. It should be noted that above apparatus **150** discussion is not intended to be exhaustive, rather a detailed discussion of material handling apparatus **150** is discussed below in conjunction with FIGS. **13-30**.

[**0105**] Automatic control of material handling apparatus **150** enables the present invention to prepare several libraries or members. Moreover, automated control reduces possible errors that can be caused by manual control. In addition, automated control may enable the present invention to prepare relatively small sample sizes (e.g., ranging between nanoliter to milliliter sizes). This advantageously provides high throughput preparation and testing of the material compositions.

[**0106**] Material screening device **160** analyzes materials provided on material handling apparatus **150** and provides data to computer **110** based on that analysis. The analysis of material compositions may also be automated and controlled by computer **110**. Material screening device **160** may include a station such as, for example, a solubility testing station, a birefringence station, spectroscopy stations (e.g., Raman, infrared, X-ray), a melting point station, an electromagnetic signal absorption (e.g., UV-Vis absorption) station, partition coefficient (log P) station, hygroscopicity station, and other suitable devices. One or more of these stations may provide data that enables computer **110** to determine the quality and characteristics of a specific material. For example, computer **110** may determine the quality of a salt produced based on the characteristics measured by material screening device **160**. In another example, material screening device **160** may provide data on the crystal structure of a material to computer **110**. A detailed description of several material screening devices **160** is described below.

[**0107**] User interface equipment **180** enables a user to input commands to computer **180** via input device **182**. Input device **182** may be any suitable device such as, for example, a conventional keyboard, a wireless keyboard, a mouse, a touch pad, a trackball, a voice activated console, or any combination of such devices. Input device **182** may enable a user to enter commands to perform drug selection, library building, screening, etc. If desired, input device **182** may enable a user to control material handling apparatus **150** and material screening device **160**. Using input device **182**, for example, a user may calibrate apparatus **150** prior to use in a process. In another example, a user may manually control material screening device **160** to measure materials formulated in material handling apparatus **150**. A user may monitor processes operating on pre-formulation system **100** on display device **184**. Display device **184** may be a computer monitor, a television, a flat panel display, a liquid crystal display, a cathode-ray tube (CRT), or any other suitable display device.

[**0108**] Communication paths **190** may be any suitable communications path such as, for example, a cable link, a hard-wired link, a fiber-optic link, an infrared link, a ribbon-wire link, a blue-tooth link, an analog communications link, a digital communications link, or any combination of such links. Communications paths **190** are configured to enable data transfer between computer **110**, apparatus **150**, device **160**, and user interface equipment **180**. Communications path **190** may also enable data transfer between apparatus **150** and device **160**.

[**0109**] Various processes can be implemented on pre-formulation system **100**. Processes may include several steps or stages to achieve a desired result (e.g., salt selection, polymorph testing).

[**0110**] Many neutral pharmaceutically active compounds contain functional groups such as amines or carboxylic acids that can react with acids or bases to form salts. In general, salts tend to be more water soluble and have higher melting points than the corresponding neutral compounds. Salt selection for a drug candidate is not necessary if the neutral compound has suitable properties. However, salts of drug candidates often have desirable properties that are useful for formulation or bioavailability. Desirable properties of a salt compared to a neutral compound may include the ability of

the salt to form crystals that are produced more easily or cheaply, crystals that are more stable, more filterable, less hygroscopic, more soluble in water, or have a higher melting point or a more favorable log P for administration. For instance, for pharmaceutical compounds listed in the Physicians' Desk Reference (2000) that are salts, more than 50% of the neutral compounds of the salts are insoluble in water (they have a solubility of less than 1 mg/mL). In contrast, less than 20% of the corresponding salts, i.e., the listed pharmaceutical compounds, are similarly insoluble. Further, more than 30% of neutral bases listed in the Physicians' Desk Reference (2000) have a melting point below 120° C., while under 10% of their corresponding salts have a melting point below 120° C. Having a higher melting point is often desirable for easier formulation.

[0111] The selection of a salt for a drug candidate of interest is largely limited to the number of experiments that can reasonably be performed in the time allotted. Since the counter-ion affects the physical property of the drug candidate salt, different salts of the same drug candidate will crystallize under different conditions and will have different physical properties. Thus, it is necessary to perform a number of different recrystallization experiments to generate crystals for different drug candidate salts. By having a number of different drug candidate salts, one can identify those salts that are likely to be the most useful for drug formulation and administration.

[0112] Table 1, below, lists common anions for salts and Table 2, below, lists common cations for salts.

TABLE 1

Anion	Count	% of Total	Cumulative % of Total	Cumulative %: No. of Compds
Cl	156	60.9	60.9	
SO_4	26	10.2	71.1	71%:2
Mesylate	11	4.3	75.4	
Br	10	3.9	79.3	79%:4
Tartrate	9	3.5	82.8	
Citrate	8	3.1	85.9	
Maleate	7	2.7	88.7	
Acetate	4	1.6	90.2	90%:8
Besylate	4	1.6	91.8	
NO3	3	1.2	93.0	
PO4	3	1.2	94.1	
Fumerate	3	1.2	95.3	95%:12
Succinate	3	1.2	96.5	
Benzoate	1	0.4	96.9	
Gluconate	1	0.4	97.3	
Glucoronate	1	0.4	97.7	
Lactate	1	0.4	98.0	
methylsulfate	1	0.4	98.4	
Oleate	1	0.4	98.8	
Napsylate	1	0.4	99.2	99%:20
Tannate	1	0.4	99.6	
Xinafoate	1	0.4	100.0	
Total	256		100.0	

[0113]

TABLE 2

Cation	Count	% of Total	Cumulative % of Total	Cumulative %: No. of Compds
Sodium	57	76.0	76.0	
Potassium	5	6.7	82.7	83:2

TABLE 2-continued

Cation	Count	% of Total	Cumulative % of Total	Cumulative %: No. of Compds
Calcium	4	5.3	88.0	
Magnesium	1	1.3	89.3	89:4
Ammonium	1	1.3	90.7	
Tromethamine	1	1.3	92.0	
t-Butylamine	1	1.3	93.3	
Piperazine	1	1.3	94.7	95:8
Silver	1	1.3	96.0	
Zinc	1	1.3	97.3	
Lithium	1	1.3	98.7	
Gold	1	1.3	100.0	100:12
Total	75			

[0114] In Tables 1 and 2, the count number and percent of total indicate the number of drugs and the percentage of the total that a particular anion or cation was used as part of an active pharmaceutical ingredient, based on a survey of compounds in use from the Physicians' Desk Reference (2000). The cumulative percent of the ions is shown in the fourth column. Thus, as shown in Table 1, the two most common anions of active ingredients are chlorides and sulfates, accounting for over 70% of the drugs on the market as of the printing of the 2000 Physician's Desk Reference (PDR). This is highlighted further in the fifth column, which shows that the top two anions account for 71% of drugs on the market at that time, the top four account for 79%, the top eight 90%, and the top twelve 95%. As shown in Table 2, the two most common cations of API's are sodium and potassium, accounting for over 80% of the drugs on the market at the time. For cations, the top two cations account for 83% of drugs on the market at the time, the top four account for 89%, and the top eight account for 95%. With the combinatorial or high throughput techniques of this invention, both anionic and cationic salts can be screened, such that for most drug candidates, most if not all commonly used pharmaceutically useful salts can be tested.

[0115] In some embodiments of this invention, at least two, four or six different salt forms of one or more drug candidates are produced and screened for desired properties. In other embodiments, at least eight, more specifically at least 10, at least 12, at least 16, at least 20, or at least 24 different salt forms of one or more drug candidates are produced and screened for desired properties. In one embodiment, salt reactants comprising the two, four, six or eight most common anions or cations, as shown in Tables 1 and 2, are used for screening. In another embodiment, high throughput screening is performed using salt reactants for both anions and cations. Thus, salt reactants for the two, four, six or eight most common anions and cations are used.

[0116] The number of solvents that may be used for salt selection may be any number desired. In one embodiment, the number of solvents is two four, six, eight, 12, 16 or more. The screening of salt and solvent combinations (discussed below) can be at the rate of at least eight at a time, at least 12 at a time, at least 24 at a time, at least 36 at a time, at least 48 at a time, or at least 96 at a time. Depending on how the library is designed, there can be different salts in a plurality of wells; alternatively, there can be different solvents in a plurality of wells, etc.

[0117] In one embodiment, a different salt is present in each row of a substrate, wherein a row comprises a number of wells. The substrate may be a microtiter plate or another substrate on which wells may be formed, e.g., using the salt reaction apparatus described herein. Each column, which also comprises a number of wells and is perpendicular to the row containing the salt, contains a different solvent. See, e.g., **FIG. 15**, which shows an example of a microtiter format containing rows and columns. The library is not limited in this manner. This rate of testing allows for rapid discovery of the appropriate salt(s) for further investigation.

[0118] **FIGS. 2A and 2B** show an illustrative flow diagram of salt selection process **200** which is in accordance with the principles of the present invention. Generally, process **200** dispenses a drug candidate compound in a receptacle in an array format (e.g., an 8 by 12 array) and subjects each drug candidate to various combinations of one or more salt reactants and, optionally, a solvent. In one embodiment, each receptacle contains at least one drug candidate, a stoichiometric amount of at least one salt reactant, and, optionally, a solvent. In a preferred embodiment, each receptacle contains one drug candidate, a stoichiometric amount of one salt reactant and a solvent. Depending on the interaction of mixture of the drug candidate, salt reactant and solvent, a salt may form and precipitate or crystallize. Salts may then be screened and analyzed to determine whether the properties and characteristics are suitable for a particular drug application.

[0119] Processing selected drug candidates or salts for discovery and characterization required at least two, but preferably at least three steps that are performed in a combinatorial or high throughput mode. One required step is dissolution of drug candidates or salts to form a solution. Another required step is crystallization (e.g., by evaporation, cooling or precipitation with an anti-solvent) of drug candidates or salts from the solution. An optional processing step prior to crystallization may include separating any remaining solids from the solution by filtration or centrifugation. This separation or filtering step may be performed to eliminate nucleation sites in the solvent provided to the crystallization step. Process **200** includes the preparation, crystallization, filtration, and other steps that are performed for salt selection.

[0120] Prior to preparing solutions comprising the drug candidate and the salt reactant, a user may interact with a computer (e.g., computer **110** of **FIG. 1**) to generate a model library. At step **210**, one or more computer generated libraries are generated to enable process **200** to prepare substantially every possible combination of materials that can be mixed within a given set of constraints. Thus, when these mixtures are prepared and then crystallized, the present invention can determine which mixture provides the best salt. Each individual mixture is commonly referred to as a library member or member. The computer generated model library may be generated using a number of parameters (also called constraints) that typically include materials such as drug candidates, salt reactants, solvents, environmental conditions, reaction parameters, etc. Parameters may be selected by a user or a software program. Preferably, a user selects one or more drug candidates for modeling in the library and other parameters such as library size (e.g., a 96 well array). A library member usually comprises a drug candidate, a salt reactant and a solvent. The solvent, referred to as a library solvent in method **200**, is used for crystallizing the salt produced by the reaction of the salt reactant and the drug candidate. Computer generated library designs are preferably modeled by software programs running on computer **110** (shown in **FIG. 1**). The computer generated library may be based on user input and information available from database **114**. The computer generated library is described in more detail in conjunction with **FIGS. 4 and 5**.

[0121] Persons skilled in the art will appreciate that computer need not be used to prepare a library. A person could manually prepare a library using any suitable method.

[0122] At step **212**, a drug candidate and a salt reactant are mixed together. An optional mixing solvent, which may be different or the same as the library solvent, may be added to the salt reactant and drug candidate. The drug candidates, salt reactants and optional mixing solvents are reacted together to produce drug candidate salts. At optional step **214**, after the drug candidate salts have been produced, the drug candidate salts are isolated. At step **216**, the library solvents provided at step **210** are added to the drug candidate salts to produce the library members.

[0123] In a preferred embodiment, the drug candidate mixture described at step **212** is prepared in a reactor assembly. Reactor assemblies are typically constructed in microtiter format (e.g., an 8×12 96-well plate). Microtiter format is particular useful for performing high throughput reaction of materials. However, any other format may be used (e.g., a 384 well plate). In addition, this enables process **200** to construct a library in reactor assembly **1300** in accordance with the computer generated library provided at step **210**.

[0124] At step **212**, drug candidates may be mixed with salt reactants according to the computer generated library at step **210**. The mixture may optionally comprise one or more mixing solvents to provide a salt solution. The drug candidate is typically dispensed (into reaction containers) as a solution or a slurry, but it can be also be dispensed as solid. A liquid dispensing device is illustrated in **FIG. 23**. A solid dispensing device (not shown), for example, is sold as Powdernium by AutoDose of Geneva, Switzerland. Assuming that the drug candidate is in a solution or slurry, the solvent may or may not be driven off across the plate in parallel (such as by blowing nitrogen over the library or with a solvent evaporator, e.g., Genevac HT-8 (Genevac Inc, Valley Cottage, N.Y. 10989) under reduced pressure or vacuum. If the drug candidate is dispensed in the reaction solvent, then solvent removal is unnecessary.

[0125] After dispensing of the drug candidate, the chosen salt reactant (e.g., an acid or base in solution, slurry or solid format) is dispensed into the wells of the array. For anion salts, the corresponding acid is used. For example, hydrochloric acid, sulfuric acid, mesylic acid and bromic acid may be used for chloride, sulfate, mesylate and bromate salts of compounds. For cationic salts, one may use the corresponding hydroxide or other base. For instance sodium hydroxide and potassium hydroxide may be used for sodium and potassium salts. Magnesium and calcium salts of drug candidates may be formed by using magnesium or calcium acetate, oxide or carbonate. Amine salts may be formed by mixing the amine of choice itself with the drug candidate. In one embodiment, the salt reactant is dispensed automatically into the wells of the array, as discussed in more detail below.

In another embodiment, the salt reactant is dispensed manually into the wells of the array.

[0126] The salt solution is subjected to various conditions to allow the drug candidate to react with the salt reactant under the conditions imposed. Common reaction conditions are a temperature of about room temperature or higher with shaking in sealed vials. The temperature may be approximately 20° C., 30° C., 40° C., 50° C., 60° C., 70° C., 80° C. or higher. In one embodiment, the temperature is raised to approximately 70° C. to allow the drug candidate to react with the acid or base. Depending on the drug candidate and the salt reactant, a reaction between the drug candidate and the reaction solvents may or may not occur.

[0127] Individual vials or wells may contain magnetic stirring fleas that are tumbled (e.g., rotated) by a magnetic field or a rotating magnet. The rotating stirring fleas promote mixing of the materials contained within the vials or wells. A detailed explanation of a device that provides magnetic stirring is described in U.S. Pat. No. 6,176,609, which is hereby incorporated by reference in its entirety.

[0128] At optional step **214**, after each library member is prepared, any remaining salt reactants and optional solvents are removed from the reaction mixture. This may be done by any method known in the art, including, e.g., methods used for crystallization, such as evaporation, cooling or addition of an anti-solvent.

[0129] At step **216**, one or more library solvents are added to each well in accordance with the computer generated library and the drug candidate is dissolved in the solvent.

[0130] At optional step **220**, after each library member is prepared, an aliquot of the salt solution is taken from each reaction container and filtered by a filtration assembly. Each salt solution is filtered so that a "seedless" salt solution is used for crystallization at step **222**. FIGS. **16-20** illustrate various filtration apparatuses that provide filtration in accordance with the principles of the present invention.

[0131] If seeding is desired, a seed may be added separately, so that seeded recrystallization is controlled.

[0132] At step **222**, the filtered salt solutions are crystallized. Salt crystallization can occur by 1) cooling the solution, 2) precipitating the solution by adding an anti-solvent that causes precipitation, 3) evaporating the solution, or 4) slurrying the solution. If salt crystallization or precipitation occurs on a multi-well plate or a substrate, such as the universal substrate described herein, the plate or substrate may be screened by various identifying and characterization devices. If desired, characterization can be performed while recrystallization is occurring. The salt reactants and solvents that may be used to crystallize or precipitate the salts are described below in solvent selection section.

[0133] Each library member is screened to determine if a salt has formed. Screening is performed at step **225** and can be implemented using material screening device **160** (shown in **FIG. 1**). Screening at step **225** may be performed primarily as a high-throughput screen that quickly characterizes each library member. Data obtained during the screening may be provided to a computer (e.g., computer **110**). For example, screening at step **225** may obtain a sufficient quantity of data on each library member such that process **200** can be used to quickly analyze the salt. The apparatus and methods described herein provide several screening methods and devices that can determine birefringence, log P, crystallinity, solubility, and melting point of each library member in situ.

[0134] At step **230**, process **200** can perform a quick preliminary assessment on the suitability of each salt before additional time consuming tests are performed. Analysis can include user-defined selection by selecting which library members should be explored further. Salt selection can also be performed, for example, by computer. A computer can run software programs that analyze the data. For example, results of the screening can provide information regarding whether the salt formed a solid, whether the solid was amorphous or crystalline, and information regarding the solubility, log P and melting point of the crystal.

[0135] At step **240**, process **200** determines if a salt should be selected for further testing or if it should be discarded. If none of the salts produced in the library are suitable for additional testing (e.g., screening), the process returns to step **212** so that new library compositions can be prepared. The data obtained from these salts, however, is stored on a database and used for future analysis. Preferably, process **200** continues to prepare library compositions based on computer generated library models generated in step **210**. However, if step **240** determines that there is at least one suitable salt, process continues to step **250**.

[0136] At step **250** in **FIG. 2**B, the salt selected in step **240** is resynthesized in bulk format. This step is only necessary if sufficient quantities of the salt selected in step **240** were not produced. In step **250**, multiple samples of the same material composition are deposited in a different reactor assembly. If desired, additional solvents may be applied to the existing library compositions to obtain, for example, additional salt characteristics. The application of new materials may be based on a library modeled at computer **110** (**FIG. 1**). Then the newly-formulated library compositions are crystallized to form salt.

[0137] At step **255**, the salts are screened again to obtain property and characteristics data, if more data are required. This screening can be used to provide a more in-depth characterization of the salts than screening step **225**. Step **255** obtains data that enables process **200** to perform a secondary analysis (shown at step **260**). At step **260**, a substantial analysis may be performed using the data provided by step **255**. At step **270**, process **200** determines if the salt should be selected for further testing. If the salt is not selected, process **200** may return to step **212** (**FIG. 2A**). If the salt is selected, then process **200** has discovered a salt that is suitable for use in another application. Persons skilled in the art will appreciate that one or more salt forms may be selected by process **200** and it will also be appreciated that process **200** may not produce any salts that are selected based on the parameters set in step **210**.

[0138] If desired, after a salt is selected process **200** may proceed to step **310** of **FIG. 3**. As described below, **FIG. 3** describes polymorph generation and characterization based on the selected salt.

[0139] Process **200** may be implemented on pre-formulation system **100** to select salts that are suitable for drug development. Process **200** may be used as precursor to another process that performs test on one or more selected

salts to determine various potential polymorphs of the salt's crystalline structure. Persons skilled in the art will appreciate that steps shown in **FIG. 2** are merely exemplary and that additional steps may be added and some steps may be omitted or modified. For example, a step can be added that causes process **200** to prepare and test every library member provided by the computer generated library in step **210** even if one or more suitable salts have been discovered. Further, daughter libraries may be formed to alter the conditions under which salts may be formed (e.g., temperature or temperature ramp rate) or to provide identical salts for destructive analyses (e.g., melting point screens).

[**0140**] **FIG. 3** shows an illustrative flow diagram of polymorph discovery process **300** which is in accordance with the principles of the present invention. Process **300** may be implemented on pre-formulation system **100** independent of other processes or it may be merged with processes such as process **200** of **FIGS. 2A and 2B**.

[**0141**] Process **300** recrystallizes one or more drug candidates or salts (i.e., subjecting them to different conditions to generate as many polymorphs as possible, preferably substantially every polymorph, for a particular drug candidate or salt thereof) and screens each of the polymorphs in a high-throughput capacity. This enables process **300** to quickly characterize and determine those recrystallization conditions that are best for developing a desired drug ingredient that possesses a suitable crystalline structure. As used herein, recrystallization and crystallization conditions refer to those conditions that affect recrystallization. These conditions include, e.g., temperature, seeding (if present), solvent(s), etc.

[**0142**] Process **300** begins at step **310**. At step **310**, process **300** is provided with one or more drug candidate salts (or neutral compounds) for polymorph testing. The drug candidates can be preselected, for example, by a user via user interface equipment **180** (shown in **FIG. 1**). Drug candidates may also be provided by salts selected in process **200** of **FIGS. 2A and 2B**. Alternatively, step **310** may be provided with one or more drug candidates that can be used for polymorph testing.

[**0143**] Once a drug candidate is provided at step **310**, the drug candidate may undergo recrystallization at step **320**. If desired, recrystallization may involve several steps to form crystals from a particular drug candidate. For example, after a drug candidate has been selected, it may be mixed with solvents **322** in a reaction assembly (e.g., reaction assembly **1300** of **FIG. 13** or reaction assembly **1500** of **FIG. 15**). The drug candidate and solvents may be dispensed into a reaction assembly using a liquid dispensing assembly as described for salt selection process **200**. The solvents may be mixed in accordance with a computer generated library **321** to provide as many different crystallization mixtures for a particular set of constraints. Solvent selection is described further below.

[**0144**] The number of solvents that may be used for polymorph generation and characterization may be any number desired. In one embodiment, the number of solvents is two, four, six, eight, 12, 16, 24, 36, 48, 96 or more. The number of solvents that may be used for polymorph generation and characterization for a single assay can be at the rate of at least eight to ten at a time, at least 12 to 14 at a time, at least 24 at a time, at least 36 at a time, at least 48 at a time, or at least 96 at a time. The term solvent in this respect means both a single solvent (e.g., heptane or water) as well as combinations of solvents (e.g., heptane mixed with water), as described herein.

[**0145**] In one embodiment of this invention, at least one drug candidate is used in a process of generating and characterizing polymorphs. In other embodiments at least two, three or four drug candidates are used to generate and characterize polymorphs.

[**0146**] If further desired, recrystallization may include filtering the mixtures to provide "seedless" or "pure" solutions for crystallization. A filtering step is performed formulation and prior to crystallization. Crystallizing filtered solutions eliminates nucleation sites that can bias formation of crystals during the crystallization step. Filtering may be accomplished using filtration assembly **1600** of **FIG. 16**.

[**0147**] Various recrystallization conditions (e.g., temperature, pressure, time, etc.) may be varied to provide various crystal formation. **FIGS. 21 and 22** illustrate, for example, an apparatus that can be used to crystallize the mixtures. One advantage of this apparatus (e.g., crystallization assembly **2100** of **FIG. 21**) is that crystals may grow, form or re-salt on a removable substrate. This substrate may be provided to one or more screening devices such that crystals are scanned for their properties and characteristics at step **330**.

[**0148**] To perform crystallization or recrystallization under a variety of crystallization conditions, daughter libraries may be created from drug candidates, mixtures, or salts thereof. A daughter library is created by taking one or more aliquots from one or more members in a parent library contained within a reactor assembly. A parent library may include mixtures that are prepared at the beginning of recrystallization step **320**. An aliquot is a definite fraction of a whole.

[**0149**] To perform daughtering, a pipette, operated either manually or automatically (e.g., robotically), draws a portion of a member from the parent library and dispenses that aliquot into another container (e.g., crystallization assembly) to provide a daughter library member. A limited number of members of the parent library may be daughtered or all the members may be daughtered at least once to create a daughter library. Thus, a daughter library may be smaller than the parent library in terms of either mass, volume or moles and/or in terms of the number of members. Daughtering is performed, for example, to allow for multiple experiments on identical mixtures, solutions, or samples to avoid having to recreate the parent library. There is known equipment that can perform daughtering, such as hand pipetters, hand-multichannel pipetters, or robots (such as Matrix or CyberLab or Hydra robots). Any number of daughter libraries may be produced, provided that the original library is of sufficient volume. In one embodiment, at least one, two, four, eight or twelve daughter libraries are produced.

[**0150**] After the mixtures from the parent library and daughter libraries are crystallized, each library member is screened. Step **330** provides primary screening that provides data to step **335**, which analyzes the data to determine if any polymorphs have formed.

[**0151**] The crystals may be screened for any physical property that would help characterize and/or identify a

polymorph. The crystals may be screened for birefringence, melting point, solubility, hygroscopicity, IR pattern, Near IR pattern or Raman pattern, crystal morphology, X-ray powder diffraction pattern or any other suitable screening method to determine if crystals (or polymorphs) have formed. In general, at least two properties are screened. In one embodiment, Raman pattern, X-ray diffraction pattern, melting point, birefringence and hygroscopicity screens are performed to adequately characterize the crystalline structures.

[0152] At step **340**, process **300** determines whether a polymorph should be selected being produced in bulk for further testing, if sufficient quantities of the drug candidate have not been produced during process **300**. If the polymorph is unsuitable, the process may revert back to step **320** such that the same or different drug candidates can undergo recrystallization. If the polymorph is selected, process **300** may prepare several of the same crystals at step **345** so that they can be screened and characterized at step **350**.

[0153] At step **350**, the screening is more detailed than the screening performed at step **330**. The crystals may be screened for at least two properties, three properties, four properties or five properties to identify and characterize polymorphs, wherein the properties are determined by, e.g., birefringence, melting point, solubility, hygroscopicity, IR pattern, Near IR pattern, Raman pattern, crystal morphology or X-ray powder diffraction pattern or, if sufficient amounts have been produced, single crystal X-ray diffraction, thermogravimetric analysis, nuclear magnetic resonance or differential scanning calorimetry. In one embodiment, the crystals are screened for at least birefringence, melting point, solubility, Raman pattern and X-ray powder diffraction pattern. Preferred embodiments include Raman and/or X-ray diffraction spectroscopy. The process may be performed using a solubility testing station, a birefringence station, spectroscopy stations (e.g., Raman, infrared, X-ray), a melting point station, an electromagnetic signal absorption (e.g., UV-Vis absorption) station, partition coefficient (log P) station, using the apparatus described herein.

[0154] The data obtained in step **350** may provide a substantial quantity of information to enable process **300** to analyze the polymorphs or crystalline structures (step **360**). At step **365**, process **300** may determine if the polymorph (e.g., neutral drug candidate compound or salt thereof) is suitable for use as an active pharmaceutical ingredient (step **370**). If the polymorph is not suitable, then that particular drug candidate is not used, at least for the drug application prescribed for process **300** (step **375**). The data obtained from analysis, however, may be stored for future reference.

[0155] As illustrated in **FIGS. 2A, 2B**, and **3**, processes use computer generated libraries as a template for preparing library members. For example, libraries containing various combinations of drug candidates, salts, crystals, and other pre-formulation materials may be generated prior to library preparation. **FIG. 4** shows an illustrative library **400** that can be generated in accordance with the principles of the present invention. Library **400** can include any suitable number of library elements **410**. Preferably the number of library elements modeled in each library **400** is the same as the number of library members **410** that can be prepared on hardware (e.g., a substrate). Any number of rows and columns of library members **410** can be created, thus providing flexibility in library generation. This is illustrated by the variable "N", which indicates that any suitable number of rows and columns can be designed in library **400**. The row may, for example be Industry typically uses a substrate that has 96 wells or vials for formulating or mixing various materials. Therefore, if library **400** is modeled to have, for example, eight rows and twelve columns (a typical microtiter plate), library elements **410** may be readily implemented in practice. Likewise, if a 384 well substrate is being used, then library **400** may be modeled to have, for example, 16 rows and 24 columns.

[0156] Regardless of the size of library **400**, each library element **410** includes at least two materials. The materials in each library element **410** can differ by drug candidates, different known crystal structures of drug candidates, solvents and salt reactants. **FIG. 4** shows a few example materials **420** that can be used to model library elements **410**. Based on materials **420** and other factors, a computer (e.g., computer **110** of **FIG. 1**) can model substantially every possible combination of library elements that can be practically constructed. For example, library element **411** illustrates one such possible combination that includes a drug candidate, the salt reactant tartaric acid, and heptane. Thus, generating libraries provides the present invention with a foundation to prepare and test several different material compositions. This facilitates salt selection and provides a basis for discovering polymorphs for a particular drug candidate.

[0157] A large number of solvents are known that can be used in recrystallization, either for salt selection and/or for polymorph generation. Table 3 (shown in **FIGS. 29A, 29B** and **29**C) lists a number of exemplary solvents along with some of their physical properties. Given the large number of solvents that may be used, it is advantageous to cluster solvents into groups based upon certain shared physical properties or other shared characteristics of the solvents and then pick at least one solvent from each group to test in recrystallization. This process ensures that a wide variety of different types of solvents will be used for recrystallization, which is advantageous for identifying polymorphs or desirable crystals of drug candidate salts.

[0158] Table 3 shows solvents along with their chemical class, a reference number (#) assigned to different classes of solvents (for statistical sort purposes), molecular weight (MW), density (n), molar volume (V_m), melting point (MP) (in ° C.), boiling point (BP) (in ° C.), enthalpy of evaporation (ΔH_{vap}), Hildebrand solubility parameter (δ), dipole moment (μ), log solubility in water (log S), partition coefficient (log P), viscosity, index of refraction, pKa (in water and dimethylsulfoxide (DMSO)), dielectric constant (ϵ) and ionization potential (IE) and pK_{a+}. Other parameters known to those in the art could be included, such as, without limitation, the cost in US dollars per kilogram, cost of disposal or storage, degree of toxicity or environmental safety. The description of the solvents and physical properties provided herein does not limit the type of solvent or the physical properties of the solvent that may be used in the salt selection and polymorph workflows.

[0159] One or more of the physical properties of the solvents in a solvent library may be used to cluster solvents into groups. The solvents in a particular group will have similar physical properties for the one or more properties that has been chosen as a criteria. The physical properties of

the solvents may be one or more of those listed in Table 3 or may be other physical properties known in the art. One may use from one to n properties to cluster the solvents into groups, wherein n is the total number of physical properties that have been provided for a library of solvents. Each solvent may be independently sorted into a group with other solvents that have the same defined characteristics for all of the selected physical properties. One may use any number of properties to cluster solvents, including from four to 20, four to 16 or six to eight properties to cluster the solvents. In one embodiment, the class of the solvent (e.g., whether it is an alcohol, ketone, etc.) is not employed as one of the physical properties used in grouping the solvents.

[0160] For any particular physical property, the selection criteria may be defined to provide for two or more different subsets. In one embodiment, the selection criteria for single physical property solvents may provide for two, four, six, eight or twelve subsets. For example, one may provide four definitions for dividing the solvents based upon one physical property (e.g., the solvent's density) and provide two definitions for dividing the solvents based upon another physical property (e.g., the solvent's dipole moment). The solvents would then be clustered into eight groups based upon the definitions of these two physical properties.

[0161] In a preferred embodiment, the physical properties of a large number of solvents are kept in a database. During library design for polymorph generation or salt selection, a user can define both the specific physical properties and the selection criteria for these physical properties in order to cluster the solvents into groups based upon the particular physical properties chosen and the selection criteria for these physical properties.

[0162] One may design solvent groups to form from two groups up to n groups, wherein n is the total number of solvents in the designated solvent library. In one embodiment, the number of solvent groups is four to 96 groups. In another embodiment, the number of solvent groups is six to 64, eight to 48 groups, ten to 40 groups or 12 to 24 groups. In another embodiment, the number of solvent groups is eight to 24 groups, 16 to 24 groups, 20 to 40 groups or eight to 12 groups. In general, a smaller number of solvent groups are used for the salt selection workflow as compared to the polymorph characterization workflow. For salt selection, the number of solvent groups is generally in the range of 16 to 24 groups, while for polymorph identification and characterization, the number of solvent groups is generally around 20 to 40.

[0163] In one embodiment, in order to provide diversity of the types of solvents that are used for salt selection or polymorph generation, a solvent library may be clustered into groups of solvents having particular similar physical properties or characteristics and at least one solvent from each group is used in the salt selection or polymorph generation. In another embodiment, a number of solvents from a single group may be selected and used in salt selection or in polymorph generation. This may be particularly useful at later stages in polymorph characterization, to identify potential facile, stable or commercial methods for generating a particular polymorph for an active pharmaceutical ingredient, or to prepare focused solvent libraries.

[0164] Solvent group design may be performed by any method known in the art, including manual design or computer design. Commercially available computer programs can be used, including JMP™, available from SAS Institute, Inc., Cary, N.C.

[0165] In general, solvents are chosen to have a boiling point higher than the temperature at which the crystallization will be run. Other physical properties that are preferred are those in which non-toxic solvents are used. In another embodiment, one or more solvents such as ethanol, water, cyclohexane, propanol, acetonitrile, dioxane, methyl ethyl ketone, ethyl acetate, isopropyl acetate, propyl acetate or toluene are used as a solvent in the methods described herein.

[0166] In one embodiment of a salt selection array, one axis of the array (e.g., the rows of a microtiter plate or other substrate) contains a constant amount of the drug candidate of interest mixed with a number of different salt reactants, wherein each row of the array contains a different salt reactant. In general, the drug candidate is mixed with one equivalent of the salt reactant (e.g., an acid or base). However, in another embodiment, the drug candidate may be mixed with 0.5, two, 1.5, three or four equivalents of the salt reactant.

[0167] The opposite axis of the array (e.g., the columns of the microtiter plate) contains a number of different solvents, wherein each column of the array contains a different solvent. In a preferred embodiment, the solvents have been clustered as described herein. Thus, each well of the array contains a different combination of salt reactant and solvent.

[0168] The salt reactant and drug candidate may be subjected to conditions in which a salt may form prior to addition of the solvent, e.g., by heating, stirring, shaking or any combination thereof. An array of solvents may then be added and the presence of crystals or precipitates of drug candidate salts may be determined. Alternatively, the drug candidate, salt reactant and solvent may be mixed together prior to subjecting the array to conditions under which a drug candidate salt and crystal or precipitate thereof may form. In one embodiment, the array can be subjected to salt synthesis and crystallization using one or more of the apparatus described herein.

[0169] In another embodiment, one axis of the array (e.g., the row) contains the drug candidate of interest mixed with a number of different salt reactants while the opposite axis (e.g., the column) contains solvents or compositions of two or more solvents, wherein each column contains a different solvent or solvent composition. In one embodiment, the solvent compositions in the array or part thereof may be different concentrations of the two solvents relative to each other. The concentrations of the solvents relative to one another may be any concentration desired. In one embodiment, an array of solvent compositions (e.g., gradient) for solvents A and B can be expressed in the following formula:

$$x*A(100-x)*B=0 \quad (1)$$

[0170] where x is the percentage.

[0171] If desired the gradient can be determined using a linear function, a non-linear function, a polynomial function, an exponential function, etc. For instance, one may vary the concentration of water and heptane in this manner. Similarly, an array of solvent compositions using three, four or more different solvents may be produced, wherein the relative

concentrations of the solvents to each other are varied in the array. In a preferred embodiment, the solvents in the solvent composition have been clustered as described herein. As discussed above, the array can then be subjected to conditions in which drug candidate salts would likely form crystals.

[0172] A single drug candidate (either a salt or a neutral compound) is typically tested for polymorph generation and characterization, although two, four, six, eight or more may also be characterized. Because different drug candidate salts do not have to be formed, more solvents are typically used for polymorph generation and characterization than is typical for salt selection. However, except for the larger number of solvents that are generally used, solvent group selection for polymorph generation and characterization is similar to that for salt selection. Thus, in one embodiment, a library of solvents may be divided into more groups for recrystallization compared to that for salt selection, while in another embodiment, more solvents within a single group may be used to recrystallize a drug candidate salt.

[0173] In one embodiment of a polymorph array, each well contains a constant amount of the drug candidate of interest and a different solvent. The solvents may be selected by any method known in the art. For example, the solvents may be selected from different industrially important categories of solvents, including aromatics, ketones, water, halogenates, alcohols, esters, nitrites, as well as solvent mixtures that span a wide range of polarity and dielectric constant. In a preferred embodiment, the solvents are selected by the solvent selection method described previously, by dividing a library of solvents into groups based upon a variety of different physical properties or characteristics. More preferably, the solvents are not selected based upon their chemical class. After the solvent has been added to the drug candidate, they are mixed under conditions to dissolve the drug candidate, optionally filtered, and then subjected to conditions in which crystals are likely to form.

[0174] Using an array of different types of solvents, whether based upon the chemical class or their physical properties, provides a large amount of information regarding which types of solvents recrystallize the drug candidate. Further, using a wide variety of solvents is likely to provide a large number of different polymorphs of the crystalline drug candidate, if they exist. See, e.g., **FIG. 7**, which shows changes in crystal morphology of a drug candidate after crystallization from different solvents. These solvents included those that are miscible in heptane and those that are miscible in water. Once one or more solvents have been identified that recrystallize the drug candidate, other solvents that are of the same chemical class or share physical properties or characteristics with the identified solvents may be used in further experiments. These experiments can be performed to generate and characterize polymorphs of the drug candidate as well as to find the best recrystallization solvent for the particular drug candidate.

[0175] In another embodiment of a polymorph array, the array contains the drug candidate of interest mixed with compositions of two or more solvents, wherein each well contains a different solvent composition. See, e.g., Example 3. In one embodiment, the solvent compositions in the array or part thereof may be different concentrations of the two solvents relative to each other. The concentrations of the solvents relative to one another may be any concentration desired. In one embodiment, an array of solvent compositions for solvents A and B may be determined using equation 1. Similarly, an array of solvent compositions using three, four or more different solvents may be produced, wherein the relative concentrations of the solvents to each other are varied in the array. In a preferred embodiment, the solvents in the solvent composition have been clustered as described herein. As discussed above, the array can then be subjected to conditions in which crystals would likely be synthesized, and the presence of crystals and polymorphs can be determined. One can use different concentrations of solvents to determine at what concentration a solvent causes the drug candidate to crystallize. In addition, one can use different concentrations to determine whether different types of crystals are formed in different concentrations of solvent.

[0176] In another embodiment, solvent group design may be performed by providing a database containing information associating the physical or chemical properties of particular solvents with the production of crystallographic forms of drug candidates, identifying in the database which physical properties are associated with producing a large number of crystallographic forms, and designing new libraries using these identified physical or chemical properties as criteria for grouping solvents.

[0177] **FIG. 5** shows an illustrative flow chart of library design process **500** in accordance with the principles of the present invention. Library design process **500** may be used, for example, to generate library **400** illustrated in **FIG. 4**. At step **510**, a user may define or select one or more sources using a user terminal (e.g., user interface equipment **180** of **FIG. 1**). Sources may include materials such as salt reactants, solvents, drug candidates, mixtures of solvents, etc. that are used to prepare a library. Also at step **510**, a user may define or select a library layout. A library layout may represent the layout in which a library will be created on a substrate (e.g,. a substrate with an 12 by 8 matrix array of wells) or a reactor assembly. Alternatively, a library layout is not necessarily confined to actual physical parameters, rather it can be provided in an intangible format (e.g., on a computer).

[0178] The user can identify source materials and library layouts by entering identifying information manually or by selecting identifying information from a pre-defined source such as database **114** of **FIG. 1**.

[0179] At step **520**, process **500** may define the composition of each library member based on the sources selected in step **510**. The composition of each library member is defined by a mapping sequence that assigns materials to each library member. The mapping sequence may be automatically generated or defined by a user. Automatically generated mapping sequences may provide an exhaustive mapping of material compositions than can be used to create libraries.

[0180] When step **520** has completed defining the composition of each library member, process **500** optionally proceeds to step **530**. At step **530**, a recipe file is generated based on the composition defined at step **520**. The recipe file may embody handling instructions that can enable instruments such as material handling apparatus **150** (**FIG. 1**) to prepare the library. Step **530** is optional because the library mapping parameters can be integrated with software that controls a material dispensing apparatus to prepare members of substrate according to the library.

[0181] Persons skilled in the art will appreciate that the above discussion with respect to **FIGS. 4 and 5** is not intended to be an exhaustive description of library designing. The discussion does, however, discuss a portion of the various features pertinent to describing the present invention. For example, WO 00/23921, provides a substantial description of library designing.

[0182] After a library is designed the process proceeds to prepare one or more libraries using material handling apparatuses. **FIG. 6** shows an illustrative flow diagram of combinatorial library preparation process **600** that controls hardware to automatically prepare libraries in accordance with the principles of the present invention. Automated step may be performed manually if desired.

[0183] At step **610**, the user may define hardware resources that are available for use in process **600**. The user may define hardware resources such as automated liquid handling robots, pump controllers, solid or powder dispensing systems, and other dispensing equipment. In defining the hardware, the operating characteristics of such hardware may also be identified. For example, characteristics such as configuration of syringes attached to a dispensing device (e.g., in series of parallel), motion limits, step size and reference positions for arm movements, dispensing capacity of syringes, etc. may be identified. Other hardware resources may include temperature controllers for regulating the temperature or temperature ramp rate of a substrate or pressure of a reaction vessel.

[0184] At step **620**, a recipe file or other instructions that include the library design is received by process **600**. Step **620** may analyze the data and develop a set of material handling instructions that can control the hardware to synthesize a library. The material handling instructions may be provided to, for example, electronic circuitry **112** of **FIG. 1** so that control commands can be provided to material handling apparatuses. Then at step **630**, the material handling instructions are executed and a library is prepared in accordance with the recipe file received at step **610**.

[0185] Software that can perform process **600** is described in more detail in WO 00/67086, which is hereby incorporated by reference in its entirety.

[0186] After salts, crystals, or polymorphs are created in a library format, they are screened for desired properties and characterization. The present invention utilizes high throughput screening that provides sufficient information that enables the process to proceed to the next step. Screening tests are performed to obtain data on each library member. Screening tests can be primary or secondary depending where in the process the test are performed. A minimum number of screening tests may be performed to identify the materials in the library, determine the crystallinity of the materials, and determine the solubility of the materials. Additional tests may be performed to obtain more data on one or more library members.

[0187] Screening tests may provide quantitative and/or qualitative data. Quantitative data enables the present invention to perform analysis based on numerical data. This data is well suited for use in software programs operating on computers because it can be categorized quickly and accurately. Qualitative data, however, provides information that does not require intensive number manipulation and relatively quick material characterization. For example, an identity screen can run with sufficient precision to determine if members of the library are different from each other or from a standard. But the identity screen may not be so thorough that it identifies each member of the library. In another example, a crystallinity screen may determine certain crystal characteristics, such as morphology, without determining every (or even most) characteristics of a crystal (e.g., such as melting point, unit cell, etc.).

[0188] Screening tests may be implemented on instruments that determine, for example, solubility, partition coefficient (log P), birefringence (while the sample is wet and/or dry), melting point, crystal morphology, hygroscopicity, and other physical characteristics. Other screening test instruments may provided data using, for example, X-ray diffraction, Raman spectroscopy, IR or Near IR spectroscopy, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy (NMR), gas chromatography and liquid chromatography. These tests are preferably performed in parallel or in a rapid serial or automated mode such that the screening method does not delay the overall process.

[0189] As illustrated in **FIGS. 2A, 2B** and **3**, screening test are performed in different steps of the process. One or more screening test may be performed at each screening step in a process. Several screening steps provide greater quantities of data so that library members are more fully characterized than characterizations performed by a single screening test. For example, in one embodiment a primary screening step (e.g., step **225** of **FIG. 2A**) may perform at least 4 different tests (e.g., solubility, log P, crystallinity and Raman spectroscopy) to determine which library S members should be selected for bulk synthesis. Primary screening steps preferably use fewer tests than a secondary screening step so that high throughput screening can be maximized.

[0190] A secondary screening step (e.g., step **255** of **FIG. 2B**) may also perform several high throughput screening test to provide the process with a thorough characterization and identification of the bulk sample. Secondary screening test may include test such as IR spectroscopy, Near IR spectroscopy, UV-Vis absorption, X-ray diffraction, melting point, and pK_a. Other tests that can be performed on bulk samples include NMR, differential scanning calorimetry, thermogravimetric analysis and elemental analysis.

[0191] A process may perform solubility, birefringence X-ray diffraction, hygroscopicity and/or Raman spectroscopy in high throughput mode to quickly and accurately characterize library members. In particular, when using only solubility, birefringence, and Raman tests, these tests adequately characterize any salts that may have formed. In addition, these test also determine whether polymorphs of drug candidates (or salts thereof) have formed. If desired, a more detailed identification of the different polymorphs can then be accomplished through additional screening test and analysis.

[0192] Solubility is performed by sampling the supernatant mother liquor from the recrystallization step of polymorph generation or from the crystallization or precipitation step of salt selection, as described above. The liquid sample is subjected to a concentration detector to determine the amount of the drug candidate (or salt) in the solvent. The drug candidate (or salt) concentration may be detected using liquid chromatography, thin layer chromatography, gas

chromatography, absorption in the UV-Vis range, infrared (IR), fluorescence or any other suitable technique. In one embodiment, liquid chromatography coupled with an ultraviolet radiation detector may be used to determine drug candidate concentration. An example of an liquid chromatography system is an Agilent 1100LC system.

[0193] Sampling for the solubility test is typically performed at a temperature in which recrystallization or precipitation has occurred. Solubility testing can be performed as a high throughput screen, which can be performed in a rapid serial mode or in parallel. The testing will provide solubility information for the particular solvent in which the drug candidate salt is present at which the solution was sampled. In one embodiment, one may determine the solubility of one or more drug candidates under a variety of conditions in parallel microtiter plates or other assembly comprising a plurality of wells by forming arrays of solvents or solvent mixtures at temperatures ranging from 0° C. to 70° C. and measuring the concentration of the compound in the supernatant. In a preferred embodiment, the temperature is measured at a temperature in which the drug candidate or salt is dissolved ($T_{initial}$) and at the final temperature, in which the drug candidate or salt has crystallized (T_{final})

[0194] The partition coefficient, also called log P, is a well known measure of solubility in a water/1-octanol mixture. In a high throughput mode, log P is determined by measuring the concentration of the drug candidate salt in both water and 1-octanol at a particular temperature. In a preferred embodiment, the solubility in 1-octanol and the solubility in water is measured in separate wells of a microtiter plate as part of the overal process, with those measurements used to determine log P. In an alternative embodiment, water saturated with 1-octanol and 1-octanol saturated with water may be used as solvents. The concentration may be detected using liquid chromatography, thin layer chromatography, gas chromatography, absorption in the UV-Vis range, infrared, fluorescence, or any other technique that determines concentration known to those of skill in the art. Using any suitable detection device, log P is determined by dividing the concentration in 1-octanol by the concentration in water and taking the log of that number.

[0195] Birefringence testing may be used to determine the crystallinity of a sample. In particular, birefringence testing indicates the quantity of crystals formed, size of the crystals, and shape of cyrstal (e.g., needle structure, blade structure, tabular structure, or any other structure). **FIG. 7** shows several crystal structures that can be detected using birefringence testing in accordance with the principles of the present invention. The crystal's structure may provide information in deciding which library members are suitable for large scale synthesis. For example, needle crystals are often more difficult to filter than tabular crystals.

[0196] Birefringence testing may be performed by passing light through wet or dry samples in the library. Preferably, the samples are arrayed on a transparent substrate located between two parallel and perpendicularly aligned cross-polarized filters. A light system may be positioned above or below one of the filters to detect light refraction as it passes through samples on the substrate. Persons skilled in the art will appreciate that other devices can be used to detect birefringence of materials in such a setup. For example, an array of photo-diodes may by used to detect birefringence of a material. The light system advantageously screen the entire substrate in one pass, thus providing a relative fast indication of the suitability of the materials located on the substrate. A detailed description of a birefringence testing device is described in detail in conjunction with **FIG. 28**. Also described in conjunction with **FIG. 28** is a method for performing light scattering to detect if any crystalline structures are present.

[0197] Because crystals are birefringent structures, they have the ability to refract light. This property allows a birefringence testing station to detect if a sample on the substrate is crystalline or amorphous. Amorphous materials are typically undesirable because they tend to be unstable and more hygroscopic than crystalline forms. An example of device using a parallel light rotating and collection device is described in U.S. Pat. No. 6,157,449 ('449 patent), which is incorporated herein by reference in its entirety. A birefringence testing station may, for example, use the device in the '449 patent in conjunction with a light system.

[0198] In situ measurements of an array of material samples can be performed using birefringence or a light scattering technique. More particularly, in situ measurements are performed using a reflective optical scanning technique. A description of an apparatus that performs in-situ monitoring using the reflective scanning technique is described below in specification pertaining to **FIG. 30**.

[0199] One advantage of in-situ measuring is that it maximizes high throughput testing of material samples. For example, assume that an array of material samples are subjected to crystallization conditions while being monitored in situ. Further assume that these particular crystallization condition did not yield any crystalline structures. Instead of disassembling a crystallization assembly and providing the substrate, which does not contain any crystalline structure, to a series of screening test, in situ monitoring can provide information to avoid such an unnecessary step. Performing screening test on material samples that do not contain crystalline structures slows down the screening process for detecting new polymorphs. Thus, in situ monitoring provides information that may result in subjecting the material samples to different crystallization conditions that may produce crystals.

[0200] Hygroscopicity testing characterizes materials (e.g., crystals) according to their ability to adsorb water. Hygroscopicity can be tested in an automated manner using Raman spectroscopy, Near IR spectroscopy or in situ measurements as a series of "snapshots" to determine water gain (or loss), as described in other parts of this specification. PuuMan Oy (Kuopio, Finland) manufactures and markets the HMA (Hygroscopicity Measurement Apparatus) that is capable of measuring the hygroscopicity of eight samples simultaneously.

[0201] Hygroscopicity can also be measured by automated weighing systems. For example, vials containing samples are automatically weighed (for example using a Bohdan Automated Weighing Station (called the Balance Automator), available from Bohdan Automation (a Mettler-Toledo Company, Vernon Hills, Ill.). The vials containing samples are then exposed to a controlled atmosphere (e.g., a certain humidity) for a selected time, after which the vials containing samples are automatically weighed again, with a difference in weight being a measure of hygroscopicity. In some

embodiments, the automated weighing station can be located inside a glove box or other atmosphere controlled chamber.

[0202] Hygroscopicity can also be measure using dielectric measurements. Such dielectric measurements can be performed on a substrate having regions comprising interdigitized probes, with the samples being placed in the regions and the substrate being placed in a controlled atmosphere chamber (e.g., a controlled humidity chamber). Changes in samples dielectric properties are measured as water is gained (or lost) and hygroscopicity is determined.

[0203] In a preferred embodiment, hygroscopicity is measured in a high throughput manner using a microbalance and more particularly using sensitive mechanical resonators, whose resonance performance can be monitored and correlated with mass. In one preferred embodiment, hygroscopicity is measured using a method for screening samples created in accord with the description herein (e.g., on a universal substrate), comprising the steps of (a) providing a plurality of solid samples; (b) placing a first sample onto a mechanical resonator in signaling (e.g., electrical, magnetic, optical, thermal, or other communication) communication with a source of an input signal; (c) coupling the mechanical resonator with measurement hardware; (d) exposing the samples to a controlled atmosphere (e.g., moisture or desiccating) while on the mechanical resonator; (e) applying an input signal; (f) monitoring a response of the mechanical resonator to the moisture of the samples thereon with the measurement hardware; and (g) repeating steps (b) through (f) for each sample for which measurement is desired. In addition, this method can readily be adapted for also conducting analysis of mass change in response to a change of temperature, such as for thermogravimetric analysis.

[0204] In this preferred method, the monitoring that occurs in step (d) may employ a suitable lock-in amplifier or like hardware for monitoring the change of frequency of the mechanical resonator while maintaining the input signal to the resonator as a constant. It may alternatively employ the monitoring of the change in electrical feedback from the resonator while maintaining a constant frequency.

[0205] In a particularly preferred embodiment, the input signal is a variable frequency input signal and the monitoring step (d) includes varying the frequency of a variable frequency input signal over a predetermined frequency range to obtain a frequency-dependent resonator response of the mechanical resonator. The preferred method advantageously allows repeating steps to be performed simultaneously for analyzing an array of samples in a parallel format. Yet, as desired the repeating steps may be performed serially.

[0206] When employed in a salt selection or polymorph workflow, as described herein, the preferred method can be described as comprising the steps of (a) providing an array of different particulated pharmaceutical polymorph candidate samples; (b) providing a tuning fork resonator having at least two tines with tips and being in electrical communication with a source of an input signal; (c) adhering a quantity of a plurality of samples to at least one of the tines; (d) coupling the tuning fork resonator with measurement hardware; (e) simultaneously, for at least two samples of the array, humidifying the samples while on the tuning fork resonator; (f) simultaneously, for at least two samples of the array, applying a variable frequency input signal; (g) simultaneously, for at least two samples of the array, varying the frequency of a variable frequency input signal over a predetermined frequency range to obtain a frequency-dependent resonator response of the mechanical resonator to the humidification of the samples; and (h) graphically displaying the responses for each of the samples analyzed, such as by providing a readout of a frequency response, wherein frequency versus signal is plotted.

[0207] Another embodiment of the preferred method contemplates an apparatus for measuring small quantities of materials, comprising a plurality of resonators, and particularly tuning fork resonators having tines with tips; a holder for each resonator; a readout board; a plurality of elongated members for bridging electrical communication between the resonator and the readout board; and a frame carrying at least the resonators, holders and elongated members. The apparatus is preferably adapted for attachment to a robot arm for facilitating automation of the operation of the apparatus. The apparatus of may further comprise other components, such as a sample work surface having a recess therein for receiving a sample, a host computer, and a power source (e.g., for providing a variable frequency input signal to the resonators).

[0208] The advantages of the preferred method are numerous, including mass measurements of soft, thick, non-uniform layers or irregularly shaped samples; small sample quantity measurements (with some samples being less than about 100 micrograms and more preferably less than about 50 micrograms); certain resonators (e.g., tuning fork resonators) have a Q-factor does not decrease by more than about 1-3%, so relative change of a sample mass is accurately measured by resonator frequency change; quick measurements, in some embodiments in less than one minute (and in other embodiments in less than about 30 seconds or less than about 5 seconds for a single sample or for an entire array or library); and the ability for real-time mass tracking (or real-time hygroscopicity). The details of this preferred method are set forth in commonly owned, U.S. Patent Application No. _____, titled "High Throughput Microbalance and Methods Using Same" (Attorney Docket Number 1012-_____, filed concurrently herewith), which is incorporated herein by reference for all purposes. See also U.S. Pat. Nos. 6,336,353 and 6,182,499, which are both incorporated herein by reference for all purposes.

[0209] Raman spectroscopy may be performed using any type of unit, such as a commercially availably unit (e.g., Renishaw, Ramascope), with an X-Y stage that addresses the samples in a rapid serial mode. In some embodiments, in order to run a very high throughput screen, peak assignments may not be performed on the spectra acquired. Instead, the spectra are used as "fingerprints" to determine if different polymorphs (or salts) have formed in the high throughput experimentation. In other embodiments, peak-matching software may be used to make the determination of different identity. Raman, IR, X-ray or other fingerprint type spectra may not be quantitatively analyzed, and instead may be used for qualitative determinations about the relative sameness or differences between spectra. An example of spectra provided in a graph format is illustrated in **FIG. 9**.

[0210] Morphology or crystallinity may also be performed by inspecting each of the regions of the libraries under a

microscope, for example, with crossed polarizers. X-ray diffraction can be performed on a Bruker GADDS (Bruker AXS, Madison, Wis.), See also, U.S. Pat. No. 6,371,640, which discloses a method and apparatus of screening materials in a high throughput and library format, incorporated herein by reference.

[0211] Thus, selected screening test are used to select drug candidates for further investigation. Screening test also enable the process to perform detailed characterization of library members (e.g., bulk samples) to determine its suitability. The recrystallization condition identified based on the selected samples may be used to prepare bulk samples of the desired salts for additional characterization. One feature of the process of the present invention is the use of a "universal substrate". A universal substrate refers to a substrate having samples thereon and that can be used for a variety of tests (described above) without manual or other manipulation of the samples. This will become more apparent in the discussion below. Thus, a single substrate (e.g., array of materials) can be tested for birefringence, Raman, X-ray diffraction and melting point without handling the samples for each test.

[0212] Automated control of material screening device **160** (e.g., birefringence station, Raman station, XRD station, melting point station, etc.) may advantageously enhance high throughput screening. High throughput screening is enhanced by automated control because it allows the process to quickly characterize drug candidates and provide data to a computer (e.g., computer **110** of **FIG. 1**). Automated control may be provided by a software program operating on a computer. In particular, software programs may control material screening device **160** to characterize and identify properties of drug candidates.

[0213] For example, a software program can instruct material screening device **160** to perform an identity screen of the drug candidates. Because drug candidates are typically arranged in a library format, the software can direct device **160** to perform screening in parallel or in a rapid serial mode. Parallel screening provides characterization of two or more drug candidates simultaneously. Rapid serial mode screening provides relatively rapid screening of drug candidates on an individual basis.

[0214] Data is obtained from material screening device **160** when it characterizes and identifies properties of drug candidates. This data may be provided to the software so that analysis can be performed with respect to each drug candidate. Data analysis can include categorizing drug candidates, determining suitable drug candidates (e.g., for salt selection), experimental data categorization, and determining polymorphs (e.g., for drug candidates, salts, and other solutions). Data analysis may be performed one or more times during a process. For example, data analysis may be performed after an initial screening to determine which library compositions are suitable for further testing. (This is illustrated in **FIGS. 2A and 3** at steps **230** and **335**, respectively.) If at least one of the library compositions is suitable for further testing, secondary data analysis may be performed in the process. Secondary data analysis may yield a substantially more rigorous examination of data than primary data analysis and provide accurate results in high throughput. (Secondary data analysis in a process is illustrated in **FIGS. 2B and 3** at steps **260** and **360**, respectively.) Persons skilled in the art will appreciate that data analysis can be performed as often times as necessary to characterize and examine data.

[0215] **FIG. 8** shows an illustrative flow diagram for determining if a crystalline structure being tested is part of a particular polymorph family or is a newly discovered polymorph. Categorization flow **800** determines if any material compositions in the library member should be affiliated with an existing family of materials (e.g., existing polymorph family) or if it should be placed in a new family of materials (e.g, new polymorph family). A family comprises a group of materials (e.g., crystalline structures) that exhibit similar characteristics. The categorization of various library members is performed based on data obtained from screening tests (e.g., Raman, XRD, melting point, solubility, hygroscopicity, etc.). One advantage of analysis flow **800** is that it can categorize library members (e.g., hundreds or thousands of materials) into an appropriate family (i.e., existing or new) without relying on initial reference data. Initial reference data can also be used, and in some embodiments, reference data is preferred, such as when a known polymorph exists and others are being searched. Categorization flow **800** builds a database of reference data (e.g,. existing polymorph families) as it categorizes library members with the database being integrated with known or existing data or not. Based on this database, categorization flow **800** continuously analyzes and categorizes crystalline structures created using, for example, process **200** and/or process **300**, as described herein.

[0216] In the following discussion of **FIG. 8**, assume that there is no prior data for any of the crystalline structures discussed in this particular example. At step **810**, data obtained from a screening test of crystalline structures of the library array is provided. Any above-described screening test can be used to provide data on each crystalline structure. It is preferred that the data set is an XY dataset. For example, if Raman, XRD or another spectroscopic screening technique is used, spectra is provided. Spectra provides data such as peak location, peak height, and peak width of a crystalline structure. If, for example, a melting point screening technique is used, numerical temperature values are provided as data to step **810**.

[0217] Assuming that the data obtained at step **810** is the first set of data obtained for the first crystalline structure, there is no reference data that can be used for comparison. Thus database at step **820** is void of reference data, at least initially. In particular, step **820** does not have any reference data that represents a polymorph family. For purposes of clarity and brevity, any data that is provided from step **810** that is used in process **800** is referred to as new crystalline structure. Proceeding to step **830**, the data associated with a crystalline structure is compared to data for each known polymorph family stored at step **820**. Thus, the crystalline structure undergoes an iterative comparison process, which after each iteration, produces a correlation coefficient. A correlation coefficient is indicative of how "close", the crystalline structure is to a particular polymorph family.

[0218] Persons skilled in the art will appreciate that methods other than iterative techniques can be implemented to compare the crystalline structure to each of the existing polymorph families.

[0219] Categorization process **800** may use statistical methods to obtain the correlation coefficient. Statistical

methods may be used to determine the deviation (e.g., standard deviation) of the data associated with the crystalline structure to a reference data set. Software programs that perform such mathematical functions include MATLAB software sold by The MathWorks, Inc., of Natick, Mass., Mathemathica® sold by Wolfrum Research, Inc. of Champaign, Ill., and MathCad® sold by MathSoft of Cambridge, Mass. Persons skilled in the art will appreciate that other software programs different from the programs described above may be used to perform matrix based calculations and other mathematical calculations.

[0220] The comparison process in step **830** uses different comparison techniques differently based on the type of data provided by step **810**. One such technique is a cross-correlation technique. This technique is typically used when the measured data is obtained using Raman spectroscopy. As those of skill in the art know, Raman spectra it typically a curve or graph that represents characteristics of a crystal. Such a graph is illustrated in **FIG. 9**. The cross-correlation technique performs a point-to-point correlation to determine how "close" the measured spectra is to reference spectra. After the comparison is performed, a correlation coefficient is obtained based on how close the graphs match.

[0221] Another technique that can be implemented at step **820** is a peak matching percentage technique (e.g., peak locations are compared). This technique is typically used comparing spectra obtained by X-ray diffraction (XRD) spectroscopy. In this technique, the peak locations of an XRD graph are determined using an algorithm. Then the determined peak locations are compared to peak locations of reference data (e.g., peaks of particular polymorph family). A percentage value is obtained based on how similar the XRD peaks are to the reference peaks. This percentage value is analogous to the correlation coefficient.

[0222] After the iterative comparisons are performed, the best correlation coefficient is obtained at step **840**. The best correlation coefficient is associated with the polymorph family that the new crystalline structure set matched best.

[0223] At step **850**, the best correlation coefficient is compared to a predetermined value. Typically, the predetermined value is a user-defined correlation coefficient that sets the threshold for determining whether the data associated with the crystalline structure should be associated with an existing polymorph family.

[0224] If the correlation coefficient exceeds the predetermined value, that crystalline structure is grouped into the polymorph family associated with that best correlation coefficient at step **860**. After step **860**, process **800** returns to step **810**, which provides the next new crystalline structure to step **830**.

[0225] If the correlation coefficient does not exceed the predetermined value, a new crystalline polymorph family is created based on the data obtained on the new crystalline structure at step **870**. In the event that there was no reference polymorph family for any comparison to be performed, the crystalline structure is automatically used to create a new polymorph family at step **870**. The data associated with the new polymorph family is provided to step **820** for use as a reference as an existing polymorph family. Also, after step **870**, process **800** returns to step **810**. Data from a whole series of libraries based on a single drug candidate can be sorted in continuous process so that one set of families are created that are indicative of the individual forms of the drug candidate.

[0226] Thus, analysis process **800** illustrates crystal structure categorization based on screened data. Persons skilled in the art will appreciate that steps shown in **FIG. 8** are merely exemplary and that additional steps may be added and some steps may be omitted or modified.

[0227] If desired, reference data such as a computer file, a look up table, or other suitable information source may be provided to the database in step **820**. Parameters that were used to create the library members can be provided to database in step **820**. For example, parameters such as solvents added to the salt, crystallization temperature, and other parameter used to formulate library arrays and crystallize the arrays. This data can be used as criteria in grouping crystalline structures.

[0228] Storing measured data provides a database that stores data (e.g., spectra) from each library member. This advantageously enables currently measured data to be compared to other previously screened libraries. In some embodiments, when a new family of polymorphs is discovered in step **825**, data from previously identified families may be compared to newly acquired data. This enables analysis process **800** to determine if the "new" family corresponds to a previously identified family such that the data can be assigned to an existing family. This effectively reduces the total number of families of data and allows for a high correlation within a family or group of data. Yet, user defined variation between families or groups is still preserved. In other embodiments, if original data is not provided, the first experimentally determined data can be used as the "starting" information (e.g., step **820** can use data from a designated well or a designated piece of information).

[0229] An illustrative example of pre-formulation system **100** (**FIG. 1**) that implements process **800** to categorize different library members is described in conjunction with FIGS. **9-12**. In the following example, assume that each library member of a 96 well substrate has been tested using a device (e.g., an infra-red device, UV-Vis absorption device, a Raman device, an X-ray device) that obtains data. Using such devices, the data can be arranged in a graphical format. **FIG. 9** illustrates spectral data obtained from four different library members using a Raman device. The spectral data shows that each of the library members contain polymorphs of the same drug candidate, but are similar enough to be classified as part of the same family or group.

[0230] **FIG. 10** illustrates spectral data obtained from three different library members using, for example, an X-ray diffraction device. **FIG. 10** shows that these three library members also have polymorphs, but are each different from each other such that they are not part of the same family group.

[0231] **FIG. 11** shows an illustrative interactive display screen **1100** that includes several spectral graphs of screened library members. Display screen **1100** shows that spectra **1105** are arranged in array format **1108**. Preferably, spectra **1105** are arranged so that they coincide with the layout of the substrate in which they were screened. As shown in **FIG. 11**, not every portion of array **1108** has spectral element. This may be because a crystal did not form during the crystallization (e.g., recrystallization) process.

[0232] **FIG. 11** also shows that a user can enter and change spectrum sorting parameters **1110**. For example, a user can enter a minimum grouping correlation coefficient. As described above in conjunction with **FIG. 8**, the correlation coefficient may be used to determine if a crystalline structure belongs to a particular family. The value entered for the correlation coefficient can range between −1 and 1. The closer the correlation coefficient is to 1, the more stringent the criteria becomes for placing a particular library element in an existing family. For example, if there are ten library elements and the correlation coefficient is 0.9, each library element may be associated with a new family—thus creating ten different families. If the correlation coefficient is closer to zero, then matching a particular library element to an existing family becomes less stringent, thereby producing fewer new families. The value selected for a correlation coefficient typically ranges from about 0.5 to about 0.9. The correlation coefficient selected may, for example, be the predetermined value used at step **850** in process **800**.

[0233] A user can select whether to use a fixed reference (e.g., a predetermined reference) or an arbitrary reference (e.g., a library element) for providing a baseline in determining family grouping selection. Persons skilled in the art will appreciate that additional parameters may be entered or modified as suitable within the spirit of the invention. A user may also change the image size of array **1108** by changing width and height parameters **1115**. Users can submit their entries by selecting send overlay **1120** or they can reset their entries by selecting reset overlay **1122**.

[0234] In another embodiment, categorization process **800** may be implemented with an XY dataset where similarity among xy data sets is measured by a correlation coefficient (CC) ranging from −1.0 to +1.0, with +1.0 being a perfect match to be in the same group, which is used for data deemed of insufficient quality. The sorter has a default group, namely the junk group. The parameters for determining the data to be junk or not can be set by the user, with each data set being checked to see if it is junk before being placed in this default location. When a data set is not put into the default location, a new group may be created by comparing the xy data set from the remaining data to a reference and for each unclassified sample xy data set using the reference set from each existing group (or one can pull out all sets from each existing group). Comparison of the sample data to the reference set can provide a CC value (or comparison of the sample data to the sets and get a best CC value from the comparisons). This is followed by retention of the best CC and the Group where the CC comparison came from. If the best CC is less than the specified value, then the sample is put in the new group; otherwise the sample is put into the group from which the best CC was obtained. The user can override the automated classification by performing comparisons visually and assigning groups manually. This can also be implemented on peak locations, peak heights or other data. Thus, for XRD data, it is currently preferred that peak locations are used to determine a correlation coefficient.

[0235] In another embodiment, the process also allows the user to define a recycle bin, where data can be designated for re-running through the correlation process. In this manner, the user can identify data that should be sorted based on different parameters. In still another embodiment, the user can iterate the correlation process, by running multiple correlations based on at least one different parameter.

[0236] **FIG. 11A** shows one example of a dialog box **1150** for the user to define the parameters used in correlating the spectra. One side of the box **1150** allows the user to define the automatic junk classification **1152**, which as described above allows for removal of data from the classification workflow. The do it check **1154** enables or disables this feature, with the settings that the user can define included in the remainder of the box **1152**. The moving average point **1156** is used for smoothing the signal of the data. The minimum peak height **1158** is used for setting the height that a peak in the xy data set must meet in order to be considered to be a peak for correlation purposes (e.g., this feature can set background noise levels and allow the correlation process to ignore the noise). The minimum zero crossings **1160** allows the user to set the minimum number of zero crossings for peaks, with the implicit assumption that each peak has two zero crossings as a default. The maximum zero crossings **1162** allows the user to set the maximum number of zero crossings in a data set so that the data would be considered to have good quality. For example, spectra with too many zero crossings may signify that the spectra may simply comprise noise.

[0237] The match algorithm **1164** side of box **1150** is used for setting the correlation factors. The coverage **1166** has settings for single and all, with single comparing the sample to a master or reference data of the existing family or form only. The resulting score represents the comparison score between the sample and the reference data for a particular family. The all setting compares the sample data to all of the data already in the family, in which case that best correlation score represents the best score resulting from all the comparisons. The method **1168** allows the user to decide on what part of the data will be used for correlation. As shown in **FIG. 11A**, peak center performs correlation based on the peak locations (within an acceptable deviation as defined in the peak center band width **1172**). Other methods of correlation include full signal correlation, which uses the entire data set for correlation. Differential signal method of correlation performs correlations based on the digital difference signals (first derivative) of the sample and reference data. Baseline removed method of correlation performs correlation based on data with the curvatures and slopes removed in the data. Other methods of correlation are within the skill of one of skill in the art, including for example with spectra, peak height or peak width. The typical correlation coefficient **1170** is the setting to determine the allowable difference to obtain the best correlation coefficient. The peak center band width **1172** allows for the user to set an allowable deviation in peak centers in spectra data sets. The minimum peak height **1174** generally performs the same function as **1158**, and moving points average **1176** allows the user to average set number of data points together for correlation purposes.

[0238] **FIG. 11B** shows an example of a dialog box **1180** that allows the user to set the parameters for performing the correlation. The user sets the minimum correlation coefficient, as discussed above, with box **1182**. The user can allow for previous sorting results to be used in a new sort by either checking or un-checking box **1184**, with use of previous sort results allowing for re-cycling the data, as discussed above. The region of interest **1186** portion allows the user to define a certain portion of the data to consider in the correlation workflow, for example if only a certain region of a spectra would be of interest, then this portion can be used for correlation. As shown in box **1180**, this particular embodi-

ment allows the user to set up to five interval ranges **1190** (with a lower setting (low X) and an upper setting (high X)).

[**0239**] **FIG. 11C** shows dialog box **1192** that allows the user to manually move data from one group (e.g., family or form) to another group (or family). This feature allows the user to manually create families used for correlation or to manually change correlations.

[**0240**] When the user selects send overlay **1120** (**FIG. 11**), the process may analyze the spectral data in accordance with the parameters defined by the user. For example, the process may utilize the principles illustrated in **FIG. 8** to analyze and group each library element to an existing or a new family. **FIG. 12** shows an illustrative display screen **1200** that has organized each of the library elements of **FIG. 12** according to their respective family. In particular, display screen **1200** shows that library elements are grouped into twelve different families. Thus, each of the library elements are grouped accordingly.

[**0241**] A user may repeatedly change the correlation coefficient and select send overlay **1120** to generate different groupings of library members in spectra **1105**. For example, if user desires to generate six families of library elements, the user may change the correlation coefficient achieve such a result. A user may desire to do this because a particular number of families is known or expected. The user may know how many families are expected because a different test (e.g., a Raman, hygroscopicity, XRD, melting point) previously yielded such a result.

[**0242**] One advantage of using the software described herein is that a user can run several categorization tests based on different data sets. For example, a user can categorize library members based on data obtained from, solubility, log P, crystallinity, melting point, hygroscopicity, crystal morphology and birefringence, as well as X-RAY diffraction, infrared (IR), Near IR, and Raman spectroscopy, among other screening techniques. After categorization is performed based on two or more such tests, the results of each categorization can be cross-referenced to determine inconsistencies and/or to validate findings of potential new polymorphs.

[**0243**] As described above in conjunction with **FIGS. 2A, 2B**, and **3**, processes **200** and **300** prepare and screen, and analyze library members to group different polymorphs. Because it is an object of the present invention to provide high throughput testing of polymorphs, software can be implemented to optimize the screening process. Software can minimize the number of screening test that need to be performed for a particular library member. Thus, increasing the capacity of the number of library elements that can be tested for polymorphs.

[**0244**] **FIG. 12A** shows an illustrative flow diagram of a software process **1270** that determines which library members should be subjected to further testing in accordance with the principles of the present invention. Process **1270** begins at step **1272** in which each of the library members are subjected to an initial screening. Screening, as described above, provides data to a computer, and based on that data, process **1270** can determine whether a particular member is suitable for additional testing. Preferably, the initial screening is a relatively fast screening such as birefringence testing.

[**0245**] At step **1274**, process **1270** determines whether the data associated with a particular library element meets certain criteria. The criteria, which is provided by step **1275**, includes data that provides a basis or threshold value for selecting which library member should be selected to performed additional testing. For example, if birefringence testing is used, the criteria may be whether any type of crystal structure is present in the library member. The criteria that can be selected for setting the threshold can be selected by a user or the computer program making the determination.

[**0246**] In one embodiment, later screening tests (such as Raman, XRD, etc.) can be performed only on samples having a birefringence image with an arithmetic mean above a determined point. The arithmetic mean may be in this case the mean of all the pixel intensities from an image of the library member under birefringence conditions.

[**0247**] If the data shows that a crystal structure is present in the library member, then that member is suitable for additional testing at step **1276**. If, however, the data indicates that no crystal structure is present in that library member, that member is marked as not suitable for additional testing at step **1278**. Once a library member is selected, more screening tests (e.g., Raman, XRD, melting point) may be performed. Because performing additional tests take time, process **1270** efficiently eliminates unnecessary testing, thereby maximizing the throughput of the overall process (e.g., workflow).

[**0248**] If desired, the selective screening process can be progressive. That is, assume that a particular library element was selected in an initial screening and was subjected to a second screening (e.g., an XRD screening). Applying the principles described in process **1270**, the same library member does not have to be subjected to additional screening test if it fails to meet a minimum criteria standard based on the second screening.

[**0249**] The following describes several apparatuses that are used to implement processes for selecting salts and discovering polymorphs. In addition, the following discussion describes how such apparatuses are used in conjunction with the processes illustrated in **FIGS. 2A, 2B**, and **3**.

[**0250**] Processing of the selected drug candidate or salt(s) for discovery and characterization of suitable forms requires at least two, but preferably three steps, to be carried out in a combinatorial or high throughput mode. The two required steps are dissolution of the drug candidate or salt(s) thereof, and crystallization of the candidate from solution. The optional third step that can occur between the dissolution and crystallization steps is separation of any remaining solids from the solution by filtration or centrifugation. This optional step may be necessary to eliminate nucleation sites for the crystallization step.

[**0251**] A general reactor assembly is shown in **FIG. 13**. A reactor assembly is used for formulating drug candidates, solvents, acids, bases, etc. Reactor assemblies can be used to dissolve solutions for salt selection or to dissolve solutions for polymorph testing. Reactor assemblies such as reactor assembly **1300** of **FIG. 13** are suitable for containing reactions of interest.

[**0252**] **FIG. 13**, for example, illustrates a cross-sectional view of reactor assembly **1300** that can be used for preparing

library members in accordance with the principles of the present invention. As illustrated in **FIG. 13**, reactor assembly **1300** is constructed in microtiter format. Reactor assembly **1300** includes reactor block **1302** that is constructed with one or more wells **1304**. Each reactor block **1302** can receive reaction vessels **1306**. Materials such as drug candidates and solvents are mixed in reaction vessels **1306**. Reaction vessels **1306** are isolated from one another to prevent cross-contamination among the reaction vessels. This can be accomplished by securing sealing sheet **1308** over reaction vessels **1306** by fastening cover plate **1310** to reactor block **1302** with fastening device **1312** (e.g., a bolt, screw, clamp, etc).

[**0253**] Persons skilled in the art will appreciate that any suitable number of wells **1304** may be constructed. For example, a reactor assembly may have **96** wells or it may have **384** wells.

[**0254**] Reactor block **1302** and cover plate **1310** may be constructed of any suitable material such as metals (e.g., steel, aluminum), plastics, and ceramics. Materials such as aluminum or an aluminum alloy may be preferred because they have desirable thermal and structural properties. Reaction vessels **1306** may be plastic or glass, with glass being preferred. Sealing sheet **1308** is typically made from a material that is chemically resistant to the reaction of interest taking place in reaction vessels **1306** as well as being elastic for its sealing properties. Sealing sheet **1308** may be constructed from materials such as Teflon®, silicone rubber, Vitron®, Kalrez®, or equivalents. If desired, sealing sheet **1308** may be constructed with two or more such materials.

[**0255**] Materials can be dispensed into reaction vessels **1306** by hand or by automated robots. Automated equipment may increase the speed and accuracy of step **212** (**FIG. 2A**). Liquid handling robots such as those sold by Cavro Scientific Instruments, Inc. of Sunnyvale, Calif. may be used for automatically dispensing materials. The description associated with **FIG. 6** explains in more detail how the present invention can control robots to dispense materials into reaction vessels **1306**.

[**0256**] **FIG. 13** provides a general example of one such reactor assembly that can be used in the present invention. **FIG. 15** illustrates a more detailed reactor assembly that can be used for formulating a library. **FIG. 15** is discussed below in the apparatus section of the detailed description. Also described in the Apparatus section are other assemblies and tools that facilitate preparation of materials. For example, FIGS. **24-28** illustrate heating devices that heat materials contained within the reactor vessels.

[**0257**] Heating and/or agitation of the reaction mixtures in each vessels is often used to promote dissolution of the candidate material in the solvent. Prior to dissolution, mixing/stirring balls or magnetic stirrers (e.g., fleas) may be added to the reactor by hand or with a device such as that shown in **FIG. 14** (as discussed in detail below). The reactor block may then be placed on a rocking, rotating, or vortexing plate that is fixed with a heating element for mixing and heating reaction contents. The magnetic stirring apparatus described above may also be used to agitate the materials. Also, the heating element may be programmable to provide a desired heat cycle.

[**0258**] Adding a glass or metal ball to each vial can improve agitation during the dissolution/synthesis step. **FIG. 14** illustrates both a three-dimensional view and an exploded three-dimensional view of object dispensing assembly **1402** that dispenses several objects in parallel in accordance with the principles of the present invention. Dispensing assembly **1402** can be secured over a reactor assembly such as reactor assembly **1300** using flaps **1409** that extend from sidewalls **1408** to line up with the outer edges of reactor block **1302** (shown in **FIG. 13**).

[**0259**] Dispensing assembly **1402** has a cover **1404** that covers a cavity **1406** formed by sidewalls **1408** and bottom plate **1411**. Bottom plate **1411** is preferably constructed with a plurality of holes that align to receptacles (e.g., wells or vials) in batch reactor **1300** when dispensing assembly is attached to batch reactor **1300**. Also included in dispensing assembly is a separation assembly **1410**. Separation assembly **1410** includes isolation plate **1412** and sliding plate **1414**. Isolation plate **1412** may have an array of guide holes that guides an object (e.g., ball or magnetic stirrers) to the holes of sliding plate **1414**. The operation of dispensing assembly **1402** will be more apparent in the following paragraph.

[**0260**] An excess of objects (e.g., balls) is held in cavity **1406**. From this excess of objects, a single object is placed in each guide hole of isolation plate **1412** by shaking assembly **1402**. A single object is transferred into each hole of sliding plate **1414** by moving sliding plate **1414** to a first position that aligns the holes in it with the guide holes in isolation plate **1412**. In this first position, the holes in sliding plate **1414** do not align with the holes in bottom plate **1411**. The objects cannot be dispensed directly into the receptacles in the reactor base below, therefore, one ball is retained in each hole of sliding plate **1414**. Only one ball is retained in sliding plate **1414** because it is constructed with a thickness that substantially equal to the thickness (e.g., diameter of ball) of the object. Sliding plate **1414** is then moved to a second position which aligns the holes therein with the wells or vials in the reactor base below (via the holes in bottom plate **1411**), and simultaneously moves these same holes out of alignment with the guide holes in isolation plate **1412**. This permits the object contained within each hole in bottom sliding plate **1414** to drop into the corresponding receptacle below. It should be noted that dispensing assembly **1402** can be modified to dispense different diameter balls by changing separation assembly **1410**. The parallel dispensing device shown in **FIG. 14** may be used for dispensing other small solids such as stirring fleas.

[**0261**] Regardless of whether agitation objects (e.g., balls) are added to the reactor assembly, an array of solvents or solvent mixtures is added to vials contained within the reactor assembly. The contents are sealed in their respective vials and then agitated at a specified temperature for a predetermined period of time. The temperature typically ranges from about 20° C. to about 10° C. lower than the boiling point of the most volatile solvent in the array. The time period typically ranges from about one hour to about 24 hours. In addition, the mixture may be accelerated by mechanical agitation. In a preferred arrangement the solution is mixed through the use of a vortexer, sonicator, shaker, incubator, or other suitable shaking and heating devices.

[**0262**] Once the solution is fully mixed, the supernatant liquid may be isolated from any residual solid either by hot filtration or by centrifugation. The concentration of the solid

dissolved in the supernatant liquid can then be measured by using any suitable technique such as liquid chromatography, gas chromatography, thin layer chromatography, infrared or Raman spectroscopy, and UV-Vis adsorption (as discussed below).

[0263] After the materials are mixed, the cover of the reactor assembly is removed and aliquots of the solution (typically a supernatant or mother liquor) are removed and transferred to a glass substrate or a universal substrate and allowed to cool. Glass substrates such as borosilicate reactor plates sold by Zinsser Analytic GmbH of Frankfurt, Germany, may be used in the process. As the solution cools, crystals may form. The rate in which the substrate is cooled can be controlled. For example, the substrate may be subjected to a chilled bath, a thermal module, or a chilling incubator which is sold by Torrey Pines Scientific, Inc., Solana Beach, Calif. Alternatively, particularly when volatile solvents are used, evaporation techniques may be used to generate crystals. If desired, precipitation and slurry techniques can also be used.

[0264] After cooling, evaporating, precipitating, or slurry, the supernatant may be removed in a suitable manner (e.g., by aspirating with a pipette and/or wicking away the solvent with filter paper). Supernatant removal can be performed either manually or automatically using a computer controlled device. Supernatant removal can also be performed in serial (e.g., rapid serial mode) or in parallel (e.g., a twelve tip pipette can be used for parallel pipetting). The supernatant and the crystals can both be analyzed for their composition, identity, and properties.

[0265] The above description described how a reactor assembly and substrate are used for performing the processes of the present invention. The following embodiment describes various assemblies that advantageously provide generation of and high throughput screening of salts and polymorphs. **FIGS. 15, 16** and **21** illustrate three different assemblies that have several components in common. Although three assemblies are shown, those of skill in the art will recognize that the functions of these assemblies may be combined into two assemblies or into one assembly. Three assemblies are used herein to provide a process that can be implemented relatively quickly using each assembly. When the assemblies of **FIGS. 15, 16**, and **21** are coupled for use with automatic robots, the process may be performed more quickly and accurately.

[0266] **FIG. 15** illustrates reaction assembly **1500** which is in accordance with the principles of the present invention. Reaction assembly **1500** is used for a dissolution process, which can include, for example, mixing an array of solvents to a drug candidate and heating the mixture to prepare hot saturated solutions. In addition, dissolution processes can include mixing acidic or basic reactants to a drug candidate to form salts. Moreover, the mixture of chemicals added to formulation assembly **1500** may based on a library model.

[0267] Reaction assembly **1500** is generally similar to batch reactor **1300** in **FIG. 13**, but is different in several respects. Reaction assembly **1500** includes a bottom plate **1510** that has a shock-absorbent layer **1512** positioned on top. Shock-absorbent layer **1512** may include a foam pad or other elastic material. Positioned above these parts is reactor base **1514**, which is constructed with an array of holes that can receive vials **1516**. Reactor base **1514** and shock-absorbent layer **1512** are secured to bottom plate **1510** using bolts **1511**. A barrier sheet **1518** and a septum sheet **1520** are positioned over vials **1516**. Barrier sheet **1518** is designed to seal the top openings of vials **1516** and to prevent solvents from mixing with other vials. Barrier sheet **1518** may be made of Teflon or other suitable material. Both barrier sheet **1518** and septum sheet **1520** may be pierced by a needle or cannula. Reactor cover **1522** is placed over septum sheet **1520** and has holes **1523** therethrough to allow a needle or cannula to pass through. Reactor cover **1522** is secured to reactor base **1514** with bolts **1521**.

[0268] Although bolts **1511** are specifically discussed herein, other means such as clips, clamps or vices for securing parts of reaction assembly **1500** can be used. **FIG. 15** also shows a registration pin **1515** that allows parts (e.g., reactor base **1514**, barrier sheet **1518**, etc.) to be aligned when being secured together. Several registration pins **1515** may be used to provide accurate alignment.

[0269] Vials **1516** pass through the holes of the reactor base **1514** so that the bottom of vials **1516** rest on shock-absorbent layer **1512**. Typically vials **1516** are closed at the bottom (i.e., like a test tube with a rounded or flat bottom). Shock-absorbent layer **1512** is made of a resilient material (such as foam) that provides resistance to vertical displacement when downward pressure is applied to vials **1516**. Thus, assembly **1500** isolates each vial when the reactor parts are secured together and provides tolerance for dimensional differences among vials **1516**. **FIG. 15** shows 96 vials in an eight by twelve array, but those of skill in the art will recognize that a different number or arrangement of vials may be used in any particular experiment or format.

[0270] If desired, ball dispensing assembly **1402** (shown in **FIG. 14**) may be used to dispense balls into each vial **1516** prior to sealing reactor cover **1522**.

[0271] **FIG. 16** illustrates a partially exploded view of filtration assembly **1600** which is in accordance with the principles of the present invention. After the mixture is prepared in reaction assembly **1500**, aliquots from each vial may be placed in filtration assembly **1600**. Filtration assembly **1600** separates particles (e.g., supernatant) of the aliquot, thereby providing a "seedless" solution of the aliquot that can be tested. In addition, filtration assembly **1600** facilitates preparation of an array of parent solutions, which may be daughtered for additional testing.

[0272] Liquids are taken from individual wells from the reaction assembly **1500** using a manual or automated pipetting instrument (as described herein) and transferred to the corresponding vials in the array of wells in filtration assembly **1600**. The bottom portion of filtration assembly **1600** includes bottom plate **1610**, fasteners **1611**, shock-absorbent layer **1612**, reactor base **1614**, and vials **1616**. These parts (**1610-1616**) may be the same parts (**1510-1516**) as that of the reaction assembly **1500**. This allows for common parts to be prepared and used in different assemblies, which reduces manufacturing costs.

[0273] Filtration assembly **1600** differs from reaction assembly **1500** by the addition of filter subassembly **1630** and top plate **1624**. In addition, filtration assembly **1600** contains a sealing layer **1617** that is similar to barrier sheet **1618** except that sealing layer **1617** has pre-formed holes for allowing the filtered solution to enter vials **1616**. These holes

have a slightly smaller diameters than vials **1616**, thus when filter subassembly **1630** is secured to base **1614** such that sealing layer **1617** provides a seal between vials **1616**.

[**0274**] Filter subassembly **1630** in **FIG. 16** has two primary functions. Filter assembly **1630** facilitates filtering of the samples received from reaction assembly **1500**, and it allows sampling of the filtrate from vials **1616**. These functions can be accomplished by combining filter subassembly **1630** with a top plate **1624**. Top plate **1624** provides at least two positions for a cannula or needle to deliver or aspirate solutions to vials **1616** in filtration assembly **1600**. This arrangement allows for fluid communication between vials **1616** and the top of filter assembly **1600**. Specifically, top plate **1624** has holes **1625**A and **1625**B that correspond to some of or all of vials **1616** in reactor base **1614**. For example, hole **1625**A may be used to introduce fluid and hole **1625**B may be used to withdraw fluid from vials **1616**. Details of the apparatus for introducing solutions to be filtered into vials **1616** or withdrawing filtered solution from vials **1616** are discussed below.

[**0275**] Filter subassembly **1630** is shown in detail in **FIG. 17**. Filter subassembly **1630** includes a bottom mid-layer **1632** to support filter layer **1634**. Filter layer **1634** is used to separate nucleation sites or other undissolved materials from the solution so that a substantially pure solution is provided to vials **1616** (shown in **FIG. 16**). Filter layer **1634** may be populated with an integrated filter and gasket **1635**. Sealing plate **1636** is fitted over filter layer **1634** and provides support for top mid-layer **1638**. Bottom mid-layer **1632** has receiver hole **1633**A and adjacent hole **1633**B located over the upper opening of some or all of the vials or wells in reactor base **1614** (**FIG. 16**).

[**0276**] Holes **1633**A and **1633**B permit introduction and withdrawal, respectively, of a solution to vials **1616** (**FIG. 16**). Sealing plate **1636** supports a large o-ring **1740** and small o-ring **1744** for each region or vial. When filter subassembly **1630** is assembled, each large O-ring **1740** forms a seal between sealing plate **1636** and top mid-layer **1638**. This seal, formed by large o-ring **1740**, prevents vapor crosstalk between vials **1616**. Another seal is formed when a needle passes through small o-ring **1744**. Persons skilled in the art will appreciate that other materials may be used to provide seals. For example, seals may be formed with valves such as a Merlin valve sold by Merlin Instrument Co. of Halfmoon Bay, Calif.

[**0277**] **FIG. 18** illustrates o-ring sheets **1850** that may be positioned on sealing plate **1636** (**FIG. 16**) in accordance with the principles of the present invention. Large o-ring **1851** and small o-ring **1852** can be manufactured in sheets for easier positioning on sealing plate **1636**. As illustrated, o-ring sheet **1850** is constructed in a four-by-four array of o-rings. Thus, if a reactor base has 96 wells, then six o-ring sheets **1850** would be required to fully populate a 96 well assembly. Other sizes of o-ring arrays may be used based on the size of each o-ring array and the overall number of regions or vials in the reactor assembly. For example, the o-rings may be arranged in an 6×8 array, an 8×8 array, or any other suitable combination.

[**0278**] **FIG. 19** shows a close-up isometric view of a portion of **FIG. 17**. In particular, **FIG. 19** shows first channel **1920** and second channel **1930** that are formed when filter subassembly **1630** is assembled. First channel **1920** may correspond to hole **1633**A, which may be used for introducing liquid into the filtration assembly. In addition, **FIG. 19** shows filter **1634** positioned between bottom mid-layer **1632** and sealing plate **1636**. Thus, when liquid is deposited into first channel **1920** via hole **1633**A, it is filtered before being deposited in the receptacle. Second channel **1930** may correspond to hole **1633**B, which provides a path in which a needle or cannula can directly withdraw filtrate.

[**0279**] In an alternative embodiment, filters may be cut to size so that individual filters are placed into bottom mid-layer **1632**, instead of single sheet of filter paper. Filter paper may be cut to size by knife edge ring **1921** that are part of bottom mid-layer **1632**. Knife edge ring **1921** may, for example, be associated with the first channel. When a user places filter paper on bottom mid-layer **1632** and impresses it onto each knife edge ring **1921** (only one shown), an array of filter disks on mid-layer **1632** is provided.

[**0280**] **FIGS. 20A and 20B** illustrate how pipette system **2060** dispenses into and/or retrieves materials out of vials **1616** using filtration assembly **1600**. In particular, **FIG. 20A** shows a cross-sectional view of filtration assembly **1600** and pipette system **2060** that has needle **2020** extending through hole **1625**A. Passing needle **2020** through hole **1625**A enables the process to utilize filtration assembly **1600**. **FIG. 20B** illustrates an enlarged view of filtration assembly **1600** encircled with dashed line "6B" in **FIG. 20A**. Here, needle **2020** is inserted into hole **1625**A such that it pierces barrier sheet **1618**, septum sheet **1620**, and protrudes through small o-ring **1744**. As described above, when needle **2020** and small o-ring **1744** interact, a seal is formed. This seal enables solvent to be dispensed into hollow channel **2060** without risk of contaminating other vials. Solvent is dispensed into hollow channel **2060** and is passed through filter layer **1634** or, alternatively, through a filter disk (not shown) to receiver **2061**. Receiver **2061** is located in bottom middle layer **1632** and is typically made of chemically resistant material (e.g., plastic) that is designed to prevent wicking away of the solvent passing through filter layer **1634**.

[**0281**] The seal between the needle **2020** and small o-ring **1744** should be capable of withstanding sufficient pressure to allow the liquid to be injected into the channel **2060**. Bottom mid-layer **1632**, sealing plate **1636**, and top mid-layer **1638** are typically made of metal (such as stainless steel or aluminum). The filter material in filter layer **1634** or filter disk can be made of an appropriate filtering material that is stable with respect to the solvent media, including materials such as glass microfiber filter pads, cellulose, Teflon®, paper, and other materials used for sample filtration with organic solvents. Filter layer **1634** can comprise a single sheet of filtering material so long as the process is run to avoid cross talk between different array members. Alternatively, several pre-cut filters may be positioned above channel **2061**.

[**0282**] **FIG. 20C** illustrates how pipette **2060** can either dispense or retrieve solvent directly from vial **1616**. For example, needle **2020** can extend through hole **1625**B, barrier sheet **1618**, septum sheet **1620**, and filter assembly **1630** to directly access vial **1616**. This advantageously provides fluid communication between needle **2020** and vial **1616** without using filtering sheets of filtering assembly **1600**.

[0283] Pipette system **2060** can dispense or retrieve liquids at a specified temperature to prevent undesired crystal formation or precipitation. Pipette system **2060** may utilize, for example, heat sink **2042** and a cartridge heater (not shown) (e.g., a FIREROD heater) to maintain a specified temperature. A cartridge heater may be housed in cavity **2043**. Extending from the needle **520** is a wire (not shown) that is wound around heat sink **2040**. Because the wire is coupled to heat sink **2040**, heat generated in heat sink **2040** is conducted to needle **2020**. Thus, needle **2020** is maintained at a temperature that prevents aspirated liquid from cooling. Other designs may be employed to maintain the liquid at the desired temperature, such as a heated tip on a needle, as shown in U.S. Pat. No. 6,260,407, which is incorporated herein by reference in its entirety.

[0284] **FIG. 21** illustrates crystallization assembly **2100** that is designed to permit the formation of crystals in accordance with the principles of the present invention. Mixtures may be obtained from vials **1616** of filtration assembly **1600** and dispensed in crystallization assembly **2100**. Alternatively, mixtures may obtained from vials **1516** of reaction assembly **1500** (shown in **FIG. 15**). Crystal formation may occur, for example, by cooling the mixture, evaporating the mixture, by precipitating the mixture, or by slurrying the mixture.

[0285] One benefit of having separate filtering and crystallization assemblies is that the array of filtrates taken from filtration assembly **1600** can be placed into two or more crystallization assemblies **2100**, allowing for crystallization under different conditions or methodologies. For example, this methodology allows for a temperature study to be performed in which more than one array of solutions is crystallized, each at a different temperature. As mentioned earlier, using interchangeable parts in the different assemblies allows for efficiency in inventory and parts uniformity. The different assemblies also permit flexibility in process flow for each part of the recrystallization procedure.

[0286] Crystallization assembly **2100** has lower reactor base **2160**. Reactor base **2160** has recessed region **2161** that is constructed to receive substrate **2164**, which is resting on top of pad **2162**. Pad **2162** should be selected to help avoid breaking the substrate. This pad is preferably foam, silicone rubber, or another resilient material.

[0287] Substrate **2164** provides a suitable surface for crystal formation. Moreover, substrate **2164** can be transferred to the desired analytical equipment to enable characterization of the array of crystals. The substrate may be constructed from an optically transparent material, such as glass, to allow for direct optical studies of the crystals on the substrate. It can also be made of other materials such as plastic. Substrate **2164** may have a substantially flat surface on which the crystals are contained. Substrate **2164** may have distinct regions on its surface to support crystals formation. For example, those distinct regions may be round, square, etc. The regions may also be recessed to readily retain crystals. Thus, dimples or wells can be used. (A dimple herein is defined as a depression with a rounded concave surface, and a well is a recess with one or more defined sidewalls.)

[0288] Above substrate **2164** is gasket **2166** having an array of holes (not shown) that correspond to the array of regions on substrate **2164**. When assembled, these lower components (pad **2162**, substrate **2164**, and gasket **2166**) will fit into recessed region **2161** so that gasket **2166** is secured substantially flush against the upper outside edges of reactor base **2160**. Crystallization reactor **2168** is placed over these components and secured to reactor base **2160** using bolts **2170** or other securing means (clips, clamps, nuts, etc.). The securing means should provide sufficient force to compress gasket **2166**, which in turn seals the regions on substrate **2164** from potential crosstalk.

[0289] Crystallization assembly **2100** also includes sheet **2172** (typically made of Teflon®) and septum **2174** (which may be identical to barrier sheet **2118** and septum **2120**, respectively) and reactor cover **2176** covering crystallization reactor **2168**. Reactor cover **2176** is similar to reactor cover **2122** for reaction assembly **1500**, having holes through which needle **2020** may pass. The parts over crystallization reactor **2168** are secured to crystallization reactor **2168** by bolts **2178** (although other clamping, clipping or securing means may be used). Thus there are two sets of secured components in crystallization assembly **2100**. The first set includes crystallization reactor **2168**, gasket **2166**, substrate **2164**, pad **2162**, and reactor base **2160**. The second set includes sheet **2172**, septum **2174**, and reactor cover **2176**, which together are coupled to crystallization reactor **2168**. These separate sets permit the bottom part of crystallization assembly **2100** to be assembled without the upper portion, resulting in more flexibility in being able to use part or all of crystallization assembly **2100** for pre-formulation testing.

[0290] Reactor cover **2176** and septum **2174** may not be used if evaporation studies are to be tested with the material samples contained within cyrstallization assembly.

[0291] **FIG. 21A** illustrates an alternative embodiment of a crystallization assembly **2102** that is designed to permit formation of crystals in accordance with the principles of the present invention. Crystallization assembly **2102** includes similar parts as crystallization assembly **2100** such as reactor base **2160**, substrate **2164**, and reactor **2168**. Not included with crystallization assembly **2102** is pad **2162** and gasket **2166**. Instead substrate **2164** is positioned directly on top of reactor base **2160** and o-rings **2104** are added to crystallization assembly **2104**. O-rings **2104** may be comprised of a sheet of o-rings (as shown in **FIG. 21B**) or it they can be a two-dimensional arrays (e.g., 4×4 array of individual o-rings). When crystallization assembly **2102** is assembled, o-rings **2104** are pressed flush against substrate **2164** and reactor **2168** to provide effective isolation of material samples deposited into the crystallization assembly **2102**.

[0292] **FIG. 21C** is a partial cross-sectional view of crystallization assembly **2102** that illustrates how the through-holes of reactor **2168** and respective portions of substrate **2164** are isolated from each other by o-rings **2104**. Also shown in **FIG. 21C** are the wells **2106** in which o-rings **2104** reside. Thus when substrate **2164** is pressed against reactor **2168**, o-rings **2106** are pressed against substrate **2164** and wells **2106**, thereby providing a substantially airtight seal that isolates each region of the substrate.

[0293] When aspirating from or dispensing material into a sealed vial through a septum using a needle or similar device, the accuracy in controlling the volume of material transferred can be affected by the changing volume and pressure within the vial. One solution to this problem has been to use a coaxial needle, which consists of two tubes

attached together along their axises. One tube is used to transfer material to or from the vial, and the second tube is used as a vent to equilibrate pressure between the vial interior and the surroundings.

[0294] The coaxial needle device presents several shortcomings. Because the two-tube assembly is much larger than a single needle, it will create larger holes when piercing a septum that may not seal properly when the needle is removed. Also, because the tips of the tubes remain at a fixed distance with respect to one another, the range of depths in the vial to which material can be introduced or withdrawn is limited. Dispensing a large amount of material into a deeper vial, for example, may lead to material flowing out of the vent tube if the tip of the vent tube becomes submerged. These shortcomings of the prior art are addressed by the venting needle device described in conjunction with **FIGS. 22A and 22B**.

[0295] **FIG. 22A** shows a venting needle assembly **2200** that can be used to aspirate from, or dispense materials into, sealed vials or receptacles. Venting needle assembly **2200** comprises venting needle **2202**, liquid handling needle **2204**, body **2206**, guide rods **2208**, springs **2210**, and guide block **2212**. Body **2206** is attached to a liquid handling system (not shown) that controls aspiration and dispensation of liquid through liquid handling needle **2204**. Liquid handling needle **2204** extends a fixed distance from body **2206** and passes through movable guide block **2212**. Venting needle **2202** also passes through movable guide block **2212**, essentially parallel to liquid handling needle **2204**, and extends a fixed distance from the lower face of guide block **2212**. Guide block **2212** is attached to guide rods **2208**, and configured so that it can slide along the central axis of liquid handling needle **2204**. Guide rods **2208** are configured to slide into body **2206** when force is applied to the lower face of guide block **2212**. Springs **2210** are located on guide rods **2208**, between body **2206** and guide block **2212**. These springs return guide block **2212** to a fully-extended position, determined by the length of guide rods **2208**, when there is no force on the lower face of guide block **2212**.

[0296] As described above, reactor assembly **1500**, filtration assembly **1600**, and crystallization assembly **2100** each include a sealing layer (e.g., septum) for isolating each vial or receptacle from each other. For purposes of brevity and clarity, venting needle assembly **2200** is described in conjunction with reactor assembly **1500**. Venting needle assembly **2200** is not limited to being used only with reactor assembly **1500**, but it can be used with any suitable assembly comprising sealed vials or receptacles. If desired, venting needle assembly **2200** can be used in place of pipette system **2060**.

[0297] After reactor assembly **1500** is sealed, each vial contains a fixed volume of material. Venting assembly **2200** prevents the pressure from changing when aspirating liquid from or dispensing liquid into a sealed vial, which permits increased accuracy in controlling the volume of material transferred. Venting assembly **2200** accomplishes this by using a dual needle assembly, wherein one needle is used to aspirate/dispense and the other is used to vent the vial.

[0298] In a typical material transfer process, venting assembly **2200** is lowered over reactor assembly **1500**, either manually or by mechanical means, until the lower surface of guide block **2212** contacts the upper surface of reactor cover **1522**. Both venting needle **2202** and liquid handling needle **2204** extend far enough from guide block **2212** to extend through holes **1523** above the vial of interest, and pierce septum sheet **1520** and barrier sheet **1518** (if present). When venting needle **2202** pierces septum sheet **1520** (and barrier sheet **1518**, if present), it provides an open passageway between the upper portion of the vial and the surrounding atmosphere, which maintains equilibrium between the pressure in the vial and the ambient pressure (i.e., pressure outside the sealed vial). Thus, when liquid is aspirated from or dispensed into the vial by liquid handling needle **2204**, the pressure does not change because venting needle **2202** provides the substantially constant pressure with the vial.

[0299] Body **2206** may be pushed towards the top of reactor assembly **1500** until liquid handling needle **2204**, which is attached to body **2206**, reaches the desired depth within the vial for dispensing or aspirating a liquid. Body **2206** may contain a mechanism (not shown) the heat liquid handling needle **2204** to a predetermined temperature. As liquid handling needle **2204** extends into the vial, guide rods **2208** slide further into body **2206** and as springs **2210** compress, as shown in **FIG. 22B**. During this procedure, venting needle **2202** extends a fixed depth into the sealed vial, preferably with the tip of venting needle **2202** located near the top of the vial, above any liquid which may be present. This device thus permits transfer of a liquid to and from vials having different depths while maintaining a venting passage that equilibrates pressure between the interior of the vial and the ambient atmosphere. When the transfer of liquid is complete, body **2206** may be pulled away from reactor assembly **1500**, causing liquid handling needle **2204** to withdraw from the vial and springs **2210** to expand until guide block **2212** reaches its fully-extended position, as shown in **FIG. 22A**. Pulling body **2206** further away from reactor assembly **1500** removes both venting needle **2202** and liquid handling needle **2204** from reactor assembly **1500** through holes **1523**. The device may then be inserted into another hole over a different vial and the above procedure repeated.

[0300] Temperature is an important parameter in the various formulations, filtration, and crystallization operations that enable salt selection and polymorph production. For example, in some methodologies it is desirable to heat reaction assembly **1500** to dissolve as much drug candidate as possible in the solvent(s). In processes where temperature is important (e.g., during crystallization), any of assemblies **1300**, **1500**, **1600** or **2100** (shown in **FIGS. 13, 15, 16**, and **21**, respectively) may be placed in an oven, cooler, or other temperature-controlled chamber (such as the Torrey Pines incubator cited herein).

[0301] It may be desirable in some processes to have precise control of temperature. One method for controlling the temperature of the assemblies during certain stages of the workflow is shown in **FIG. 23**, which depicts three-axis robot **2300**, having arms **2305** and **2310** and plurality of pumps **2334**, situated by work surface **2330**. Pumps **2334** are in fluid communication with a solvent or other liquid and in fluid communication with needles **2320** and **2322**. Heated block assembly **2350** is positioned on work surface **2330**. Heated block assembly **2350** is configured to contain reaction assemblies **1500**, filtration assemblies **1600** and those assemblies to assist mixing material samples. It may be

desirable to heat filtration assembly **1600** to prevent crystallization during the filtering process. Not shown in **FIG. 23** is a magnetic stirring device that can tumble magnetic stirring fleas to agitate materials contained within the assemblies. Also located on work surface **2330** are several temperature-controlled housings **2500**. Temperature-controlled housing **2500** is described in more detail in conjunction with the description accompanying **FIG. 25**. Housing **2500** can contain an assembly such as the reactor assembly **1300**, reaction assembly **1500**, filtration assembly **1600**, or crystallization assembly **2100**. **FIG. 23** also shows deck assemblies **2370** that hold various assemblies for use in a workflow.

[**0302**] Detailed structure of the temperature-controlled housing is not critical to this invention, and may simply comprise insulated walls with a resistive heater regulated by a thermocouple for temperature control. These types of heaters are sold commercially as the FIREROD™ heaters available from Watlow of St. Louis, Mo.

[**0303**] **FIG. 24** illustrates an exploded view of temperature-controlled housing **2350** shown in **FIG. 23**. Temperature-controlled housing **2350** includes tub **2410** and tub support fixtures **2430** and **2440**. Tub **2410** is constructed from a material (e.g., aluminum) having desired thermal conductive properties. As shown, tub **2410** has pockets **2412** and **2414** for containing an assembly (e.g., reactor assembly **1500** or filtration assembly **1600**). Tub **2410** has fluid channels (not shown) in which a fluid or gas is provided to heat or cool the tub. Fluid inlet/outlet ports **2354** provide connections to allow a desired heating or cooling fluid or gas to flow through the channels, thereby heating or cooling an assembly placed in housing **2350**. The temperature-controlled housing shown in **FIG. 24** may be surrounded by an insulating layer to improve thermal control and stability.

[**0304**] Another embodiment that facilitates temperature control of a reactor or assembly is shown in **FIG. 25**. **FIG. 25** illustrates thermal control chamber **2500** having top **2570** and bottom **2580** that mate to form an enclosure. Top **2570** has cavity **2572** therein and bottom **2580** has cavity **2582** therein, which together define the enclosure. Cavity **2572** is preferably sized to accommodate at least one of the assemblies **1300**, **1500**, **1600**, or **2100** (shown in **FIGS. 13, 15, 16**, and **21**, respectively).

[**0305**] In a preferred embodiment, top **2570** has holes **2574** to allow for communication through top **2570**, (e.g., by a needle, cannula or pipette), for aspirating or dispensing liquids into the regions, vials or wells of the assembly in the cavity when top **2570** and bottom **2580** are closed together. A fluid that heats or cools the thermal control chamber may flow through top **2570** and/or bottom **2580**. The fluid flow preferably maintains a specific temperature substantially throughout the assembly contained therein. A temperature variation of about 2° C. across the enclosed assembly is generally acceptable, but a temperature variation of less than about 1° C. is desirable. Top **2570** and bottom **2580** are made of a material (e.g., aluminum) with good heat transfer properties. Suitable fluids with well-characterized thermophysical properties (e.g., water, glycol, etc.) flow through top **2570** and/or bottom **2580** for heating or cooling.

[**0306**] Thermal control chamber **2500** can apply a thermal profile to the assembly contained therein. The thermal profile may, for example, subject the assembly to a range of temperatures that vary with time or to a temperature that is substantially the same for the chosen time period throughout the thermal control chamber. For example, the temperature of the thermal control chamber may ramp up to a predetermined temperature a specified rate, stay at the predetermined temperature for fixed period of time, and then ramp down to ambient temperature after a specified period of time.

[**0307**] **FIG. 25** shows thermal control chamber **2500** wherein top **2570** and bottom **2580** are connected by hinge **2586** that allows the top and bottom to pivot with respect to each other. This configuration allows for easier alignment and fastening of the top and bottom of the thermal control chamber that contains an assembly such as crystallization assembly **2100** (shown in **FIG. 21**). When top **2570** is pivoted about hinge **2586**, it aligns with bottom **2580** so that cavities **2572** and **2582** meet to enclose the assembly within the chamber.

[**0308**] A typical fluid flow path can occur as follows. Thermal fluid enters either top **2570** or bottom **2580** first and then flows through the inlet, transverse, and outlet conduits. Then fluid passes through external conduit **2588** and into the other half of the chamber where the flow pattern is repeated. Thus, if the thermal fluid enters top **2570** first, it will flow through the top, exit the top and be channeled into bottom **2580**, flow through the bottom, and then exit the bottom. The flow direction may also be reversed if desired, so the thermal fluid enters the bottom before the top. Rotating fluid transfer hinge **2587** may be provided on either side of hinge **2586** which allows top **2570** and bottom **2580** to pivot with respect to each other without adjusting external conduits **2588**. This function could also be accomplished with flexible external conduits and a loop, however, the arrangement shown in **FIG. 25** is a preferred embodiment as it avoids the need for flexible tubing.

[**0309**] Although not shown in **FIG. 25**, chamber **2500** has a window that provides a means for a device to monitor the arrays of material samples contained within chamber **2590**. A glass sheet is coupled to this window with a gasket. Preferably a purge of dry gas (e.g., nitrogen) is provided to prevent condensation from developing when chamber **2590** cools. This ensures that the monitoring equipment has an unobstructed access to the material samples. For example, in-situ measuring requires an unobstructed access to monitor the materials samples that are subjected to crystallization conditions.

[**0310**] The structure that facilitates fluid flow is shown in more detail in **FIG. 26**, which depicts a cutaway view of the channels that define the fluid path in top **2570** and/or bottom **2580** of thermal control chamber **2500**. The heating/cooling fluid enters via fluid inlet **2590**, which leads to inlet conduit **2592**. A plurality of transverse conduits **2594** lead from inlet conduit **2592** to outlet conduit **2598** and to fluid outlet **2599**. Inlet conduit **2592** and outlet conduit **2598** are preferably larger in diameter than the transverse conduits **2594** so that the fluid entering inlet **2590** will flow uniformly through all of transverse conduits **2594**. This flow pattern for the heating/cooling fluid assists in uniform heating or cooling of control chamber **2500**

[**0311**] Transverse conduits **2594** pass on either side of holes **2574**, if present. Larger conduits **2592** and **2598** may be formed by drilling holes through a block and then plugging one end of each with a large plug **2595** for ease of

manufacture. Smaller transverse conduits **2594** can be formed in a similar manner, with both ends of the drilled holes capped off by small plugs **2596**.

[**0312**] In operation, a thermal fluid such as water, glycol, or glycerol is transported from a uniform temperature reservoir (not shown) to top **2570** or bottom **2580** of thermal control chamber **2500** through a fluid line using a constant or variable-speed pump. The thermal fluid enters inlet conduit **2592** through inlet port **2590**. The thermal fluid flows through transverse conduits **2594** and into outlet conduit **2598**. The thermal fluid then exits through fluid outlet **2599**, where it then returns to the reservoir or is routed through another top or bottom.

[**0313**] A heat pump or other device may be used to regulate the temperature of the thermal fluid in the reservoir by adding or removing heat through a heat transfer coil located in the reservoir. In one embodiment, a processor receives signals from temperature sensors located in the reservoir, and adjusts the amount of heat added to or removed from the thermal fluid through the coil. One or more temperature sensors (not shown) may also be mounted in the top or bottom of the thermal control chamber and connected to the processor. Temperature control can then be achieved by varying both the temperature of the thermal fluid in the reservoir and the flow rate through the conduits. To adjust the flow rate of thermal fluid through the fluid flow system, the processor communicates with a valve located in a reservoir outlet line. Various parts of the system can also be insulated to improve temperature control and stability.

[**0314**] **FIG. 27** shows a cross-sectional view of thermal control chamber **2500** with crystallization assembly **2100** enclosed therein. This view shows insulation **2591** can be packaged with thermal control chamber. Cross-sectional view **2700** illustrates additional details of the components just described above in conjunction with **FIGS. 21, 22, 25**, and **26**.

[**0315**] Determining the melting point of salts and drug candidates is an important characterization technique for the screening process. In particular, differences in melting point among crystals or amorphous precipitates of a given compound comprise one of the best indicators for determining the existence of polymorphs.

[**0316**] In one embodiment of the present invention, a melting point station is employed to determine the melting point of the solid material contained in each region of an array following salt formation, precipitation, crystallization, or other similar procedure in the process. Melting points of various materials may be determined by controllably raising the temperature of the substrate containing the array while monitoring the birefringence image (if present) of one or more regions of the array. The temperature at which the birefringence image from a region of the array disappears indicates a transition from the solid to the liquid state. This transition state corresponds to the melting point of the solid matter (generally crystals or amorphous solid) in that region.

[**0317**] Generally, this measurement is based on melting point measurements known in other fields of endeavor. See, e.g., Magill, J. H. "A new method for following rapid rates of crystallization. II. Isotactic Polypropylene."*Polymer* 1962, 3, 35-42; Ding, Z. and Spruiell, J. E. "An experimental-method for studying nonisothermal crystallization of polymers at high cooling rates", *J. of App. Polymer Science Part B—Polymer Physics,* 1996, 34, 2783-2804; Garetz, B. A., et al., "Birefringence and diffraction of light in ordered block-copolymer materials"*Macromolecules,* 1993, 26, 3151-3155; Carlson, E. D. et al. "Mechanical and Thermal Properties of Elastomeric Polypropylene"*Macromolecules*, (1998), 31(16), 5343-5351; and Carlson, Eric David, "A rheo-optical investigation of the relaxation and crystallization behavior of stereoblock polypropylene synthesized from 2-arylindene metallocene catalysts," Stanford Ph.D. Dissertation (1998); each of which is incorporated by reference.

[**0318**] A melting point apparatus designed to determine melting points of an array of solids on a substrate is shown in **FIG. 28**. Melting point apparatus **2800** determines the melting points of an array of samples by monitoring the optical properties of the samples for phase transitions. Melting point apparatus **2800** can also measure recrystallization kinetics during thermal cycling. Melting point apparatus **2800** can use a light scattering or birefringence measuring technique to determine when a sample transitions from a crystalline structure to an amorphous liquid. When performing birefringence measuring, a transmissive or a reflective technique can be used.

[**0319**] Apparatus **2800** detects the melting point of material samples as follows. First, a sample array is prepared via crystallization. Those of skill in the art will appreciate that a sample array can be prepared by other methods other than crystallization. For example, an evaporation or a precipitation method can be used. It will also be appreciated that solid materials (e.g., may be prepared by hand or automatically by a robot. The sample array may be contained on a glass slide (e.g., universal substrate) or other transparent material that is placed into a carrier block. If desired, the carrier block can be covered to contain any moisture that forms from products of material decomposition such as condensation, solvent vapors, etc. Finally, the carrier block is placed into a temperature chamber such as thermal control chamber **2500** or is placed within two insulated plates **(FIGS. 28A and 28B)**, which form a quasi-isothermal block.

[**0320**] After the material samples are placed in the temperature chamber, an individual light source and a detector are aligned to each material sample in the array. Operating in transmission mode, each light source transmits a light signal through a material sample. The light source can any suitable device such as, for example, light emitting diodes, lasers, or incandescent lights. Collimated, polarized, intense, monochromatic light is preferable for operation, but weak light (e.g., incandescent light) can also be used. The light signal can comprise a wavelength ranging between about 300-2000 nanometers (nm). If desired, a single light source can be distributed to each material sample by, for example, a fiber-optic bundle, a telecentric lens, a telescope, collimating optics, or other similar apparatus. Alternatively, a single light source or an array of light sources may be moved across each material sample to illuminate a single material or a row of such materials at a time. Persons skilled in the art will appreciate that any suitable arrangement of light sources can be used to provided light-scattering or birefringence testing.

[**0321**] If a reflective technique is used, the light path does not pass through the material samples. Rather, the reflection

of light off a crystalline structure is detected. This technique is described in detail in conjunction with in-situ measuring assembly **3000** of **FIG. 30**. The reflective technique operates generally as follows. Light emitted from a light source passes through a first polarizer, then it reaches a beam splitter that redirects the light towards a material sample. If desired, the light can be "pre-polarized" (e.g., a laser) so that a first polarizer is not needed. Light reflected from the material sample passes back to the beam splitter, but passed through the beam splitter. If the light signal has been altered (e.g., polarized) by the material sample, then it may pass through a second polarizer that is rotated 90° from the first polarizer and detected by a detector.

[**0322**] Light provided by the light source first passes through a polarizing filter, then through the material sample, through a second polarizing filter that is oriented at 90° with respect to the first polarizing filter. If the material sample does not contain a crystalline structure, then the light signal will be extinguished by the second polarizing filter, thereby preventing a detector from detecting the light signal. If the material sample contains a crystalline structure, however, the crystal will rotate the polarization of the light, thereby allowing some of the light to pass through the second polarization filter. Any light that passes through the second polarization filter is detected by the light detector.

[**0323**] Various detection methods can be used to detect light emitted by the light source(s). Individual detectors such as photodetectors (e.g., silicon photodiode, photovoltaic cell, etc.) may be positioned with respect to each material sample. Each photodetector is connected to a computer (e.g., computer **110**) that monitors the output of each detector. Based on the output signals of the photodetectors, the computer can determine at what temperature a crystalline structure melts. Likewise, if a detector such as a camera, a charge-coupled device (CCD) a digital camera, or a video camera is used to detect phase transitions, aa computer may register the transitions and calculate the melting point temperature.

[**0324**] Initially, before the chamber begins to heat the material samples, each detector can ascertain whether a crystal structure is present. Because each detector is connected to a computer or other data logging device, each detector can constantly monitor each material sample. This is useful because when the material samples are heated, they eventually melt, and the detectors detect this phase transition. When the crystal melts, it becomes amorphous, and light is no longer able to pass through the second polarizing filter. When a detector no longer detects a previously existing light signal, it is at this temperature that the crystal has melted.

[**0325**] The temperature of the material samples are ramped up at user defined rate to a user defined maximum temperature. The rate of temperature increase is precisely controlled and uniform throughout the material samples. This enables apparatus **2800** to accurately measure melting point temperatures. Alternatively, the temperature can be step up in controlled increments. Furthermore, the temperature of each material sample can be controlled individually.

[**0326**] The above discussion was primarily directed to birefringence testing, but the present invention is not limited to such. Different birefringence testing can be performed. For example, the polarization angle of one or both polarization plates can be modulated. The frequency of the light can be modulated. In another approach, the above mentioned light scattering approach can be implemented by removing the polarizer plates. Light scattering, for example, is another testing method that can be implemented to detect crystalline structures contained in the sample array.

[**0327**] Apparatus **2800** includes two main assemblies: thermal platform **2810** that can support and controllably heat and cool an array (i.e., a substrate containing samples), and opto-mechanical platform **2830** that permits simultaneous optical imaging of some or all of the regions on the array.

[**0328**] Thermal platform **2810** includes thermal platform top **2812** and thermal platform base **2814**, which when assembled together create cavity **2816** that supports a substrate or suitable testing platform (e.g., a carrier plate). Thermal platform **2810** is made of any suitable material that has high thermal conductivity such as aluminum, aluminum alloys, or copper. Other materials such as indium, lead, tin, or silver may be used to form part or all of thermal platform **2810** to enhance conductivity and improve temperature uniformity. The substrate may be constructed from borosilicate glass, or is a Zinnser™ plate, or is made of some other optically transparent or translucent material. The substrate is preferably positioned to provide optimal thermal conduction with thermal platform **2810**. For example, substrate **2164** (**FIG. 21**) can be placed in thermal platform **2810**.

[**0329**] Thermal platform **2810** is shown in detail in **FIGS. 28A and 28B**. **FIG. 28A** shows an isometric view of melting point apparatus **2800** (computer not shown) that shows thermal platform **2810** and light source array **2832**. As described above, thermal platform **2810** includes thermal platform top **2812** and thermal platform bottom **2814**, which are also shown in **FIG. 28A**.

[**0330**] Thermal platform **2810** is shown to be in an OPEN position. That is, pneumatic press **2860** is in a position such that thermal platform top **2812** and thermal platform bottom **2814** are not pressed against each other. Pneumatic press **2860** is used to assist opening and closing thermal platform **2810**.

[**0331**] **FIG. 28B** shows a cross-sectional view of the **FIG. 28A** taken along line **28-28**. Thermal platform **2810** is also shown to be in the OPEN position. One skilled in the art will appreciate that when thermal platform **2810** is closed, thermal platform top **2812** and thermal platform bottom **2814** are pressed flush against one another to fully enclose substrate **2864** contained therein. Preferably, a glass cover sheet is placed over substrate **2864** to contain any products of composition (e.g., condensation, out-gassing).

[**0332**] Both thermal platform top **2812** and thermal platform bottom **2814** have through holes **2823** in which resistive heating elements can be contained. Theses resistive heating elements, which are described in more detail below, provide a mechanism for heating substrate **2864** at a controlled rate while maintaining a uniform temperature distribution.

[**0333**] Referring back to **FIG. 28**, thermal platform base **2814** is designed to be heated by elements attached to or embedded within thermal platform base **2814**. In a preferred embodiment, thermal platform base **2814** contains channels (not shown) that are similar to conduits **2592**, **2594**, and **2598** in **FIG. 26**. A thermal fluid from a reservoir (not

shown) can flow through these channels to heat the substrate in a controlled manner, as described above. A thermal fluid at a lower temperature can also flow through these channels or an adjacent set of such channels to cool thermal platform base **2814**.

[**0334**] Alternatively, one or more resistive heating elements **2822** may be attached to or embedded in thermal platform base **2814** to provide a mechanism for heating thermal platform base **2814**. Resistive heating elements **2822** may include, for example, wire-wound resistive heaters, thermoelectric devices (e.g., peltier junctions) and thin- or thick-film resistor heaters. Resistive heating elements **2822** may be embedded or attached to thermal platform base **2814** to permit improved control of thermal uniformity or specific temperature profiles in thermal platform **2810**. Different resistive heating elements **2822** may be capable of distributing different quantities of heat (i.e., the power consumption may vary). Various resistive heating elements **2822** that have different power consumption may be placed strategically on thermal platform top **2812** and thermal platform base **2814** to promote uniform temperature distribution. A combination of channels for heating/cooling by flow of thermal fluid and resistive heating elements **2822** may also be used. Those skilled in the art will recognize that other methods of heating or cooling thermal platform base **2814** in a controlled manner may also be used.

[**0335**] Another method for heating or cooling the material samples is to subject the samples to a gaseous bath such as that provided by a convection oven. Yet another method is to heat each material sample individually, or in a serial fashion with individual heaters.

[**0336**] Thermal platform **2810** may also have one or more embedded or attached thermal sensors **2820** that can be used in connection with appropriate external equipment (e.g., datalogger, computer, etc.) to monitor the temperature of the platform. These sensors may be in the top or bottom of platform **2810**, and may include one or more of the following: thermocouples, resistance temperature detectors (RTD's), or semiconductor-based thermistors. One or more of these sensors may be located either in the top, in the bottom, or in both the top and bottom of thermal platform **2810**. Signals obtained from these sensors are preferably connected to a computer (e.g., computer **110** of **FIG. 1**) to permit automated monitoring and control of the temperature. The sensor signals can be processed using appropriate control software to regulate current in resistive heater elements, if present, or to regulate the temperature and flow rates of thermal fluids in channels, if present, or to provide more accurate control of both heating and cooling rates in thermal platform **2810**.

[**0337**] Various sensor arrangements can be used to accurately determine the melting point of crystalline structures. The temperature of each material sample may be individually measured, interpolated from an array of neighboring sensor, or extrapolated from a single sensor. Sensors may be located on thermal platform **2810** or some other heat transfer medium (e.g., convection oven). Sensors may be located directly on the sample substrate such as directly below a well containing a material sample.

[**0338**] Thermal platform **2810** implements a heating system that is capable of raising the temperature of thermal **2810** platform and an enclosed substrate from ambient temperatures to a user defined temperature. at a user defined rate. For example, the user can select the maximum temperature to be about 200° C., 280° C., 300° C., or any other suitable temperature. The rate at which the temperature can be increased or decreased can also be set by the user. For example, a user may set the rate of temperature deviation at about 0.5° C. per minute, 1.0° C. per minute, 2.0° C. per minute, or some other suitable temperature variation. Persons skilled in the art will appreciate that thermal platform **2810** may heat or cool an enclosed substrate to any suitable temperature. In addition, thermal platform **2810** may heat or cool an enclosed substrate at any rate. Moreover, thermal platform **2810** may cycle the temperature to perform recrystallization studies.

[**0339**] Thermal platform top **2812** is constructed with an array of upper optical holes **2813** that corresponds to an array of lower optical holes **2815** of thermal platform base **2814**. Holes **2813** and **2815** are similar to holes **2574** in thermal control chamber **2560** shown in **FIG. 25**, are located above and below some or all of the regions on a substrate when the substrate is placed in thermal platform **2810**. Holes **2813** and **2815** are associated with a region of a substrate are constructed to provide an optical pathway that passes through thermal platform **2810**. This optical path is preferably in a direction substantially perpendicular to the enclosed substrate, and intersects at least a portion of the region of the substrate associated with the upper and lower holes.

[**0340**] Opto-mechanical platform **2830** in **FIG. 28** includes light source array **2832** and sensor array **2834** arranged on opposite sides of thermal platform **2810**. Opto-mechanical platform **2830** may be similar to that taught in U.S. Pat. No. 6,157,449, which is incorporated herein by reference in its entirety. Light source array **2832** may includes one or more laser diodes, light emitting diodes (LEDs), or other controlled light sources **2833**. Alternatively this array may comprise one or more light sources that are segregated by mirrors or prisms to form an array of beams. Sensor array **2834** includes a group of sensors **2835** such as photo diodes, charge-coupled devices (CCDs) or other optical sensors, which are preferably positioned on the side of thermal platform **2810** that is opposite light source array **2832**. First polarizing sheet **2840**, typically a commercially-available polarizing filter or polarizing mirror, is mounted between the light source array and the thermal platform. Second polarizing sheet **2842** is mounted between thermal platform **2810** and sensor array **2834** at a cross-polarizing orientation of approximately 90° with respect to first polarizing sheet **2840**.

[**0341**] If desired, the orientation of second polarizing sheet **2842** may not be positioned exactly at 90° with respect to first polarizing sheet **2840**. Rather, second polarizing sheet **2842** may be positioned a few degrees (e.g., 1-5 degrees) above or below a perfect 90° cross-polarization. This slight deviation from perfect cross-polarization prevents extinction of unaltered light signals provided by a light source. But this deviation still allows for detecting changes in crystals using a birefringence monitoring technique and/or a light scattering monitoring technique.

[**0342**] Light source array **2832**, light sensor array **2834**, polarizing sheets **2840** and **2842**, and thermal platform **2810** are configured so that optical path **2850** exists between one

or more of the light sources and opposing light sensors that passes through polarizing sheet **2840**, thermal platform **2810** including a region on the substrate mounted therein, and second polarizing sheet **2842**. The orientation of second polarizing sheet **2842** filters or blocks nearly all of the light that originates from light source array **2832** and traverses optical path **2850** without passing through any materials. Thus, if light passing through a material and has its polarization changed, it may pass through second polarizing sheet **2842** and be received by light sensor array **2834**. If this occurs, then the birefringence image of the material (e.g., crystal) may be obtained.

[**0343**] The melting point apparatus described above permits detection of phase transitions, including the solid-to-liquid transformation, that may occur on individual wells or regions of a substrate. A substrate containing deposits of candidate salts, neutrals, solid precipitates, or filtrates to be characterized may be located on one or more regions of the substrate. This substrate may be placed into thermal platform **2812**, which in turn is placed into opto-mechanical platform **2830** to perform optical scanning. Thermal platform **2810** is configured so upper and lower optical holes **2813** and **2815** align with optical paths **2850**. This operation may be performed manually or automatically using robot arms to provide for a more fully automated procedure which reduces the possibility of errors in handling the samples.

[**0344**] The temperature of the thermal platform containing the substrate and one or more material samples is then increased at a defined rate and monitored. In a preferred embodiment, one or more temperature sensors in contact with the substrate are used to provide real-time temperature data to an external data collection and processing device such as computer (e.g., computer **110** of **FIG. 1**). The computer may also be interfaced to the heating/cooling system described above to provide feedback for better temperature control. In a typical process, the temperature of the thermal platform is raised from ambient temperatures to about 200° C., or from ambient temperatures to about 300° C., at a rate of about 0.5° C. per minute, 1.0° C. per minute, 2.0° C. per minute, or any other suitable rate.

[**0345**] The optical signal received by each light sensor **2835** is monitored by a computer in real time. Transformation of a material candidate or other material on a region of the substrate from a solid to a liquid state will generally cause an abrupt decrease in the amount of light reaching the sensor that lies on the optical path passing through that region or well. This effect arises primarily because amorphous liquids have a much weaker "birefringence polarizing effect" on light than solid crystalline materials. The temperature at which the optical signal associated with a given region or well of the substrate changes can then be detected by the computer and recorded, yielding a measure of the melting point of that particular sample. The entire array of materials on the substrate or any subset thereof may be characterized for melting points during a single thermal ramp-up cycle, as the individual sensor corresponding to each region will provide a distinct signal as the temperature of the entire substrate reaches the melting point associated with the material located at said region.

[**0346**] Slower rates of temperature increase tend to yield more accurate melting point values by reducing transient errors associated with finite heat transfer delays between the thermal platform and the substrate. The actual ramp-up rate chosen for a given measurement set will generally reflect a compromise between accuracy and overall time required to complete the set.

[**0347**] In the case of polymorphs, it is possible to measure more than simple melting points with this test, inter-polymorph transitions may also be observed. Inter-polymorph transitions may include transitions from one polymorph to another (e.g., solid to solid transitions). In this case, a detectable shift in the intensity of filtered light reaching a sensor (where the change may be an increase or a decrease) would indicate a transition from one solid form to another, particularly if the same region of the substrate undergoes a melting transformation at some later time and higher temperature during the set of measurements.

[**0348**] **FIG. 30** illustrates an in-situ monitoring assembly **3000**, which can be used to observe crystallization of library members in accordance with the principles of the present invention. As shown, in-situ monitoring assembly **3000** is positioned below work surface **2330** of **FIG. 23**, which provides support for devices such as thermal control chambers **2500**. In this configuration, work surface **2330** has optical pathways leading to the regions (or vessels) where materials are being formed so that in-situ monitoring device **3000** can perform measurements. As further shown, assembly **3000** is capable of moving horizontally with respect to work surface **2330** for positioning under various thermal control chambers **2500**. Assembly **3000** is positioned beneath one of thermal control chambers **2500** to perform in-situ measurement. If desired, assembly **3000** can be positioned above work surface **2330** or part of work surface **2330**. In-situ measurements may provide an advance indication of library members that have formed crystal structures. This information can be provided, for example, as input for determining which library members should be selected for testing when the crystallization step is complete.

[**0349**] Also shown in **FIG. 30** is an enlarged cross-sectional view taken from circle **3**. The cross-sectional view shows how in-situ monitoring can be accomplished using light source **3010**, diffuser **3012**, polarizer **3014**, light beam splitter **3016**, second polarizer **3018**, lens **3020**, and detector **3022**. When assembly **3000** is it preferably positioned such that the crystallization assembly (e.g., crystallization assembly **2100**) contained within thermal control chamber **2500** is within full view of lens **3020**. This enables assembly **3000** to scan two or more library members simultaneously. If lens **3020** is a telescentric lens, then light received by the lens is able to transmit the light in parallel to detector **3022**, thereby reducing image distortion caused by conventional lenses. When detector **3022** captures the light signal, it is able to provide a relatively clear picture of the material samples. Detector **3022** can be, for example, a camera, a digital camera, a television camera, a charge-coupled device.

[**0350**] Assembly **3000** operates on substantially the same principles as that previously described in conjunction with the birefringence testing mechanism of **FIG. 28**. Instead of a transmission scanning technique, however, assembly **3000** uses a reflective optical scanning technique that detects reflection of light off a crystalline structure. The reflective technique operates generally as follows. Light emitted from light source **3010**, as indicated by the dotted line, passes through diffuser **3012** and first polarizer **3014**. Then the light

signal reaches beam splitter **3016**, which redirects a portion of the light signal towards the material samples, as indicated by the change in the illustrative light path. Light reflected from the material samples passes back through beam splitter **3016**. If any portion of the light signal has been altered by any of the material samples, then it may pass through second polarizer **3018** that is rotated **900** from the first polarizer. Light that passes through second polarizer **3018** is received by lens **3020** and then captured by detector **3022**.

[**0351**] Detector **3022** may capture an image of the entire array of material samples or it may capture a portion. If it captures a portion of the array, assembly **3000** may be moved accordingly so that a complete picture or detection of the array can be obtained.

[**0352**] Use of assemblies **1500**, **1600** and **2100** allow for a complete workflow in the formulation of crystals of drug candidates. In one embodiment, the workflow begins with the original drug candidate being dispensed into vials **1516** of reaction assembly **1500**, either while vials **1516** are in a separate rack or in reactor base **1514** (e.g., with bottom plate **1510** and shock-absorbent layer **1512** attached to reactor base **1514**). The drug candidate can be in a solid state or in solution or suspension, but any solvent present with the original form of the drug candidate is removed, for example, by evaporation, wicking, or other methods known to those of skill in the art. The desired recrystallization solvent or solvent mixtures selected as discussed above are then dispensed into each vial **1516** in the desired amounts (typically with sufficient solvent to form saturated solutions in the vials). Optionally, different acids, bases, or salts are added (as discussed above in the salt selection process). Also optionally, mixing objects are placed in the vials (for example, using device **1402** such as in **FIG. 14**).

[**0353**] Barrier sheet **1518** and septum **1520** are placed over vials **1516** in reactor base **1514** (with bottom plate **1510** already attached) and reactor cover **1522** is secured to reactor base **1514** with sufficient strength to form seals over vials **1516**. Assembled reaction assembly **1500** is then placed in a heater, shown in **FIG. 23** (or **FIGS. 24 and 25**) and optionally placed on a commercially available shaker (available through VWR and made by IKA, MTS, WORKS or Lab-line). For a desired amount of time (such as 2 hours or more, 4 hours or more or 8 hours or more) and at a desired temperature (such as at least 40° C., at least 60° C. or at least 80° C.), assembly **1500** is heated and optionally stirred or shaken to allow for dissolution and/or reaction.

[**0354**] Afterwards, reaction assembly **1500** is placed on a work surface and a needle or pipette is used to sample the hot liquids in vials **1516**. This is accomplished by inserting a needle or cannula through holes **1523**, septum **1520** and barrier sheet **1518** and aspirating an aliquot of liquid (such as less than 1000 μL or less than 100 μL). The aliquot can be taken by hand or automatically, such as with the equipment shown in **FIG. 23A** as described above.

[**0355**] The aliquot of liquid is maintained in the needle or pipette that is moved to filtration assembly **1600**, which is in an assembled state. The needle is placed into the first position as shown in **FIGS. 20A and 20B**, and extended through hole **1625**A, septum **1620** and barrier sheet **1618** such that it is in sealing communication with small o-ring **1744**. The liquid is dispensed through needle **2020** into opening **2020** and the liquid is filtered through the filter **1634** before entering vials **1616**. Filtering can occur at a desired temperature by placing filtration assembly **1600** into a heater such as described above in **FIG. 23**.

[**0356**] After filtration, the filtrates (typically at a desired temperature) are aspirated by placing needle **2020** through hole **1625**B, as shown in **FIG. 20C**. Needle **2020** extends through hole **1625**B, septum **1620**, barrier sheet **1618**, filter subassembly **1630** and into vials **1616** to aspirate an aliquot of the liquid filtrate (e.g., less than 1000 μL or less than 100 μL of the filtrate). This filtrate is used for solubility at temperature testing, as described herein.

[**0357**] The needle is then moved to crystallization assembly **2100**. The needle is extended through holes **2177** in reactor cover **2176** through septum **2174**, barrier layer **2172** and into the crystallization receptacle formed by side walls **2169**. Liquid filtrate is then dispensed into the receptacle. Liquid filtrate can be dispensed to a number of different crystallization assemblies, such as multiple crystallization assemblies, glass microtiter plates and the like so that crystallization occurs under a number of different conditions or methods. After dispensing into all receptacles, the crystallization assembly is subjected to crystallization conditions, such as by lowering the temperature of the assembly (e.g., below about 35° C. or below about 25° C. or below about 15° C. or below about 5° C.) for a desired amount of time (e.g., two hours or more, four hours or more or eight hours or more).

[**0358**] After the allotted time, reactor cover **2176**, septum **2174**, and barrier sheet **2172** are removed. In an alternative embodiment, the crystallization assembly can be used without reactor cover **2176**, septum **2174** and barrier sheet **2172**, with the filtrate being deposited directly into the crystallization chambers; with this embodiment allowing for other crystallization methodologies, such as evaporation. With reactor cover **2176** removed, the mother liquor or supernatant is sampled for solubility testing, as described herein. Thereafter, the remainder of the mother liquor or supernatant is removed by pipetting and/or wicking or other methods and crystallization assembly **2100** is disassembled providing an array of crystals on substrate **2164**. This array can then be screened, as described herein. See Example 6 for an illustration of using the assemblies described herein in a crystallization workflow.

[**0359**] Although the above-described invention has been described for drug candidate compounds, this invention may be practiced with any compound of interest, particularly low molecular weight compounds. Thus, the methods, apparatus and systems described herein may be used for any compound for which salt selection and/or polymorph characterization is desired.

[**0360**] The following examples provide illustrative examples on how the present invention can be used to perform the processes described above. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

Caffeine—Salt Selection

[**0361**] A solution of caffeine in dichloromethane (25 mg/mL) was dispensed into ninety-six wells of an eight by

twelve microtiter plate reactor having removable vials (shown in **FIG. 15**) that may be 750 μl in size such that each well contained about 10 mg of caffeine. After removal of the solvent by evaporation, seven different solutions of acids in either dichloromethane or tetrahydrofuran (THF) (the salt reactants) were dispensed, with a different acid solution being dispensed into each of the twelve wells in different rows of the microtiter plate and with the first row having no acid added (only the solvent dichloromethane).

[**0362**] The following acid solutions were added to the twelve wells of each rows two through eight: row two, acetic acid in dicholomethane; row three, benzene sulfonic acid in dicholomethane; row four, hydrochloric acid in dichloromethane; row five, methyl sulfonic acid in dicholomethane; row six, succinic acid in THF; row seven, tartaric acid in THF; and row eight, toluene sulfonic acid in dichloromethane. One equivalent of acid was added to each well and the total volume was 400 μl. The reactor was sealed and shaken at room temperature for four hours. The cover was removed and the solvents evaporated. Twelve different recrystallization solvents were added to the wells, with a different recrystallization solvent being added to the eight wells of each twelve different columns, as follows: column one, ethylacetate; column two, ethanol; column three, methylethylketone; column four, nitromethane; column five, heptane; column six, aectonitrile; column seven, 2-propanol; column eight, p-dioxane; column 9, 2-methoxyethyl ether; column ten, 1-propanol; column eleven, toluene; and column twelve, water.

[**0363**] The reactor was sealed and heated to 60° C. and heated at that temperature for four hours. The cover was removed and aliquots (e.g., 200 μl) of each well were removed by pipette and dispensed to a glass microtiter plate (from Zinsser Analytics). Another aliquot was removed and added to an array of vials and diluted with acetonitrile for further dilution and liquid chromatography analyses, as described above in order to obtain a solubility measurement of the compound at 60° C. The glass microtiter plate was sealed and placed in a Torrey Pines incubator at 70° C. The temperature was ramped over 8 hours to 10° C. After sitting at 10° C. for at least ten hours, aliquots of the mother liquor were removed and diluted with acetonitrile for LC analysis, as described above. The concentration of the caffeine in the mother liquor is considered to be the solubility, with the results shown in Table 4, below:

TABLE 4

0.00	4.88	14.54	25.96	0.00	17.36	3.98	18.57	10.88	4.45	4.74	26.72
0.00	4.77	12.77	25.67	0.00	16.58	4.03	18.43	10.26	4.55	5.85	26.14
8.13	4.82	14.54	25.21	0.00	18.82	3.97	19.94	11.12	4.28	5.21	25.38
7.65	5.25	14.88	18.74	0.00	12.96	3.90	13.70	11.13	4.19	4.96	25.04
4.17	5.19	9.26	24.28	0.00	16.33	3.58	3.34	2.88	4.22	2.65	25.21
5.29	4.96	14.37	25.58	0.00	16.72	4.07	21.53	11.31	4.45	4.54	24.49
2.96	5.58	11.35	18.35	0.00	5.63	5.05	25.40	12.45	5.19	4.53	25.16
0.17	5.38	7.50	25.90	0.00	3.52	3.78	3.71	0.94	4.48	0.47	25.66

[**0364**] Note that the solubility measurements at 60° C. and 10° C. can be compared to obtain the mass of the crystals obtained, which was obtained in this case.

[**0365**] The glass plate was then placed between cross polarizing filters and scanned for wet birefringence. The remaining mother liquor was removed by pipette and residual solvent was removed by wicking with filter paper. Another image was taken between cross polarizing filter, giving dry birefringence. Birefringence images of the solids in wells were obtained under a microscope equipped with crossed polarized filters. Raman spectra were obtained on individual crystals in each of the wells, in accord with the procedures described above.

EXAMPLE 2

Naproxen—Salt Selection

[**0366**] A set of experiments, similar to Example 1, was carried out using naproxen to form salts by reaction with bases. The experimental set up was the same as in Example 1, using a solution of naproxen in dichloromethane (25 mg/mL) dispensed into 96 wells such that each well contained 10 mg of naproxen. After removal of the solvent by evaporation, seven different solutions of bases in either methanol or water (the salt reactants) were dispensed, with a different basic solution being dispensed the twelve wells of different rows of the microtiter plate and with the first row having no base added (only the solvent methanol).

[**0367**] The following basic solutions were added to the twelve wells of each row: row two, sodium hydroxide in methanol; row three, potassium hydroxide in methanol; row four, calcium carbonate in water; row five, ammonium hydroxide in methanol; row six, ethylenediamine in methanol; row seven, L-arginine in methanol; and row eight, pyridine in methanol. One equivalent of base was added to each well and the total volume was 400 μl.

[**0368**] The reactor was sealed and shaken at room temperature for four hours. The cover was removed and the solvents evaporated. Twelve different recrystallization solvents were added to the wells, with a different recrystallization solvent being added to the each of the eight wells of each different column, as follows: column one, isopropyl acetate; column two, ethanol; column three, heptane; column four, acetonitrile; column five, 1-octanol; column six, anhydrous p-dioxane; column seven, toluene; column eight, 2-butanone; column nine, water; column ten, nitromethane; column eleven, 1,2-dichloroethane; and column twelve, triethylamine. The reactor was sealed and heated to 60° C. for four hours. The cover was removed and aliquots (e.g., 200 μl) were removed by pipette and dispensed to a glass microtiter plate (from Zinsser Analytics).

[**0369**] Another aliquot was removed and added to an array of vials and diluted with acetonitrile for further dilution and liquid chromatography analyses, as described above in order to obtain a solubility measurement of the compound at 60° C. The glass microtiter plate was sealed and placed in a Torrey Pines incubator at 70° C. The temperature was

ramped over eight hours to 10° C. After sitting at 10° C. overnight, aliquots of the mother liquor were removed and diluted with acetonitrile for solubility at 10° C. by liquid chromatography analysis, as described above. The solubility of each of the salts in 1-octanol and water at both 10° C. and 60° C. were obtained using LC and plotted and used to calculate the partition coefficient, which is expressed as log P and shown below in Table 5 (pH values were not obtained):

TABLE 5

log P Values Cation	Temperature 10° C.	Temperature 60° C.
None	1.51	1.64
Sodium	−0.94	−0.77
Potassium	−0.28	−0.22
Calcium	0.68	0.78
Ammonium	−0.57	−0.50
Ethylenediamine	−1.05	−0.84
L-Arginine	−0.74	−0.85
Pyridine	0.82	1.45

[0370] The values of this experiment in Table 5 can be compared to the Log P value published in the Physicians Desk Reference for Naproxen of 1.6-1.8 at pH of 7.4. This experiment demonstrates that clearly different salt forms of Naproxen were created during this example.

[0371] The glass plate was placed between crossed polarizing filters and scanned for wet birefringence. The remaining mother liquor was removed by pipette and residual solvent was removed by wicking with filter paper. Another image was taken between crossed polarizing filters for dry birefringence.

EXAMPLE 3

Phenylbutazone—Polymorph Study

[0372] A solution of phenylbutazone in dichloromethane (25 mg/mL) was dispensed into wells of a microtiter plate having removable vials (shown in **FIG. 3**) that were 750 μl in size such that each well contained 10 mg of phenylbutazone. After removal of the solvent by evaporation, 16 recrystallization solvents were dispensed into the wells in the ratios shown below in Table 6, such that the total volume was 600 μl of solvent generating a library that included 84 unique solvent compositions. For mixtures of solvents, pure solvents were dispensed prior to mixing and mixed in the wells. The ratios shown in Table 6 are v/v ratios, thus for example 80/20 means 80 parts of the first listed solvent and 20 parts of the second listed solvent (i.e., 480 μl/120 μl). The recrystallization solvents were water (W), heptane (H), ethanol (E), dichloroethane (D), acetonitrile (A), methylethylketone (K), toluene (T), dimethylsulfoxide (S), 1-propanol (IP), nitromethane (NM), α,α,α-trifluorotoluene (FT), 2-propanol (2P), p-dioxane (I), 1-octanol (10), propylacetate (PA), and cyclohexane (CH):

TABLE 6

1	2	3	4	5	6	7	8	9	10	11	12
100	80/20	60/40	40/60	20/80	100	100	80/20	60/40	40/60	20/80	100
E	E/W	E/W	E/W	E/W	W	H	D/T	D/T	D/T	D/T	T
A	A/W	A/W	A/W	A/W	W	H	H/FT	H/FT	H/FT	H/FT	FT
1P	1P/W	1P/W	1P/W	1P/W	W	H	H/D	H/D	H/D	H/D	D
I	I/W	I/W	I/W	I/W	W	H	H/PA	H/PA	H/PA	H/PA	PA
K	K/E	K/E	K/E	K/E	E	D	D/A	D/A	D/A	D/A	A
NM	NM/E	NM/E	NM/E	NM/E	E	D	D/S	D/S	D/S	D/S	S
H	H/E	H/E	H/E	H/E	E	D	D/2P	D/2P	D/2P	D/2P	2P
10	10/E	10/E	10/E	10/E	E	D	D/CH	D/CH	D/CH	D/CH	CH

[0373] The reactor was sealed and heated to 60° C. for four hours. The cover was removed and aliquots (e.g., 200 μl) were removed by pipette and dispensed into individual regions of a glass microtiter plate (from Zinsser Analytics), creating an array of ninety-six liquids. The Zinsser plate was sealed in the crystallizer and placed in a Torrey Pines incubator at 70° C. The temperature was decreased to 10° C. over an eight hour time period. After sitting at 10° C. overnight, aliquots of the mother liquor were removed and diluted with acetonitrile to determine the solubility of phenylbutazone in the various solvents at 10° C. by LC analysis.

[0374] The remainders of the solvents were removed by pipette and any residual solvent was removed by wicking with filter. The glass plate was then placed between cross polarizing filters and scanned for dry birefringence were obtained under a microscope at 5× equipped with crossed polarized filters. Raman spectra were obtained on individual crystals in each of the wells in an automated manner, as described above. Selected spectra that show the differences between polymorphs are shown in **FIG. 9**. All of the Raman spectra collected were correlated and grouped using the software described herein. **FIG. 11** shows the spectra by well in array format **2008** as well as the user inputs into the software of minimum grouping correlation coefficient (with suggested parameters in parentheses) **2002** and whether to use a fixed reference (input of 1) or to use the first well as the reference (input of 0) **2004**. **FIG. 11** also shows the ability of the user to change the width and height of the spectra images **2006**. **FIG. 12** shows the output of the software with the spectra grouped by similarity into twelve families.

[0375] The entire recrystallization process was repeated with a different glass plate in the crystallizer, this time dispensing the hot solutions for recrystallization directly into the crystallizer subassembly (shown in **FIG. 21**, as described herein) in the same well format. The crystallizer subassembly was sealed and placed in a Torrey Pines incubator at 70° C. The temperature was decreased to 10° C.

over an eight hour time period. After sitting at 10° C. overnight, aliquots of the mother liquor were removed and diluted with acetonitrile to determine the solubility of phenylbutazone in the various solvents at 10° C. by LC analysis. The remainders of the solvents were removed by pipette and any residual solvent was removed by wicking with filter paper. Disassembly of the crystallizer gave crystals in array format, with each crystal in a separate region on a flat glass substrate. The glass substrate was then mounted vertically on an X-ray diffraction machine, as described above and data was acquired on selected elements. Comparison of the XRD two theta plots clearly shows the presence of three polymorphs, shown in **FIG. 10**.

EXAMPLE 4

Cimetidine—Polymorph Study

[0376] A solution of cimetidine in dichloromethane (25 mg/mL) was dispensed into wells of a microtiter plate having removable vials that were 750 μl in size such that each well contained 10 mg of phenylbutazone. After removal of the solvent by evaporation, sixteen recrystallization solvents were dispensed as described above in Example 3 and in Table 6, above. The reactor was sealed and heated to 60° C. for four hours. The cover was removed and aliquots (e.g., 200 μl) of individual samples were removed by pipette and dispensed to the crystallization assembly (shown in **FIG. 21**, as described herein) in the same well format. Another aliquot was removed and added to an array of vials and diluted with acetonitrile for further dilution to determine the solubility of cimetidine in the various solvents at 70° C. by LC analysis. The crystallizer assembly was sealed and placed in a Torrey Pines incubator at 70° C. The temperature was ramped over 8 hours to 10° C. After sitting at 10° C. overnight, aliquots of the mother liquor were removed and diluted with acetonitrile for LC analysis. The solvents were removed by pipette and residual solvent was removed by wicking with filter. Removing the cover and disassembly of the crystallizer gave crystals on a flat glass substrate.

[0377] The glass plate was then placed between cross polarizing filters and scanned to obtain dry birefringence and birefringence images of selected wells were obtained under a microscope equipped with crossed polarized filter. Raman spectra were obtained on individual crystals in each of the wells as described in the previous example.

EXAMPLE 5

Sample Code for Polymorph Characterization

[0378] Various programming languages can be implemented to build software that can perform categorization of crystalline structures in accordance with the principles of the present invention. Listing 1, below, illustrates a portion of Java® code that can be used to implement the categorization process described in conjunction with **FIG. 8**.

LIsting 1

```
package com.symyx.webapp.projects.polymorphs;
import com.symyx.webapp.xydata.filereader.*;
import com.symyx.webapp.xydata.*;
import java.util.*;
```

LIsting 1-continued

```
import java.io.*;
public class SignalProcessorPolymorphs {
private SignalProcessorResultPolymorphs result_;
    public SignalProcessorResultPolymorphs result( ) {
    return result_; }
    public void result(SignalProcessorResultPolymorphs
    theResult) { result_=
    theResult; }
    private SignaIProcessorPararaetersPolymorphs
    parameters_;
    public SignaIProcessorParametersPolymorphs
    parameters () { return parameters_; }
    public void
    parameters (SignaIProcessorParametersPolymorphs params)
    {
    parameters_= params; }
public Signal ProcessorPolymorphs () {
    this. initialize();
}
    private void initialized(){
        this.result(new
        SignalProcessorResuItPolymorphs());
        this.parameters(new
        SignalProcessorParametersPolymorphs());
    }
public void sort(Vector items, Vector baskets) {
    if (items == null) {
        return;
    }
    int itemCount = 0;
    float cc;
    int i =0;
    int j = 0;
    XyDataSet theSet = null;
    XyDataSet[] xySets = new XyDataSet[2];
    Vector stdltems = null;
    Vector stdBaskets = null;
    Vector ccScores = new vector();
    Float score = null;
    Float topScore = null;
    int scorelndex = 0;
    int topScorelndex = 0;
    Vector. theForm = null;
    int formCount = 0;
    float minCC = this.parameters ().minGroupCC();
    boolean useFixedReference =
    this.parameters().useFixedReference();
    // standardize items to be sorted
    itemCount = items.size();
    stditems = this.standardize(items),
    //System.out.println("made stditems");
    // standardize the known forms
    if (baskets != null) { // input not empty
    stdBaskets = this.standardize(baskets);
    }
    else {
    // no known forms yet,
    // so create new vector and put the first item in
    // there
    stdBaskets = new Vector();
    stdBaskets.add(stditems.elementAt(0));
}
//System.out.println("made stdBaskets");
// make form baskets
for (j=0; j<stdBaskets.size(); j++) {
    theForm = this.result() .addNewForm();
    theForm.add(stdBaskets.elementAt(j));
}
for (i=0; i<itemCount; i++) {
// clean out the old data
ccScores.clear();
// get the next item to be classified
theSet = (XyDataSet)stdltems.elementAt(i);
xySets[0] = theSet;
//System.out.printin{"sorting item: " + i + " " + theSet);
//System.out.println("xySets [0]: " + xySets[0]);
```

LIsting 1-continued

```
// get the forms
formCount = this.result().formCount();
//System.out.println("formCount=" + formCount);
for (j=0; j<formCount; j++) {
    xySets[1] = (XyDataSet)this.result().getFormData(j,
    useFixedReference);
    //System.out.println("xySets[1]: " + xySets[1]);
    // align the data sets
    XyDataMath.alignX(xySets);
    //System.out.println("xySets[0]: " + xySets[0]);
    //System.out.println("xySets[1]: " + xySets[1]);
    // run correlation
    cc = XyDataMath.corrcoef(xySets[0], xySets[1]);
    xySets[1].fitness(cc);
    //System.out.println("cc=" + cc);
    // add to the vector
    ccScores.add(j, new Float(cc));
}
// find out which is the best
topScoreIndex = 0;
topScore = (Float) ccScores.elementAt(topScoreIndex);
for (j=0; j<formCount; j++)
    score = (Float)ccScores.elementAt(j);
        if (topScore.floatValue() < score.floatValue()){
            topScore = score;
            topScoreIndex = j;
        }
        //System.out.println(" topScoreIndex=" +
        topScoreIndex);
}
//System.out.println("top score="
//+ topScore.floatValue());
// qualified for one of the classified forms
if (Math.abs(topScore.floatValue()-1.0f) <
java.lang.Float.WIN VALUE) {
continue; // the same data set
}
else if (topScore.floatValue() >= minCC) {
    theForm = this.result().getForm(topScoreIndex);
    theForm.add(theSet);
    //System.out.println("old Form");
}
else { // found a new form
    theForm = this.result().addNewForm();
    theForm.add(theSet);
    //System.out.println("newForm added");
}
}
}
/**
* standardize the data sets by removing the slope from the
    data sets,
* and perform normalization on them
*/
private Vector standardize (Vector theSets) {
    if (theSets == null) {
        return null;
    }
    Vector stdSets = new Vector();
    XyDataSet theSet = null;
    String fileName = null;
    int count = theSets.size();
    for (int i=0; i<count; i++) {
        //System.out.println("i:" + i);
        theSet = (XyDataSet)theSets.elementAt(i);
        //System.out.println("theSet:" +
        //theSet.header().getPath());
        fileName = theSet.header().getDataName();
        theSet = XyDataMath.removeSlope(theSet);
        theSet = XyDataMath.normalize(theSet);
        theSet.header().setDataName (fileName);
        stdSets.add(theSet);
    }
        return stdSets;
    }
```

LIsting 1-continued

```
    public Vector loadData() {
        String baseDir = "D:/raman_data/sorted_forms/";
        String listFileName = "Z_all_forms.txt";
        String fileName = null;
        String filePath = null;
        Vector fv = new Vector();
        TextFileReader dataReader = new
        TextFileReaderPolymorphsRaman ();
        filePath = baseDir + IistFileName;
        FileReader fileReader = null;
        LineNumberReader reader = null;
    try {
        fileReader = new FileReader(filePath);
        reader = new LineNumberReader(fileReader);
    }
    catch (IOException e) {
        e.printStackTrace();
    }
    XyDataSet xyData = null;
    int i=0;
    try {
    while ((fileName = reader.readLine()) != null) {
        try {
            if (fileName.indexOf{"%"} >= 0) {
                continue;
            }
                i++;
                filePath = baseDir + fileName;
                System.out.println("loading. . ."
                +.filePath);
                xyData = new XyDataSet();
                dataReader.readFile(filePath, xyData);
                fv.add(xyData);
                //System.out.printIn(xyData.header().getDa
                //taName());
        }catch (Exception e) {
            e.printStackTrace();
        }
        }
    }
    catch (Exception el) {
        el.printStackTrace();
    }
    finally {
        if (reader != null) {
            try {
                reader.close();
                } catch(IOException e) {
            }
        }
    }
    return fv;
    }
    public static void main (String[] args) {
        SignaIProcessorPolymorphs spp =
        new SignaIProcessorPolymorphs();
        if (args.length > 0) {
            spp.parameters().minGroupCC(java.lang.Float.pars
            eFloat(args[0]));
            spp. parameters().useFixedReference(true);
        }
    Vector unknowns = spp.loadData();
    System.out.println(". . . . . .");
    System.out.println("sorting. . .");
    spp.sort(unknowns, null);
    spp.result().printForms();
}
```

EXAMPLE 6

Crystallization Workflow

[0379] An exemplary crystallization workflow is shown in **FIG. 31**. In the workflow, the crystallization solvents **3101** and precipitation solvents **3103** of interest are placed in

solvent rack **3105** for use in the workflow. Array **3110** comprising the drug candidate of interest (a salt or a neutral compound) from the reaction station is placed in reactor assembly **3120**. The array can be an 8×12 array (e.g., a 96-well plate) or any other array known in the art (e.g., a 384-well plate). Crystallization solvents from the solvent rack are deposited into the wells of the array and the array is equilibrated to at least partially dissolve the drug candidate in the solvent. In one embodiment, 800 μL of the crystallization solvents are added to each well, although any volume of solvent may be used in accordance with this invention.

[**0380**] After the drug candidates have been equilibrated with the crystallization solvents to form solution, the solutions are filtered in filtration assembly **3130**. In one non-limiting embodiment, 650 μL is taken from each well of the reactor assembly and filtered in the filtration assembly and a 600 μL aliquot of each sample is removed after filtration. The aliquots may then be daughtered for crystallization analysis and other analyses into one or more different apparatus. In one embodiment, 50 μL of each sample is aliquoted into liquid chromatography (LC) vials **3140** for determination of solubility at a high temperature; 250 μL from each sample is aliquoted into crystallizer assembly **3145** to investigate crystallization by cooling; 200 μL from each sample is aliquoted into evaporation plate **3150** to investigate crystallization by evaporation; and 100 μL of each sample is aliquoted into precipitation plate **3155** along with 400 μL of a precipitation solvent to investigate crystallization by precipitation.

[**0381**] After crystallization, supernatants from the samples subjected to crystallization in the crystallizer assembly and precipitation plate are collected. The supernatant from the crystallization assembly may be aliquoted into LC vials **3165** for determination of the solubility of the drug candidate at a cold temperature (e.g., room temperature or below). The supernatant may be collected at station **3160** for any purpose desired, such as recycling or discarding the drug candidate.

[**0382**] One having ordinary skill in the art following the teachings of this invention would recognize that one could use different combinations of crystallization apparatus and/or methods. For instance, one could provide a number of crystallizer assemblies that use different crystallization temperatures, or could use crystallizer assemblies to perform precipitation or evaporation crystallization. Further, one having ordinary skill in the art would recognize that one could perform different non-crystallization analyses using this workflow, such as log P analyses.

[**0383**] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

We claim:

1. A method for performing high throughput testing of a drug candidate or salt thereof to characterize polymorphs that form from said drug candidate or salt thereof, the method comprising:

preparing a library having a plurality of members, each said member comprising said drug candidate or salt thereof and at least one solvent;

subjecting said members to at least one crystallization condition to produce at least one crystalline structure of said drug candidate or salt thereof, said at least one crystalline structure having a crystal and a supernatant;

screening said crystal of each of said at least one crystalline structure to obtain data for each of said crystals; and

characterizing each said crystal based on said data.

2. The method according to claim 1, wherein said characterizing comprises:

comparing said data of each of said crystals to data of said at least one polymorph family to obtain at least one correlation coefficient; and

categorizing said data of each of said crystals to one of said at least one polymorph family based on said at least one correlation coefficient and selection criteria.

3. The method according to claim 2, further comprising the step, prior to said comparing step, of assigning said data associated with one of said crystals to a polymorph family.

4. The method according to claim 1, further comprising filtering said members to provide seedless or pure members for said subjecting.

5. The method according to claim 4, wherein said filtering is performed using a filtration assembly or centrifugation.

6. The method according to claim 1, further comprising heating said members to promote mixing of said drug candidate or salt thereof and said at least one solvent.

7. The method according to claim 1, further comprising:

providing a rotating magnetic field; and

spinning at least one object with said rotating magnetic field to stir said drug candidate or salt thereof and said at least one solvent.

8. The method according to claim 1, wherein said preparing comprises dispensing said drug candidate or salt thereof and said at least one solvent into predetermined regions of a reactor assembly, wherein said predetermined regions correspond to said members according to said library.

9. The method according to claim 8, wherein said dispensing is substantially automated for liquid compositions of said drug candidate or salt thereof and said at least one solvent.

10. The method according to claim 1, further comprising extracting said supernatant to perform solubility testing on said supernatant.

11. The method according to claim 1, further comprising dispensing said members into a crystallization assembly.

12. The method according to claim 11, wherein said dispensing is substantially automated.

13. The method according to claim 1, wherein said screening comprises screening said members with at least two tests selected from the group consisting of solubility, log

P, melting point, birefringence, hygroscopicity, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, X-ray diffraction, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy, gas chromatography, and liquid chromatography testing.

14. The method according to claim 1, wherein said comparing comprises:

obtaining a best correlation coefficient from said at least one correlation coefficient; and

using said best correlation coefficient to perform said categorizing.

15. The method according to claim 1, wherein said at least one polymorph family comprises an existing polymorph family.

16. The method according to claim 1, wherein said at least one polymorph family comprises a new polymorph family.

17. The method according to claim 1, wherein said preparing comprises:

using a software program to generate said library; and

formulating said plurality of members based of said library based on said computer based library.

18. The method according to claim 2, wherein said selection criteria is a user-defined threshold value.

19. The method according to claim 1, further comprising after said preparing step:

daughtering said members to form a plurality of daughter libraries; and

crystallizing said daughter libraries under different crystallization conditions.

20. The method according to claim 19, further comprising determining if any crystalline forms formed during said crystallizing by screening said daughter libraries.

21. The method according to claim 1, wherein said at least one crystallization conditions comprise conditions selected from the group consisting of temperature, pressure, time, humidity, and any combination thereof.

22. The method according to claim 17, wherein said using comprises providing a user with an opportunity to enter at least one parameter to generate said library.

23. The method according to claim 22, wherein said at least one parameter comprises at least one of:

defining said drug candidate or salt thereof; and

defining a solvent library.

24. The method according to claim 23, wherein said solvent library comprises solvents selected from the group consisting of aromatics, water, alcohols, esters, and mixtures thereof.

25. A method for performing high throughput salt selection for a drug candidate, the method comprising:

preparing a library having a plurality of members, each member comprising said drug candidate, a salt reactant and at least one library solvent;

reacting said drug candidate and said salt reactant under conditions to a produce drug candidate salt;

adding said at least one library solvent to said drug candidate salt to form said members;

subjecting said members to at least one condition to produce at least one crystalline structure of said drug candidate salt, said at least one crystalline structure having a crystal and a supernatant;

screening said crystal and said supernatant to obtain data, wherein said data comprises at least two selected from the group consisting of solubility, log P, melting point, birefringence, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, X-ray diffraction, hygroscopicity, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy, gas chromatography, and liquid chromatography testing; and

selecting at least one said drug candidate salt of interest.

26. The method according to claim 25, further comprising isolating said drug candidate salt after said reacting.

27. The method according to claim 25, further comprising filtering said members after said adding.

28. A method for performing high throughput salt selection and polymorph characterization for a drug candidate, the method comprising:

reacting a drug candidate and a salt reactant in a plurality of regions under reacting conditions to produce a drug candidate salt in said regions;

adding at least one solvent to said regions;

subjecting said regions to at least one condition to produce at least one crystalline salt of said drug candidate salt, said at least one crystalline salt comprising at least a salt crystal;

screening said salt crystal to obtain information;

selecting one of said at least one drug candidate salts based on said information, wherein said selecting provides a selected drug candidate salt;

preparing a library having a plurality of members, each member comprising said selected drug candidate salt and at least one solvent;

subjecting said members to at least one crystallization condition to produce at least one crystalline structure of said selected drug candidate salt, said at least one crystalline structure having at least a crystal;

screening said crystal of each of said at least one crystalline structure to obtain data for each of said crystals; and

characterizing each said crystal based on said data.

29. The method according to claim 28, wherein said characterizing comprises

comparing said data of each of said crystals to data of said at least one polymorph family to obtain at least one correlation coefficient; and

categorizing said data of each of said crystals to one of said at least one polymorph family based on said at least one correlation coefficient and selection criteria.

30. The method according to claim 29, wherein said at least one polymorph family is an existing polymorph family or a new polymorph family.

31. The method according to claim 29, further comprising assigning said data associated with one said crystals to a polymorph family prior to said comparing.

32. A method for obtaining solubility data from at least one crystallized structure of a drug candidate or salt thereof, said method comprising:

subjecting an array of materials to crystallization conditions to form said at least one crystalline structure, wherein said crystalline structure comprises a crystal and a supernatant;

extracting said supernatant from said at least one crystalline structure such that said crystal resides on a substrate;

subjecting said supernatant to solubility testing to obtain solubility data;

screening said crystal to obtain crystal data; and

categorizing said at least one crystalline structure into either a new polymorph family or at least one polymorph family based on said solubility data and said crystal data.

33. The method according to claim 32, wherein said solubility testing comprises using a testing technique selected from the group consisting of liquid chromatography, thin layer chromatography, gas chromatography, infrared, fluorescence, log P and ultra-violet absorption.

34. The method according to claim 32, wherein said screening comprises screening said crystal with a test selected from the group consisting of melting point, birefringence, hygroscopicity, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, X-ray diffraction, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy and gas chromatography.

35. The method according to claim 32, wherein said existing polymorph family is a polymorph family in which the properties of said at least one crystalline structure have been previously discovered.

36. The method according to claim 32, wherein said new polymorph family is a polymorph family in which the properties of said crystalline structure have not been previously discovered.

37. The method according to claim 32, wherein said categorizing comprises:

comparing said crystal data of any of said at least one crystalline structure with said crystal data obtained from at least one other said crystalline structure, wherein said comparing generates a correlation coefficient; and

categorizing said at least one crystalline structure into said new polymorph family or said existing polymorph family based on said correlation coefficient.

38. A method for testing and categorizing a plurality of crystalline structures formed from a drug candidate or salt thereof, said method comprising:

preparing said plurality of crystalline structures;

screening said plurality of crystalline structures with at least two different screening techniques to obtain data on said crystalline structures;

comparing said data of each of said crystalline structures to data of said at least one polymorph family to obtain at least one correlation coefficient; and

categorizing said data of each of said crystalline structures to one of said at least one polymorph family based on said at least one correlation coefficient and selection criteria.

39. The method according to claim 38, wherein said preparing comprises:

preparing said plurality of library members, each said library member comprising said drug candidate or salt thereof; and

subjecting said library members to at least one condition to produce said plurality of crystalline structures.

40. The method according to claim 38, wherein said screening techniques are selected from the group consisting of solubility, log P, melting point, birefringence, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, X-ray diffraction, hygroscropicity, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy, gas chromatography, and liquid chromatography testing.

41. The method according to claim 38, further comprising creating a new polymorph family if said at least one crystalline structure is associated with a correlation coefficient that is below a predetermined threshold value.

42. The method according to claim 41, wherein said predetermined threshold value sets a threshold that determines whether said at least one crystalline structure should be clustered into one of said at least one polymorph family or said new polymorph family.

43. A system for performing high throughput testing of a drug candidate to characterize polymorphs that form from said drug candidate, said system comprising:

a reactor assembly configured to contain a plurality of mixtures, said reactor assembly having a plurality of regions to contain said mixtures;

a crystallization assembly configured to contain said mixtures on a substrate, wherein said mixtures are subjected to crystallization conditions to provide at least one crystalline structure;

a temperature controlled housing configured to house a subassembly, said housing maintains said subassembly at a predetermined thermal profile;

at least two screening devices that obtain data on said at least one crystalline structure, wherein said at least two screening devices perform measurements on said at least one crystalline structure located on the same said substrate; and

a computer that controls said temperature controlled housing and receives data obtained by said screening devices, wherein said computer provides crystalline structure data obtained to a polymorph grouping algorithm, said polymorph grouping algorithm further configured to:

compare said data for said at least one crystalline structure with data of at least one polymorph family to obtain a best correlation coefficient; and

cluster said data associated with said at least one crystalline structure into said at least one polymorph family based on said best correlation coefficient and selection criteria.

44. The system according to claim 43 further comprising a filter assembly that filters said mixtures to provide substantially pure mixtures to said crystallization assembly.

45. The system according to claim 44, wherein said substantially pure mixtures have no nucleation sites contained therein.

46. The system according to claim 43, wherein said reactor assembly and said filtration assembly comprise at least one common part.

47. The system according to claim 46, wherein said at least one common part comprises a reactor base.

48. The system according to claim 43 further comprising a robotic pipette system that is controlled by said computer.

49. The system according to claim 48, wherein said robotic pipette system is controlled to dispense materials into said reactor assembly.

50. The system according to claim 48, wherein said robotic pipette system is controlled to dispense materials into said crystallization assembly.

51. The system according to claim 43, wherein said subassembly is said reactor assembly.

52. The system according to claim 43, wherein said subassembly is said crystallization assembly.

53. The system according to claim 43, wherein said subassembly is a filtration assembly.

54. The system according to claim 43, wherein said temperature controlled housing is controlled by said computer to heat said reactor assembly to said predetermined thermal profile to promote dissolution of said mixtures contained therein.

55. The system according to claim 43, wherein said temperature controlled housing is controlled by said computer to cool said crystallization assembly to the predetermined thermal profile to crystallize said mixtures contained therein.

56. The system according to claim 43 further comprising a dispensing assembly that dispenses a structure in each region of said reactor assembly to promote agitation of said mixture.

57. The system according to claim 43, wherein said at least two screening devices comprise two devices selected from the group consisting of solubility, log P, melting point, birefringence, infrared spectroscopy, near infrared spectroscopy, hygroscopicity, Raman spectroscopy, X-ray diffraction, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy, gas chromatography, and liquid chromatography testing device.

58. The system according to claim 43, wherein said computer is further configured to generate a library based on at least one parameter.

59. The system according to claim 43, wherein said computer is further configured to generate a solvent library, wherein said solvent library comprises at least two different groups of solvents.

60. The system according to claim 43, wherein said computer comprises a database for storing said data.

61. The system according to claim 43 further comprising a second crystallization assembly that is configured to receive an aliquot of said mixtures synthesized in said reactor assembly, wherein said second crystallization assembly is subjected to a different crystallization condition than said crystallization assembly.

62. The system according to claim 43, wherein said computer is configured to display the result obtained by said polymorph grouping algorithm.

63. The system according to claim 43, wherein said computer is configured to allow a user to interact with said polymorph grouping algorithm.

64. The system according to claim 43, wherein said selection criteria comprises a predetermined threshold value.

65. A method for categorizing a plurality of crystalline structures, said method comprising:

providing at least one polymorph family;

selecting one of said plurality of crystalline structures;

comparing said selected crystalline structure to each said at least one polymorph family, wherein each said comparison produces a correlation coefficient;

obtaining a best correlation coefficient among each said correlation coefficient produced;

categorizing said selected crystalline structure to either (a) said at least one polymorph family or to (b) a new polymorph family based on said best correlation coefficient.

66. The method according to claim 65, wherein said providing comprises assigning one of said plurality of crystalline structures to said at least one polymorph family.

67. The method according to claim 65, wherein said providing comprises obtaining said at least one polymorph family from a database.

68. The method according to claim 65, wherein each one of said at least one polymorph family comprises characteristics that are different than the characteristics associated with any other said at least one polymorph family.

69. The method according to claim 65, wherein said correlation coefficient comprises a value that indicates how similar said selected crystalline structure is to said at least one polymorph family.

70. The method according to claim 65, wherein said comparing comprises performing a statistical analysis to produce said correlation coefficient.

71. The method according to claim 65, wherein said comparing comprises comparing data associated with said selected crystalline structure with data associated with said at least one polymorph family.

72. The method according to claim 71, wherein said data is based on a screening test selected from the group consisting of solubility, log P, melting point, birefringence, hygroscopicity, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, X-ray diffraction, UV-Vis spectroscopy, nuclear magnetic resonance spectroscopy, gas chromatography, and liquid chromatography.

73. The method according to claim 65, wherein said comparing comprises:

providing crystalline structure data based on said selected crystalline structure;

providing polymorph family data;

performing a point-to-point analysis of said crystalline structure data to said polymorph family data to obtain said correlation coefficient.

74. The method according to claim 73, wherein said crystalline structure data is Raman spectroscopy data.

75. The method according to claim 73, wherein said polymorph family data is Raman spectroscopy data.

76. The method according to claim 65, wherein said comparing comprises:

providing crystalline structure data based on said selected crystalline structure;

providing polymorph family data;

performing a peak-to-peak analysis of said crystalline structure data to said polymorph family data to obtain said correlation coefficient.

77. The method according to claim 76, wherein said crystalline structure data is X-ray diffraction spectroscopy data.

78. The method according to claim 76, wherein said polymorph family data is X-ray diffraction spectroscopy data.

79. The method according to claim 65, wherein said categorizing comprises associating said selected crystalline structure with said new polymorph family when said best correlation coefficient is below a predetermined value.

80. The method according to claim 65, wherein said categorizing comprises associating said selected crystalline structure with one of said at least one polymorph family when said best correlation coefficient is equal to or exceeds a predetermined value, wherein said at least one polymorph family that receives said crystalline structure is said at least one polymorph family that is associated with said best correlation coefficient.

81. The method according to claim 65 further comprising creating another said at least one polymorph family based on said new polymorph family.

82. The method according to claim 65 further comprising providing crystallization condition data to perform said categorizing.

83. The method according to claim 82, wherein said crystallization condition data comprises data selected from the group consisting of temperature, pressure, time, solvents, nucleation, precipitation, slurry, pH, concentration of a drug candidate, and any combination thereof.

84. A method for categorizing a plurality of crystalline structures in which no data has been previously obtained for any of said crystalline structures, the method comprising:

associating any one of said crystalline structures with as at least one reference polymorph family;

for each of said remaining crystalline structures:

comparing said remaining crystalline structures to said at least one reference polymorph family;

generating at least one correlation coefficient based on analysis between said remaining crystalline structures and said at least one reference polymorph family;

categorizing said remaining crystalline structures into said at least one reference polymorph family based on said at least one correlation coefficient.

85. A method for performing high throughput testing of a drug candidate or salt thereof to characterize crystalline structures that form from said drug candidate or salt thereof, the method comprising:

preparing a plurality of members, each said member comprising said drug candidate or salt thereof and at least one solvent;

subjecting said members to at least one crystallization condition to produce at least one crystalline structure of said drug candidate or salt thereof, said at least one crystalline structure having a crystal and a supernatant;

screening said at least one crystalline structures with at least two different screening techniques to obtain at least crystallinity and identity data on said crystalline structures; and

characterizing said crystalline structures.

86. The method according to claim 85, wherein said crystalline structures of said drug candidate or salt thereof form on a substrate.

87. The method according to claim 85, wherein said plurality of crystalline structures is eight or more.

88. The method according to claim 85, wherein said screening techniques for identity comprise at least one test selected from the group consisting of birefringence, X-ray diffractometry, Raman spectroscopy, gas chromatography, liquid chromatography, thin layer chromatography, capillary electrophoresis, Infrared spectroscopy, UV-Vis spectroscopy and near infrared spectroscopy, and wherein said screening techniques for crystallinity comprises at least one test selected from the group consisting of birefringence and X-ray diffraction.

89. The method according to claim 85, wherein prior to said subjecting step, each of said plurality of solutions is subjected to either (1) filtering to remove possible solids or (2) daughtering or (3) both filtering and daughtering.

90. A method for performing high throughput testing of a drug candidate or salt thereof to characterize crystalline structures that form from said drug candidate or salt thereof, the method comprising:

preparing a plurality of members, each said member comprising said drug candidate or salt thereof and at least one solvent;

subjecting said members to at least one crystallization condition to produce at least one crystalline structure of said drug candidate or salt thereof, said at least one crystalline structure having a crystal and a supernatant;

screening said at least one crystalline structure with at least two different screening techniques to obtain at least crystallinity and identity data on said crystalline structures; and

characterizing said plurality of crystalline structures according to said crystallinity and identity data.

91. The method according to claim 90, wherein said crystalline structures of said drug candidate or salt thereof form on a substrate.

92. The method according to claim 90, wherein said plurality of crystalline structures is eight or more.

93. The method according to claim 90, wherein said screening techniques for identity comprise at least one test selected from the group consisting of birefringence, X-ray diffractometry, Raman spectroscopy, gas chromatography, liquid chromatography, thin layer chromatography, capillary

electrophoresis, Infrared spectroscopy, UV-Vis spectroscopy and near infrared spectroscopy, and wherein said screening techniques for crystallinity comprises at least one test selected from the group consisting of birefringence and X-ray diffraction.

94. The method according to claim 90, wherein prior to said subjecting step, each of said plurality of solutions is subjected to either (1) filtering to remove possible solids or (2) daughtering or (3) both filtering and daughtering.

95. A system for performing a workflow, said workflow including preparing and testing a plurality of materials, said system comprising:

a work surface;

at least one assembly optionally mounted to said work surface, wherein said at least one assembly comprises:

a reactor assembly;

a filtration assembly; and/or

a crystallization assembly;

at least one thermal housing assembly mounted to said work surface, said thermal housing assembly configured to retain said at least one assembly; and

a robotic material handling system mounted to said work surface, said robotic material handling system configured to (a) dispense said plurality of materials into said at least one assembly and (b) retrieve a plurality of mixtures formed from said plurality of materials from said at least one assembly, thereby preparing said plurality of materials for testing.

96. The system according to claim 95, wherein said robotic handling system comprises a vented needle assembly configured for maintaining a substantially constant pressure within a sealed receptacle when aspirating a liquid out of or dispensing liquid into said sealed receptacle, said vented needle assembly comprising:

a body having a main axis;

at least one guide rod that slides in and out of said body along said main axis;

a guide block attached to said at least one guide rod such that said guide block moves in conjunction with said at least one guide rod;

a compressible spacer that provides tension between said body and said guide block;

a venting needle coupled within said guide block in parallel to said main axis, said venting needle extending beyond a first side of said guide block by a fixed length, thereby providing an open passage through said guide block; and

a liquid handling needle coupled to said body in parallel to said main axis, said liquid handling needle configured to pass through said guide block.

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