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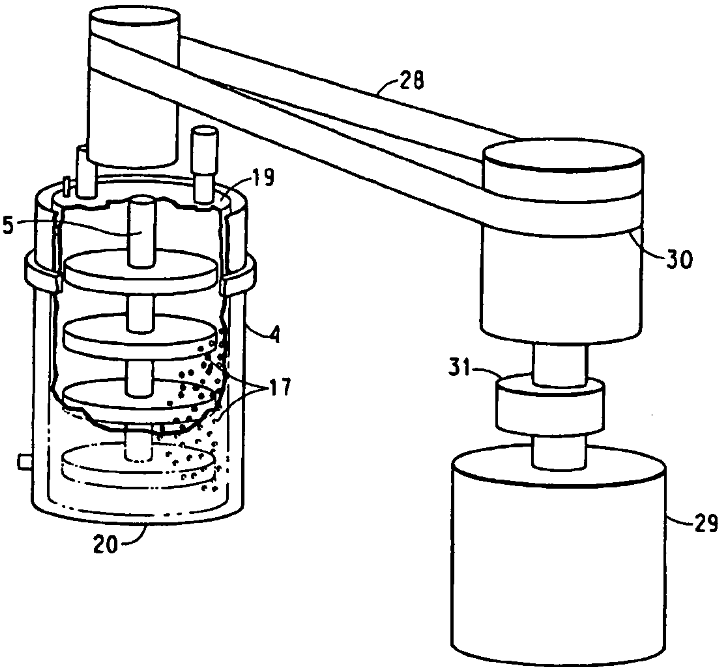
(54) Title: HIGH PRESSURE MEDIA MILL



(57) **Abstract:** This invention discloses a high pressure media mill (HPMM) and processes for use thereof.

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TITLE

HIGH PRESSURE MEDIA MILL

FIELD OF THE INVENTION

This invention discloses a high pressure media mill (HPMM) and processes for use thereof.

TECHNICAL BACKGROUND

Slurry media milling is an important unit operation in various industries for the fine and ultra-fine grinding of minerals, paints, inks, pigments, micro-organisms, food and agricultural products and pharmaceuticals. In these mills, the feed particles are reduced in size between a large number of small grinding media which are usually sand, plastic beads, glass, steel or ceramic beads. As a result of the internally agitated, very small, grinding media and the liquid medium (aqueous, non-aqueous or a mixture thereof), finer particles of submicron or nanosize particles dispersion product can be produced, which has not been previously done by conventional mills.

Supercritical fluid (SCF) processing technology has many applications in food, nutraceutical and chemical industries and is now emerging as an alternative technology in the pharmaceutical industry with applications ranging from particle formation, micro-encapsulation, coating, extraction, and purification. Carbon dioxide is the most widely used SCF for pharmaceutical applications even though other hydrocarbon gases such as ethane, propane, butane and ethylene, water, nitrous oxide ammonia and trifluoromethane have been reported for other applications. Three types of SCF processes have been disclosed. They are:

1) rapid expansion of supercritical solutions (RESS) process,
2) antisolvents process, and
3) particles from gas-saturated solution (PGSS) process.

The RESS process is limited for SCF soluble compounds because it involves dissolving the compounds in the SCF and the subsequent formation of particles by rapid expansion through a nozzle. Most drug compounds have very low solubility in SCF especially supercritical CO_2.

The antisolvent process uses the SCF as an antisolvent to precipitate particles from predissolved solvent solution with the sample principle of antisolvent crystallization process. The method developed by University of Bradford in US 5,108,109 combines the antisolvent and nozzle expansion to control particle formation. The limitation of the antisolvent process is a soluble solvent has to be used for a given compound.

Weidner (US Patent No. 6,056,791) discloses a process to dissolve CO_2 in liquid or melted drugs or polymers to form a gas-saturated solution followed by depressurization to form particles. Some apparent disadvantages with this process are that the elevated temperature required to melt the compounds could degrade the compound, and that the high viscosity of melts could limit the particle size of product.

U.S. Patent No. 5,854,311 discloses the use of 10 to 40 μm particles in powder coating applications. The process disclosed was run at no more than 30 psig.

U.S. Patent No. 5,500,331 discloses the comminution of materials with small particle milling material. U.S. Patent No. 5,145,684 discloses surface modified drug nanoparticles. The technology disclosed in these patents relates to a milled slurry, but not dry flowable nanoparticles, as a liquid media is used in the process.

Hock S. Tan and Suresh Borsadia, Particle Formation Using Supercritical Fluids: Pharmaceutical Applications, Exp.Opin. Ther. Patents (2001)11(5), Asley Publications Ltd. reviews a number of process concepts using supercritical fluid (SCF) processing methods for controlled particle formation. However the article does not describe grinding milling equipment using SCF to generate dry flowable sized micro particles.

The present invention, a high pressure media milling (HPMM) process, combines a slurry media mill with supercritical fluid (SCF) technology or with volatile gases as a milling medium to produce micron and nanosize particles in a dry free flowing powder form without a limitation of solubility and without the requirement of organic solvents or high temperature. The volatile gas may also include those cooled to a liquid state, such as liquid CO_2. The process has applications for use with a broad range of materials including heat sensitive bioactive materials and environmental sensitive electronic materials.

SUMMARY OF THE INVENTION

The present invention concerns a process for milling, comprising the steps of: a) adding grinding media and material to be milled to a high pressure media mill; b) evacuating mill to produce a vacuum; c) adding a supercritical fluid or a volatile gas to said mill; d) pressurizing and maintaining the pressure in said mill; and e) operating the mill so that product particles are reduced in size.

The process also comprises the additional step of adding liquid or solid materials to step (a) for coating product particles.

The above process uncludes an embodiment wherein the median product particle size less than 200 μm in size, preferably less than 100 μm in size, more preferable less that 1 μm. It is preferred that the product contains no residual milling fluid or gas.

The invention also includes a mill, comprising: a) a grinding chamber capable of holding material at pressures of up to 2000 psig; b) a magnetically driven stirrer in said chamber; and c) a magnetic drive.

The invention also includes the above-described mill further comprising: d) one or more ports leading into said grinding chamber for charging and discharging grinding media, materials to be ground and fluids under high pressure.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 describes the general design of a SC media mill.

Figure 2 describes a layout for a media mill pilot plant.

Figure 3 shows a PT curve for CO_2 in a SC media mill.

Figure 4 describes calculated values for pressure density curves.

Figure 5(a) shows supercritical milled TiO_2 in KNO_3 titrated against HNO_3 and KOH.

Figure 5(b) shows a scanning electron micrograph of product.

Figure 6(a) shows a micrograph of NaCl starting material.

Figure 6(b) shows a migrograph of the same material after grinding.

Figures 7(a) and (b) show a light microscope picture of the proceed material in 19a.

Figure 7(c) shows a SEM picture of ibuprofen on 19a.

Figure 8 shows a SEM picture of ibuprofen at a kv accelatioin of run 19(c).

DETAILS OF THE INVENTION

The slurry media mill described herein is capable of micron and nanoparticle slurry production and can be widely used in the chemical industry for large scale operations. The SCF is used herein as a low viscosity liquid medium for better dispersion and energy transfer during the milling. Dispersed, dry free-flowing powder is obtained as product when SCF is released after the milling process. Also, the process is not limited to the use of SCF. Under Tc (or T_{crit}, critical temperature) and Pc (or P_{crit}, critical pressure), liquid CO_2 or other volatile gases can be used as the grinding medium.

This process offers significant advantages over existing micronization processes, especially for pharmaceutical applications. These advantages include generation of dry micron and nanosize particles which are difficult or impossible to generate by micronization and other existing processes, integrated coating or encapsulation during milling process, dry fine particles for direct inhalation formulation, including dry powder inhalation and metered dose inhalation as well as oral and parenteral formulations, and integrated disruption and extraction of active ingredients from solid particles, cells, plants and the like.

The high pressure media mill (HPMM) arrangement, described herein and shown in Figure 1, is a media mill grinding chamber (4) which is pressurized with a supercritical gas, e.g. carbon dioxide. The energy required for size reduction, deagglomeration and dispersion of the product particles is derived from a mechanical stirrer (5) that controls a group of stirring discs (17) that move grinding bead media (27) in the mill grinding chamber (4). The mill grinding chamber (4) has a bottom section (20) and a top section (19). Product particles are trapped between stirring discs (17) and are exposed to colliding grinding bead media (27). Drive belt (28) is attached to motor (29) which has speed sensor (30) and torque sensor (31).

The mill is operated above the supercritical pressure and temperature of the fluid, in most cases CO_2, although any compressible gas can by used, including but not limited to hydrofluorocarbons (HFC's) and their alternates, propane, methane and the like. Selection of the pressure and temperature allow control of the viscosity and density of the fluid, which has an important effect on the flow patterns, and therefore heat and mass transfer, in the mill chamber.

The HPMM is particularly useful for the production of submicronic particles in dry form. Production of a dry well-dispersed powder is possible because the supercritical fluid is vented off, after processing. There is no need to use water (e.g., some materials, such as proteins, are unstable in water) and the drying step is eliminated. Also, the process train is simplified and integrated (e.g., surface treatment and dispersion of nanocrystalline materials; grinding, disruption of cells and simultaneous extraction of biological components occur without exposure to air/oxygen), and thereby is generally less expensive than other methods of dispersion and grinding.

The design of the media mill itself is shown, as described above, in Figure 1. The grinding chamber is a pressure vessel (4) consisting of a bottom section (20) and a top section (19). The HPMM pilot plant herein, shown as Figure 2, is assembled by attaching four stirring discs (17) to the shaft controlled by the magnetic stirrer (5) in the top head section (19) of the assembly. The bottom (20) of the vessel is attached to the head section by sealing means. The sealing means can be mechanical, magnetic or a combination thereof. Bolts can be used along with or as part of the sealing means. The connections for cooling and heating (21&22) of the jacket around the vessel are attached.

The lines of the rupture disc (10) to the catch drum (11) and drum vent (25) are attached for safety.

The plug in the charging port (13) in the head section is removed and a funnel is used to charge the grinding media and the solids to be processed. Any other liquid or solid components used to coat the particles are charged through the same port at this time. The port is closed with the plug and ready for charging with the supercritical fluid to be used.

All the valves in the supercritical media mill are closed and the valves (14, 15, and 16) from the vacuum pump (7) through the product collection filters (6) are opened to evacuate the system of all air before processing starts. This vacuum is broken with the SC fluid (1) on scale (24) to be used in the processing and is done by shutting the valves to the vacuum pump (16) and opening the valve to the SC fluid cylinder (2) to be used. This evacuation and purging is repeated three times before charging is started.

When the last pull down of the vessel is complete the weight is recorded from the cylinder scale (24). The cooling water (9) is turned on the jacket and then the vessel is charged with a specific weight of SC fluid and from the cylinder (1) and valve (2) either through the line or by using the pump (3) and then the valve for the cylinder (2) is closed. This weight of fluid is recorded. Valves (14&15) are closed to isolate the vessel.

The motor (5) is turned on to a set speed and the cooling water (8) is turned off and heating (9) is started. The heating is set at the specific temperature for the designed experiment being conducted. The data is recorded on the monitoring and control system (12) including RPM, torque, temperatures, pressure, and flow rate in GPM to the jacket until the desired test time is complete.

The heating (9) is then stopped and the cooling (8) is started and when the vessel temperature is below 25 degrees centigrade the motor drive (5) is stopped. When the cooling is complete the valve (15) is opened to collect the product in the collection filters (6). The material is recovered from the filters for use.

The bottom section (20) of the mill is removed and all the excess material left behind in the vessel and on the blades is recovered and the unit is cleaned and re-assembled for future tests.

START UP CONDITIONS

Initial experiments dealt with loading and unloading of the mill, product collection, temperature and power control and data acquisition.

Before loading with SC CO_2 the mill needs to be evacuated of air in a vacuum cycle. The vacuum cycle should be repeated at least 3 times to remove entrapped air. Monitoring of pressure and temperature is essential as small changes can lead to large pressure built-up. Monitoring allows the location in the SC region in the phase diagram (Figure 4). Furthermore, after initial testing, the following results were noted:

Fast dispersion of TiO_2 in the SC mill was noted. The primary particle size was achieved within 10 min. Polymer bead collision was sufficient to break down TiO_2 agglomerates. Polymer beads reduced wear rate, compared to SEPR.

The loading of the mill was measured with a scale to a preferred loading of 0.65 to 0.7 g/cc.

The operation conditions followed a phase diagram as shown in Figure 4. The heat exchange/mixing was relatively poor at lower RPM.

Acceptable results were achieved at 50-70 volume percent bead loading. Good circulation of mill contents was also noted.

Thermodynamics

The PT- curves for the different runs are shown in Figure 3. The effect of venting is clearly seen. Apparently, if the runs start off with a too high density (more CO_2 mass in SC mill, such as series 5,6), the pressure has to increase to 4000 psig to get to the supercritical isotherm (Tcrit = 31.1C).

series 1: only heating
series 2: heating + stirring
series 3: heating + stirring run 2
series 4: heating + stirring + TiO_2 50 g
series 5: heating + stirring + TiO_2 150 g

series 6: heating + stirring + TiO_2 150 g venting 1
series 7: heating + stirring + TiO_2 150 g venting 2

Figure 4 is a "Calculated Pressure-Density Curve" and shows the calculated values for different operating temperatures (10, 27, 31, 35, 50°C). The mill chamber of a constant volume is loaded with a known mass of CO_2. Therefore the density of CO_2 stays at a constant levels over a test run. The Figure is used to predict the pressure in the SC mill chamber for different operating temperatures and allows confirmation that SC conditions are achieved.

DEFINITIONS

The following definitions are used herein:

SC: Supercritical

SC CO_2: MG Industries, Malvern, PA

Fungicide: Famoxadone

SEPR: Ceramic grinding media from S. E. Firestone Assoc., Russell Finex Inc., Charlotte, NC

YTZ: Ceramic grinding media from S. E. Firestone Assoc., Russell Finex Inc., Charlotte, NC

Poly-Sty: Polystyrene Grinding Media from S. E. Firestone Assoc., Russell Finex Inc., Charlotte, NC

Nylon: Nylon Powder, DuPont Co., Wilmington, DE

Silver: silver particle for application in Silver Bearing Conductors, DuPont Company, Wilmington DE

Unless otherwise specified, all chemicals and reagents were used as received from Aldrich Chemical Co., Milwaukee, WI.

EXAMPLES

EXAMPLES 1-19

The following experiments were carried out with the HPMM to explore the operating range (rotor speed, pressure level, run time) and to study the effects of media charge, media type and additives. The test conditions are listed in Table 1, "Test conditions". The following (organic and inorganic) materials were tested.

- O Inorganic - insoluble in H_2O (TiO_2)
- O Organic - soluble in H_2O (dextrose, acetaminophen, ibuprofen)
- O Organic - insoluble in H_2O (famoxadone)
- O Inorganic - soluble in H_2O (NaCl)

In addition, silver bearing conductive pastes were tested. These are thick film compositions for application onto ceramic substrates and dielectric compositions by screen printing. These substrates are then fired in a conveyor belt furnace in an oxidizing atmosphere (air) to form interconnect tracks and pads in single- and multillayer microcircuits. Silver bearing conductor pads are normally used for passive SMT components attachment with low-temperature eutectic Sn/Pb solders or with conductive epoxy adhesives.

Acetaminophen (Paracetamol) was tested on the HPMM to produce particles in the 1-5 micron range for inhaler applications.

Example 19a, 19b and 19c

Ibuprofen on HPMM

Table 1 lists the conditions of the experiments with ibuprofen on the HPMM. The ibuprofen was bought from Spectrum Chemicals. The fluid for the runs was CO_2.

Run 19a Media milling of ibuprofen in supercritical CO_2.

During run 19a the temperature was maintained at 35°C. The pressure in the mill chamber was 1550 psi. The total run time was 2 hrs. Product was collected after depressurization using a vibratory screen.

Table 2 lists the produced median particle size (D50). The particle size distribution was measured with a forward light scattering device (Malvern Mastersizer 2000). The size distribution shifted to the right, indicating growth of the particles due to agglomeration and aggregation of fine product particles. Light microscope and SEM pictures confirmed this. Figures 7a and b show a light microscope picture (Nikon Optiphot) of the as received ibuprofen. Figure 7c shows a picture of the processed material (run #19a).

Figure 7c shows a SEM picture of the ibuprofen of run 19a with particles as small as 30 nanometer. The operating temperature of run 19a (35°C) was higher than the softening temperature of ibuprofen, which caused fusion/aggregation of these particles.

Run 19b Media milling of ibuprofen in liquid CO_2 and surfactant (SDS)

The objective of this run was to demonstrate that agglomeration can be avoided/reduced by a lower operating temperature and a surfactant. During run 19b the temperature was maintained at 10°C, while the pressure in the mill chamber was 600 psi (see Table 2). The total runtime was 30 minutes. 35wt% surfactant (Sodium dodecyl Sulfate, MW=288.38, supplied by ICN Biomedical Inc.).

The particle size was reduced from 33.85 microns (as received) to 1.805 micron. Figure 8 shows an SEM picture of the product of run 19b.

Run 19c: Media milling of ibuprofen in liquid CO_2 and surfactant (SDS)

As in Run 19b, ibuprofen was milled in liquid CO_2, but with 2wt% SDS surfactant used. The results are shown in Table 2.

Table 1: Test conditions

Ex. No.	Bead	Bead	Bead	Product	Prod.	CO_2	Additive
	Type	%	Size (mm)	Grams		Grams	Name/Grams
1	SEPR	80	.8-1.0	50	TiO_2	410	
2	SEPR	76	.8-1.0	150	TiO_2	410	
3	SEPR	80	.8-1.0	150	TiO_2	386	
4	SEPR	50	.8-1.0	150	TiO_2	477	
5	SEPR	70	.8-1.0	150	TiO_2	410	
6	Poly-Sty.	70	0.5	150	TiO_2	363	
7	Poly-Sty.	50	0.5	150	TiO_2	454	
8	Poly-Sty.	70	0.5	150	Dextrose	295	
9	Poly-Sty.	70	0.5	150	Dextrose	318	
10	Poly-Sty.	70	0.5	150	NaCl	340	
11	SEPR	70	.8-1.0	150	Dextrose	363	
12	SEPR	70	.8-1.0	150	NaCl	363	
13	Poly-Sty.	70	.25/.15	150	Silver	431	
14	Poly-Sty.	70	0.5	150	Silver	363	
15	SEPR	70	.8-1.0	150	Famoxadone	363	
16	Nylon	70	.5/.88	150	TiO_2	409	
17	Poly-Sty.	70	0.5	150	Silver	363	Stearic acid/ 0.75
18	Poly-Sty.	70	0.5	150	Silver	363	Stearic acid/ 0.75
19	YTZ	70	0.3	150	Acetominophen	370	
19a	SEPR	70	.8-1.0	150	Ibuprofen	370	—
19b	SEPR	70	.8-1.0	110	Ibuprofen	370	Sodium dodecyl sulfate/36 g
19c	SEPR	70	.8-1.0	150	Ibuprofen	370	Sodium dodecyl sulfate/3 g

Process monitoring and Product Characterization:

During each test run, the temperature and pressure in the HPMM, the power intake by the mill, the speed of the stirrer were monitored. The products were characterized by their size, shape, surface morphology and reactivity/activity.

The particle size distribution of the feed and the product were measured with the Microtrek UPA and Microtrek FRA by Leeds and Northrop, (see Table 2). Scanning electron micrographs (SEM) were taken using a Hitachi S-4700 (Hitachi Instruments, San Jose, CA) with the powder samples mounted on double sided sticky tape, and x-ray powder diffraction were carried out on a number of samples. The instrument used for powder diffraction studies is a Philips X-ray Diffractometer PW 3040 (Philips Analytical Instruments, Natick, MA). The technique used is powder x-ray diffraction using CuKα radiation. Figure 6a shows an SEM of the NaCl of Example 12 before grinding, and Figure 6b shows an SEM of the same material after grinding. The decrease in size of the material can be noted.

Table 2: Summary of test results (all milling tests @ 1750 rpm)

Ex.	Total time	SC time	Net Torque (zero = 14.6)	Watts	Temp.	Pressure	Energy	Specific Energy	Median particle size
No.	Hrs.	Hrs.	In-lbs.		Celsius	Psi	KWh.	KWh. /Kg	D50 [micron]
1	2.00	1.80	22.8	472	35	1400	0.94	18.89	0.34
2	1.60	0.50	25.4	526	33	1500	0.84	5.61	0.27
3	1.08	0.50	45.4	940	38	1300	1.02	6.77	0.32
4	0.83	0.50	10.6	220	37	1350	0.18	1.21	0.28
5	0.25	0.17	23.4	485	36	1550	0.12	0.81	0.28
6	0.28	0.17	10.4	215	34	1320	0.06	0.40	0.35
7	0.33	0.10	2.4	50	32	1330	0.02	0.11	0.37
8	0.25	0.17	12.4	257	35	1300	0.06	0.43	173
9	0.50	0.42	17.4	360	36	1400	0.18	1.20	185
10	0.25	0.00	7.4	153	25	570	0.04	0.26	–
11	1.00	0.83	23.4	485	40	1580	0.48	3.23	58
12	1.00	0.83	20.4	422	38	1530	0.42	2.82	4.3
13	1.00	0.75	0.9	19	35	1240	0.02	0.12	23
14	1.00	0.83	2.7	56	37	1300	0.06	0.37	1.8
15	1.00	0.66	20.4	422	33	1550	0.42	2.82	5.4
16	0.50	0.36	6.9	143	37	1375	0.07	0.48	0.33

Ex.	Total time	SC time	Net Torque (zero = 14.6)	Watts	Temp.	Pressure	Energy	Specific Energy	Median particle size
No.	Hrs.	Hrs.	In-lbs.		Celsius	Psi	KWh.	KWh. /Kg	D50 [micron]
17	1.00	0.95	6.4	133	40	1400	0.13	0.88	1.78
18	1.00	0.83	7.8	162	40	1400	0.16	1.08	28.31
19	4.00	3.70	27.4	583	46	1600	0.16	2.11	5.2
19a	2.00	2.00	5.0	104	35	1550	0.21	1.38	44.68*
19b	0.50	0.50	3.2	66	10	600	0.03	0.30	1.805
19c	2.00	2.00	3.1	61	10	600	0.13	1.11	4.106

*agglomerates

Examples 20 – 26: Dispersion of TiO_2 powder in SC mill

TiO_2 was milled using the HPMM as described herein, and compared to standard TiO_2 (R900, available from E. I duPont de Nemours and Co., Wilmington, DE). To that end, a number of particle characterization techniques were employed, as shown in Table 3 below. Isoelectric points were determined using a Matec MBS 8000(Matec Applied Sciences, MA). The isoelectric point is the pH at which the ESA = 0, a point coincident with zero zeta potential. The isoelectric point is determined by the instrument measuring the electrokinetic sonic amplitude (ESA) while titrating the dispersion in a stirred vessel against nitric acid (to lower the pH) or potassium hydroxide (to raise the pH) as shown in Figure 5a. The dispersions of the SC products were prepared by mixing in a 10^{-3} mol/dm^3 solution of potassium nitrate and then dispersing in an ultrasonic bath for 30 seconds. The isoelectric points of the supercritical milling products were not the same as that of the starting material which is indicative of some difference in the surface chemistry.

There was no discernable difference in the particle size or surface properties between the starting material and the products after supercritical milling.

The bulk density of the SC milled product was twice as high as the starting material. The flowability improved. Additionally, the materials appeared the same based on the SEM's shown in Figures 5b and 5c.

Power intake and heating/cooling of the HPMM are interactive to keep the system at the desired/selected temperature. Monitoring of temperature is essential as small changes lead to a large pressure built-up. Monitoring of temperature and pressure allows the location of the SC point in the phase diagram.

After initial testing it was concluded that dispersion occurs fast with TiO_2 in the SC mill. The polymer bead collisions were sufficient to break down the TiO_2 agglomerates. The primary particle size was achieved within 10 minutes of grinding. Loading of mill was reasonably accurate with scale. Operation conditions followed a phase diagram. There was good circulation of mill contents, though heat exchange and mixing was poor at lower mill speeds. A mill charge of 50 to 70 volume percent of grinding bead gave good grinding results. The use of polymer beads reduced wear rate, compared to the use of ceramic beads (SEPR).

TABLE 3

Example Number		Appearance	SEM	Isoelectric point	pycnometric density	pore volume distribution by N2	BET surface area, m2/g	d10, d50, d90, um	XRD, all TiO2. Crystal Size
20	starting material	clumpy white powder	done	7.5	4.22 +/- 0.01	no micro-porosity	6.2	0.32, 0.60, 1.12	2337
21	Starting material	fine grey powder	done	not enough	3.875 +/- 0.005	no micro-porosity	40.2	0.20, 0.34, 0.88	610
22	Starting material	fine grey powder	done	5.5	4.086 +/- 0.008	no micro-porosity	8.9	0.16, 0.27, 0.45	899
23	grinding media	grey beads	done	n/a	n/a	n/a	n/a	n/a	n/a
24	grinding media	fine grey powder	done	not enough	4.130 +/- 0.006	no micro-porosity	8.2	0.17, 0.32, 0.64	1636
25	grinding media	fine grey powder	done	5.6	4.155 +/- 0.006	no micro-porosity	8.1	0.16, 0.27, 0.48	1603
26	grinding media	fine grey powder	done	5.9	4.176 +/- 0.004	no micro-porosity	8.3	0.16, 0.28, 0.44	1573
Comp. B	R900 standard TiO2			9.0					

Electrokinetic results:

Isoelectric points were determined using the Matec MBS 8000, as described above. The isoelectric point is the pH at which the ESA = 0. The isoelectric points of the supercritical milling products were not the same as that of the starting material which is indicative of some difference in the surface chemistry.

There was no discernable difference in the particle size or surface properties between the starting material and the products after supercritical milling. The bulk density of the SC milled product was twice as high as the starting material. The flowability improved over the starting material.

EXAMPLES 27-31

Dispersion of precipitated Silver particles

Silver was milled using the high pressure media mill as described above. The product was characterized using scanning electron microscopy and also evaluated for particle size distribution, shape, isoelectric point and wettability.

TABLE 4

Example Number	All the trials below were dry silver powders	PSD by Microtrac, d10, d50, d90, um	Scanning electron microscopy, dry mounted	Surface tension of EtOH/ Water mixtures needed to wet powder
27		1.15, 3.09, 6.21	agglomerated with spherical primary particles appearing as about 0.5 to 1 um	> 72.6 dyne/cm
28		0.81, 1.80, 106.8, bimodal with main peak at 2, another at 100um	less regularly agglomerated, with irregular primary particles around 0.5 to 1um. Plates or crust visible too.	< 43.7 dynes/cm
29		0.20, 0.33, 0.59	crusty appearance, spherical primary particles agglomerated and around 0.3 um and less.	n/a
30		0.62, 1.78, 9.21, normal with 2 big shoulders	irregular somewhat agglomerated primary particles of around 0.7 um and less.	< 33.6 dynes/cm
31		1.17, 28.31, 260.1, main peak around 2 then many others at larger sizes	agglomerated irregular particles with some crust. Particle size 1um and less.	< 33.6 dynes/cm

Only the "as received" sample wetted into water and so isoelectric points were not evaluated. Stearic acid coating seems to be expressed in the larger size of Examples 30 and 31 over Examples 28 and 29.

Pursuing the wetting aspect of the silver powder further revealed the following. Different ethanol/ water ratios yield solutions having different surface tensions. These, in turn, will either wet, or not wet the powders. The silver Example 27 starting material is readily wetted by all solutions even as high as 72.6 dynes/cm, as was the Comparative C material. This is shown in Table 5.

TABLE 5

% EtOH	Corrected % EtOH	Ex. 27	Ex. 28	Ex. 29	Ex 30	Ex. 31	Comp. C	Measured surface, tension, dyne/cm
100	70	0	0		2, f	2, f	0	26.7
50	35	0	0		1, f	1, f	0	29.1
75	52.5	0	0	no sample	0, f	0, f	0	33.6
25	17.5	0	2, f		99, nw	99, nw	0	43.7
10	7	1	99, f, nw		99, f, nw	99, f, nw	0	54.2
0	0	0	99, f, nw		99, f, nw	99, f, nw	0	72.6

number = wet in time, S (99 = didn't wet in)
nw = sediment was not wetted
f = not wetted silver on surface formed film

The product shown in Example 28, which had no additives but had been treated in the supercritical mill, showed definite hydrophobic character. A surface tension less than 43.7 dynes/cm was needed to wet the powder. Immersional wetting was rather facile, probably due to exceptional density of the powder, but the most noticeable challenge was to internally wet the powder agglomerate when immersed.

The silvers which had been coated with stearic acid were even less wettable requiring surface tensions of less than 33.6 dynes/cm to wet them. More resolution could be achieved by using additional EtOH/ water mixtures.

Processing silver powder in the HPMM didn't change the particle size dramatically but the surface appeared modified to become more hydrophobic. Addition of stearic acid to the supercritical mill, then venting the CO_2 seemed to leave an effective coating of the surfactant on the particles which was more hydrophobic than those treated in the SC mill without stearic acid. This confirmed that the particles had, indeed, been coated in this process.

CLAIMS

What is claimed is:

1. A process for milling, comprising the steps of:
   (a) adding grinding media and material to be milled to a high pressure media mill;
   (b) evacuating mill to produce a vacuum;
   (c) adding a supercritical fluid or volatile gas to said mill;
   (d) pressurizing and maintaining pressure in said mill; and
   (e) operating the mill so that product particles are reduced in size.

2. The process of Claim 1, comprising the additional step of adding liquid or solid materials to step (a) for coating product particles.

3. The process of Claim 1 or 2, wherein said process is continuous.

4. The process of Claim 1 or 2 wherein the process is continuous and wherein said supercritical fluid is selected from the group consisting of CO_2, HFC or alternative, propane, methane and combinations thereof.

5. The process of Claim 1 or 2 wherein the grinding media is ceramic, glass, steel or polymeric material.

6. The process of Claim 1 or 2 wherein 95% of the product particles are no larger than 1 μm in size.

7. The process of Claim 4, wherein the CO_2 is in a liquid state.

8. A mill, comprising:
   (a) a grinding chamber capable of holding material at pressures of up to 2000 psig;
   (b) a magnetically driven stirrer in said chamber; and
   (c) a magnetic drive.

9. The mill of Claim 8, further comprising:
   (a) one or more ports into said grinding chamber for charging and discharging grinding media, materials to be ground and fluids under high pressure.

10. The mill of Claim 8 or 9, wherein said grinding chamber comprises two or more sections held together by sealing means.

11. The mill of Claim 8, wherein said stirrer comprises discs attached to a shaft.

12. The mill of Claim 8 or 9, wherein said grinding chamber contains milling media selected from the group consisting of ceramic, glass, metal, polymeric material and combinations thereof.

13. The mill of Claim 8 or 9 wherein the high pressure fluid is selected from the group consisting of CO_2, HFC and alternatives, propane, methane and combinations thereof.

14. The mill of Claim 8, further comprising controlling means for controlling temperature, pressure and feed rate.

15. The process of Claim 1 or 2 wherein the median product particle size less than 200 µm in size.

16. The process of Claim 15 wherein the median particle size is less than 100 µm in size.

17. The product of the process of Claim 1, 2, 3, 4, 5, 6, 15 or 16.

18. The product as described by Claim 17 wherein the product contains no residual milling fluid or gas.

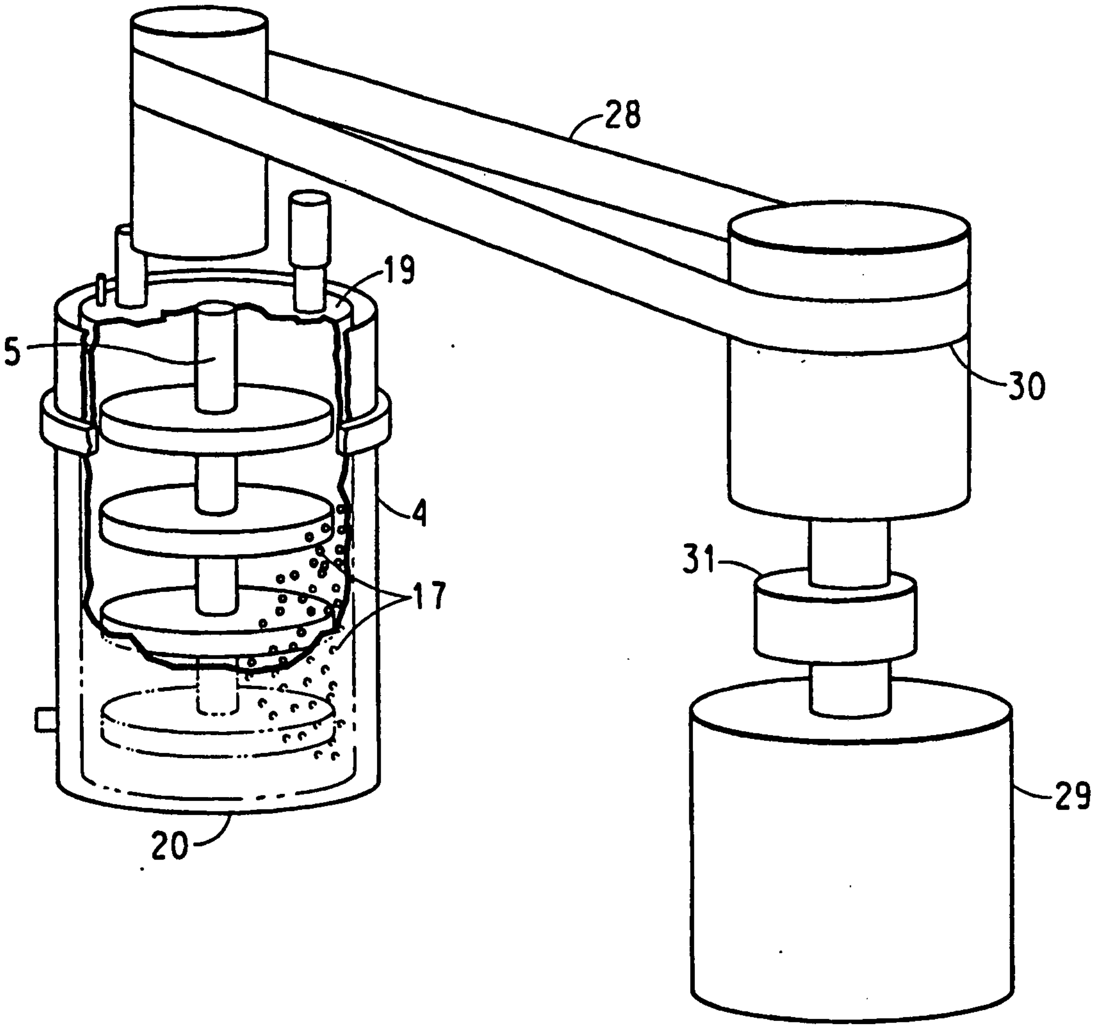

FIG. 1

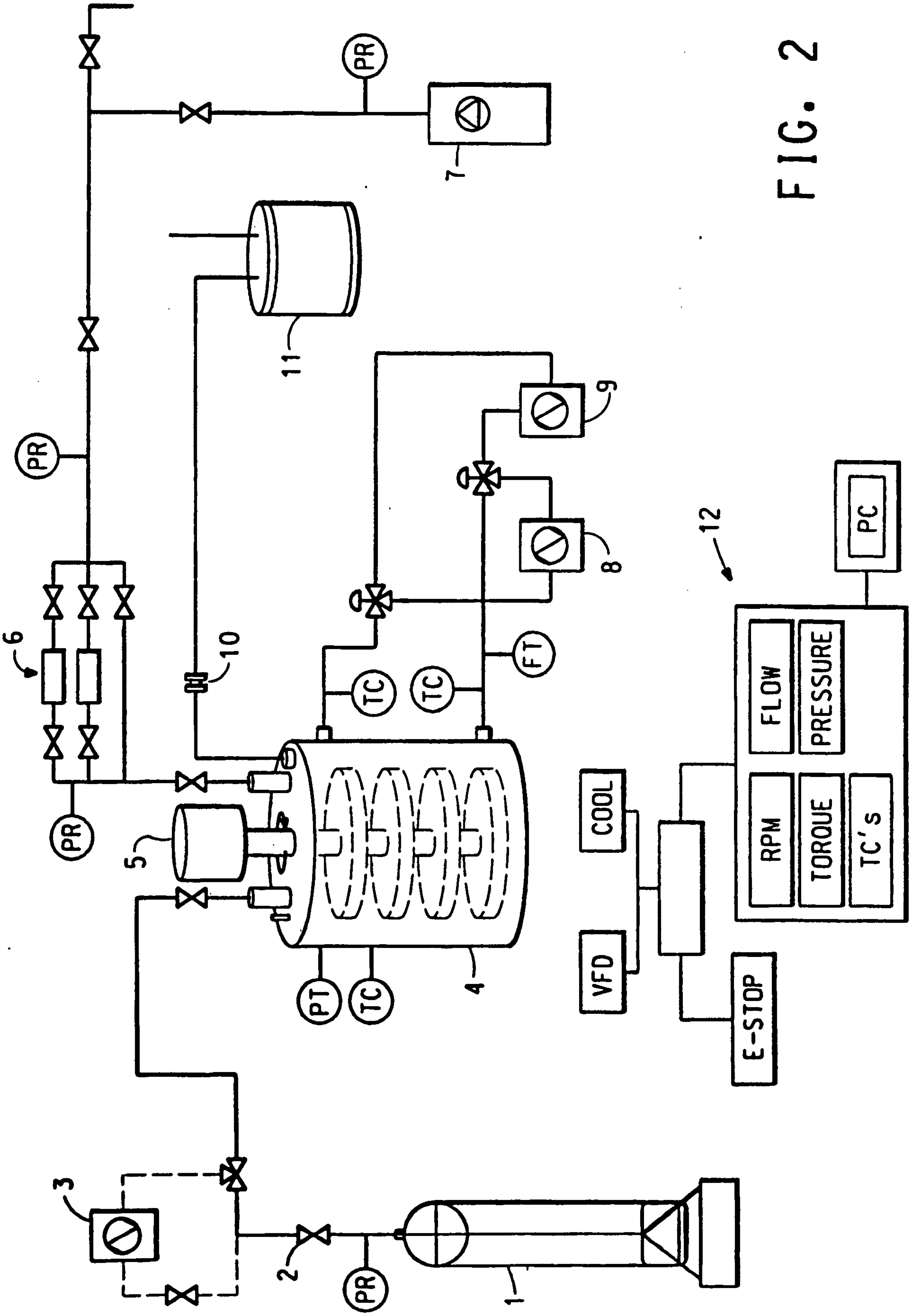
PR
7
PR
11
9
PR
6
10
8
12
PC
FT
TC
TC
FLOW
PRESSURE
PR
5
COOL
RPM
TORQUE
TC's
VFD
4
PT
TC
E-STOP
3
2
PR
1

FIG. 2

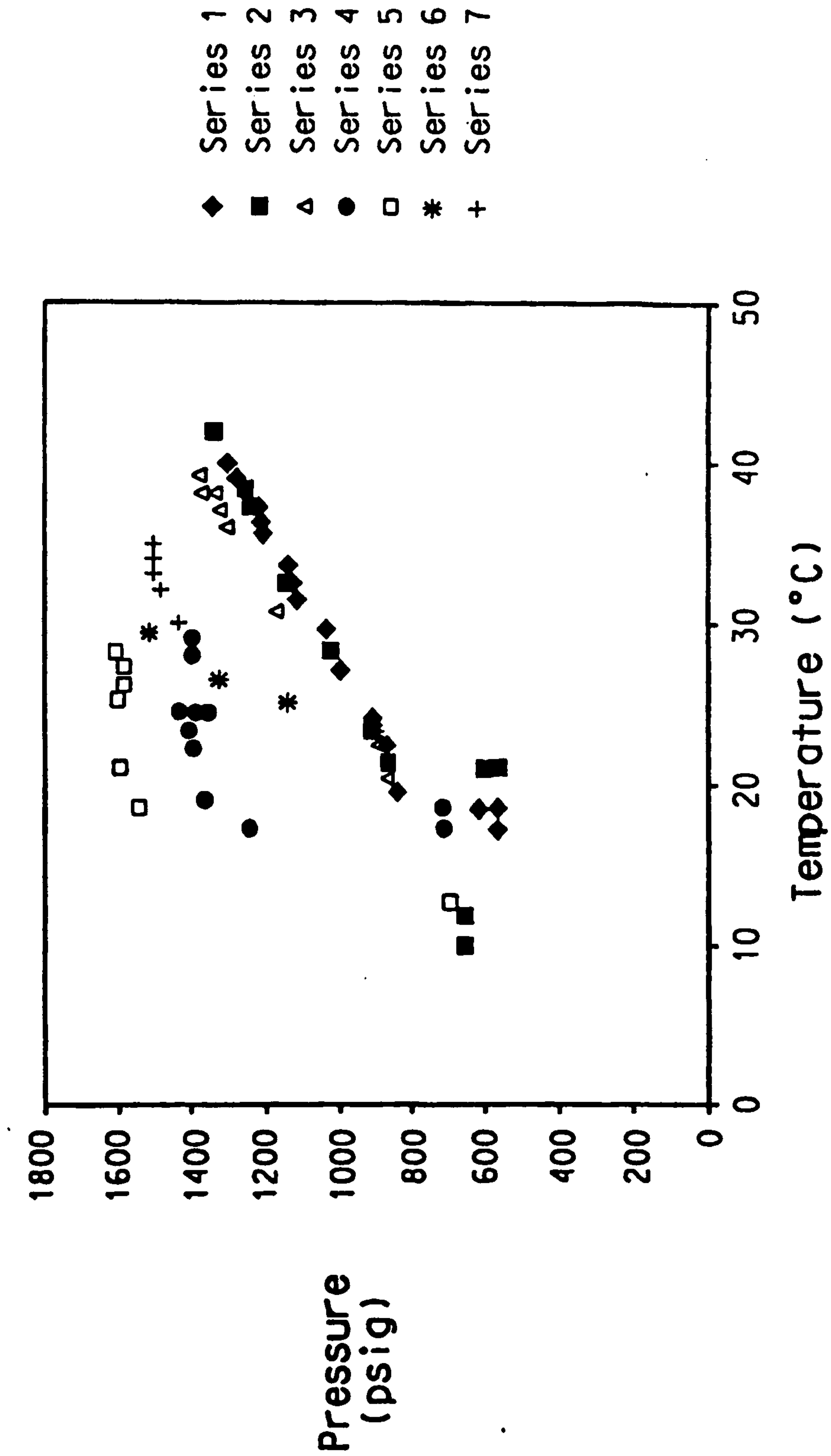
Pressure (psig)
1800
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
Temperature (°C)
◆ Series 1
■ Series 2
△ Series 3
● Series 4
□ Series 5
✱ Series 6
+ Series 7

FIG. 3

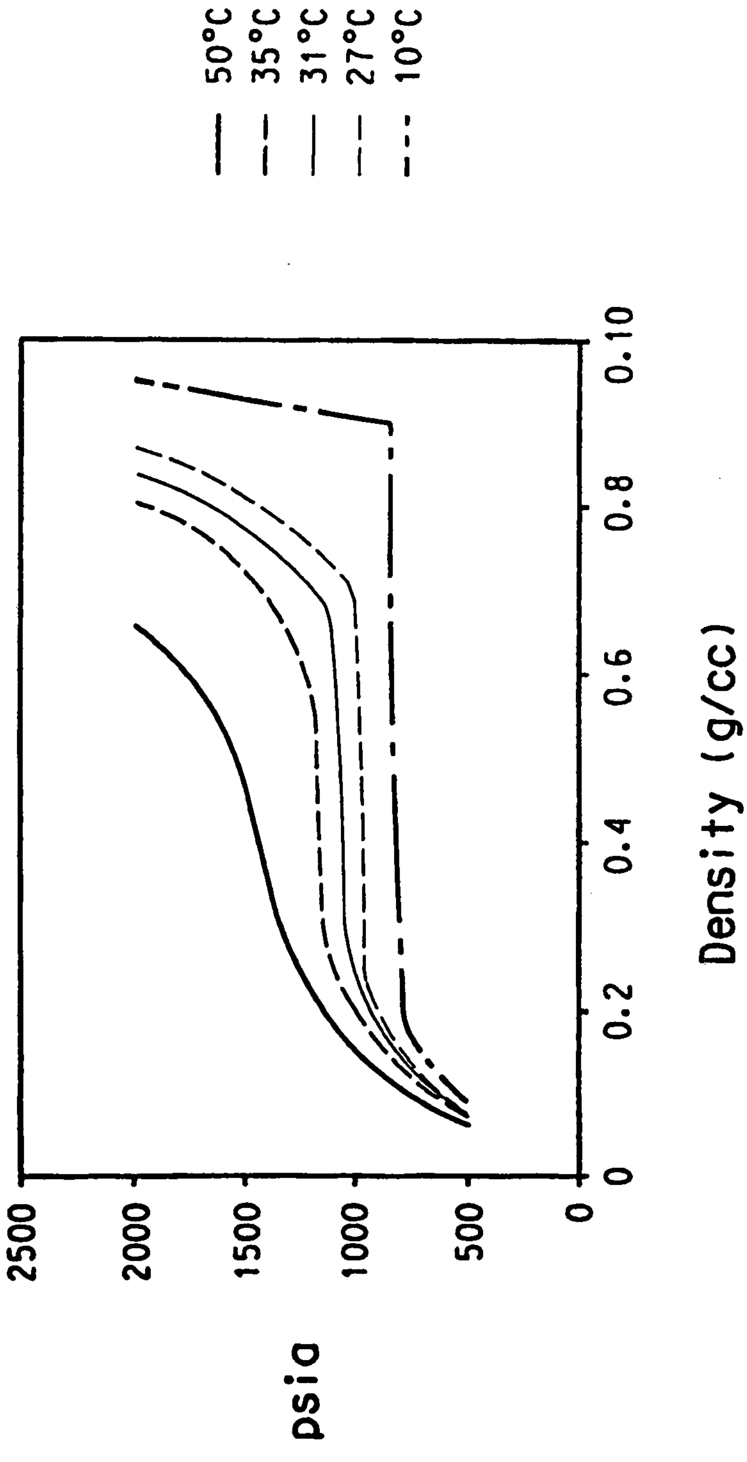
psia
2500
2000
1500
1000
500
0
0
0.2
0.4
0.6
0.8
0.10
Density (g/cc)
50°C
35°C
31°C
27°C
10°C

FIG. 4

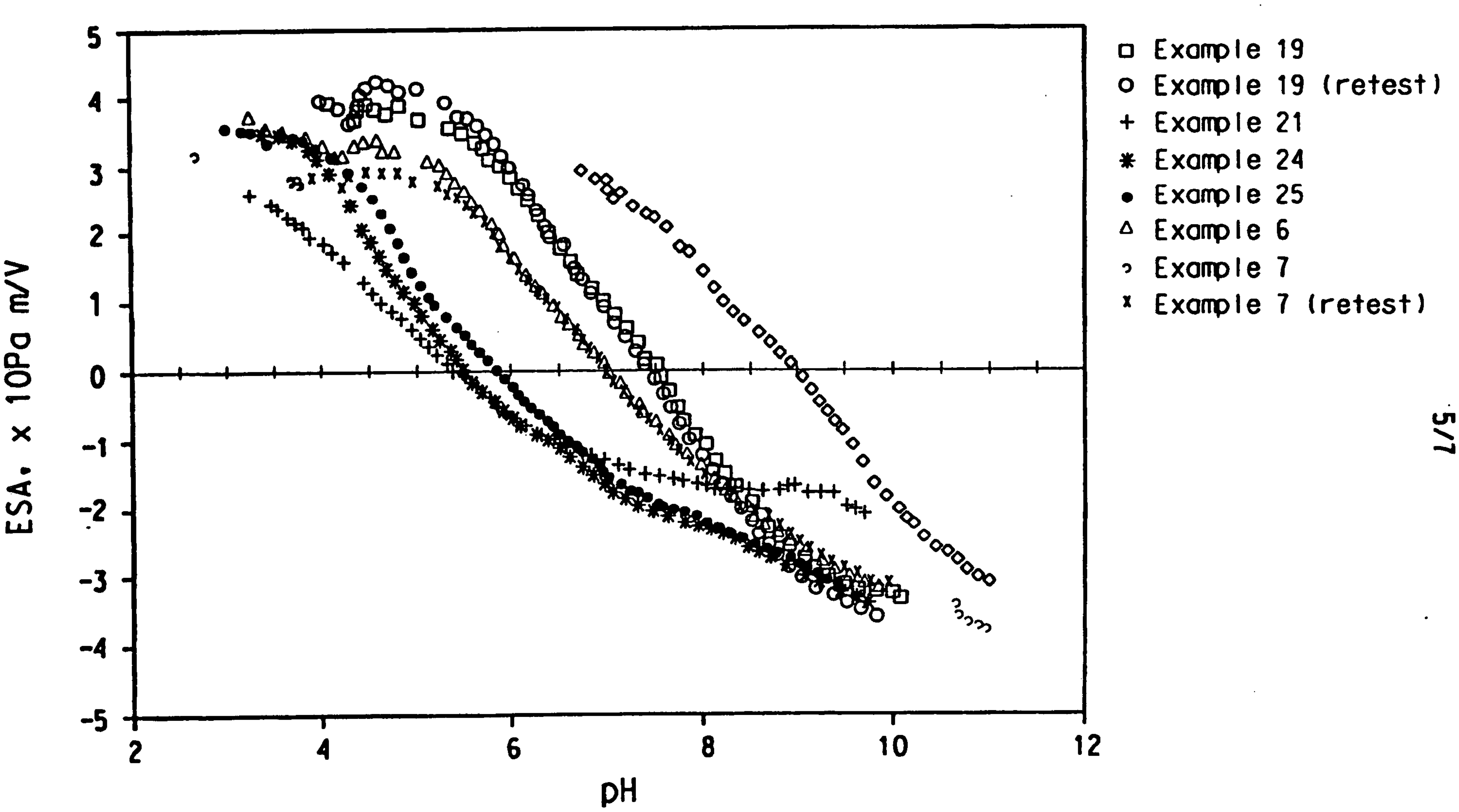
5
4
3
2
1
0
-1
-2
-3
-4
-5
ESA, x 10Pa m/V
-3
2
4
6
8
10
12
pH
□ Example 19
○ Example 19 (retest)
+ Example 21
✱ Example 24
● Example 25
△ Example 6
ↄ Example 7
ⅹ Example 7 (retest)

FIG. 5A

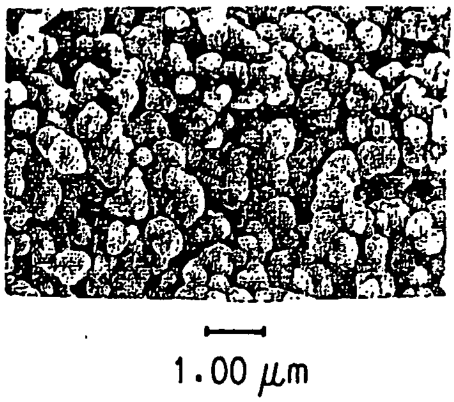

FIG. 5B

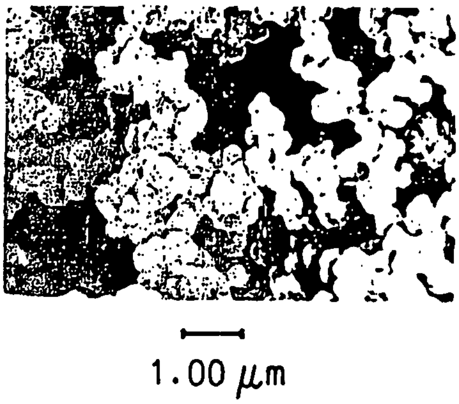

FIG. 5C

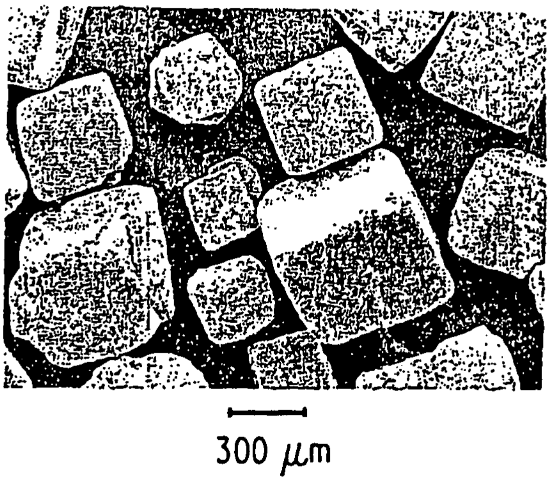

FIG. 6A

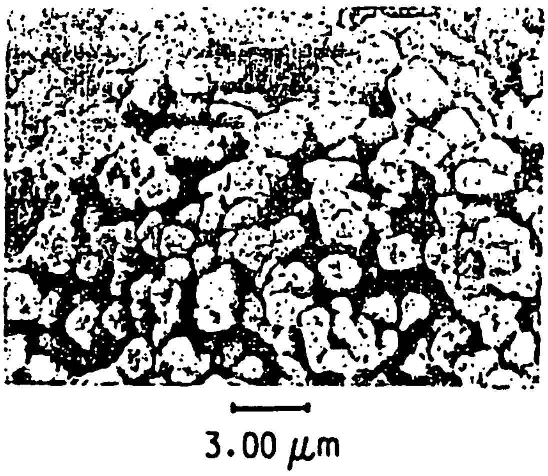

FIG. 6B

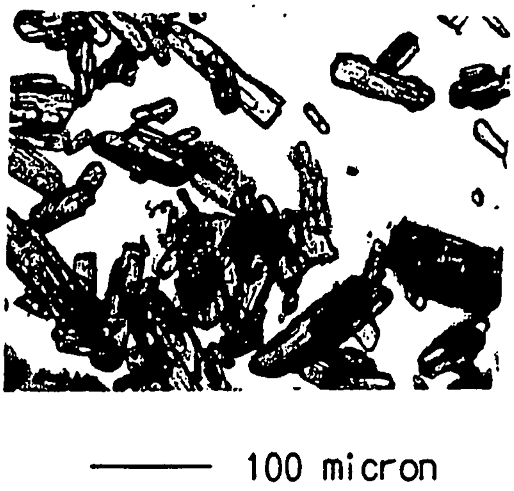

FIG. 7A

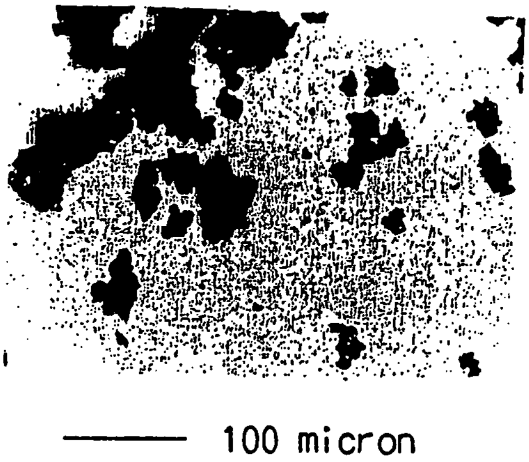

FIG. 7B

FIG. 7C

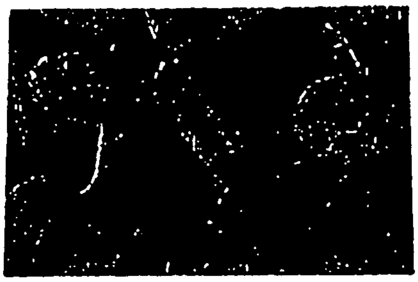

FIG. 8

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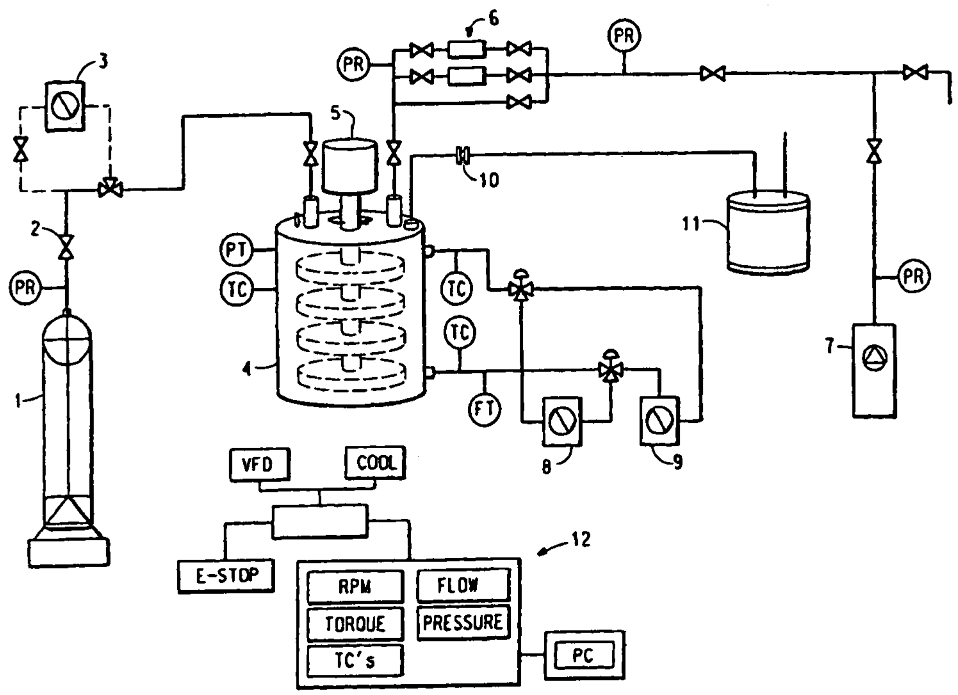
(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) **Title:** HIGH PRESSURE MEDIA AND METHOD OF CREATING ULTRA-FINE PARTICLES



(57) **Abstract:** This invention discloses a high pressure media mill (HPMM) and processes ~~for use thereof:~~ (a) adding grinding media and material to be milled to a high pressure media mill; (b) evacuating mill to produce a vaccum; (c) adding a supercritical fluid or volatile gas to said mill; (d) pressurizing and maintaining pressure in said mill; and (e) operating the mill so that product particles are reduced in size.

WO 02/094443 A3

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
13 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 02/16159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B02C17/16 B02C17/18 B02C17/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B02C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 854 311 A (RICHART DOUGLAS S) 29 December 1998 (1998-12-29) column 1, line 12 - line 15 column 2, line 33 - line 38 column 4, line 49 - line 67 column 5, line 1 - line 42 column 6, line 10 - line 18 ---	1-5,7, 15-18
Y	US 4 221 342 A (TADEMA JAN C ET AL) 9 September 1980 (1980-09-09) column 1, line 30 - line 33 ---	1-5,7, 15-18
A	US 1 040 455 A (DRAISWERKE) 24 August 1966 (1966-08-24) column 1, line 9 - line 10 column 1, line 32 - line 42 figure 2 --- -/--	1-3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search 30 August 2002	Date of mailing of the international search report 09. 01. 03
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Redelsperger, C

INTERNATIONAL SEARCH REPORT

Inte ‾ l Application No
PCT/US 02/16159

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 934 579 A (HIERSCHE WOLFGANG ET AL) 10 August 1999 (1999-08-10) column 2, line 55 - line 60 column 8, line 56 - line 59 ---	1
A	US 5 662 279 A (CZEKAI DAVID ALAN ET AL) 2 September 1997 (1997-09-02) column 10, line 4 - line 5 -----	2

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/16159

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7,15-18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,15-18

A process for milling ultrafine particles comprising the steps of:
-adding grinding media and material to be milled to a high pressure.
-evacuating the mill to produce vacuum.
-adding a supercritical fluid or volatile gas.
-pressurizing and maintaining pressure in said mill.
-operating the mill to produce particles in reduced size.
and the resulting products.

2. Claims: 8-14

A mill comprising:

- A grinding chamber capable or holding material at pressures of up to 2000 psig.
- A magnetic driven stirrer in said chamber.
- A magnetic drive.

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		JP 10028891 A	03-02-1998
US 5662279 A	02-09-1997	NONE	

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[51] Int. Cl^7
B02C 17/16
B02C 17/18 B02C 17/24

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[43] 公开日 2004 年 9 月 29 日

[11] 公开号 CN 1533304A

[22] 申请日 2002.5.22 [21] 申请号 02810582.6
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[87] 国际公布 WO2002/094443 英 2002.11.28
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地址 美国特拉华州威尔明顿
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Q·Q·赵

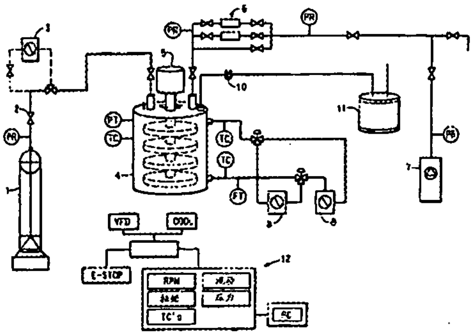
[74] 专利代理机构 中国专利代理(香港)有限公司
代理人 周慧敏 马崇德

权利要求书 2 页 说明书 15 页 附图 7 页

[54] 发明名称 高压介质磨

[57] 摘要

本发明公开了一种高压介质磨(HPMM)及其使用方法：(a)向高压介质磨中加入研磨介质和待磨物料；(b)抽空该磨以产生真空；(c)向所述磨中加入超临界流体或挥发性气体；(d)在所述磨中加压并保压；和(e)运行该磨使得产品颗粒尺寸减小。



ISSN1008-4274

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1. 一种研磨方法，包括以下步骤：

(a) 向高压介质磨中加入研磨介质和待磨物料；

(b) 抽空磨以产生真空；

(c) 向所述磨中加入超临界流体或挥发性气体；

(d) 在所述磨中加压并保压；和

(e) 运行该磨使得产品颗粒尺寸减小。

2. 权利要求1的方法，包括以下附加步骤：

向步骤(a)中加入液体或固体物料，用于涂敷产品颗粒。

3. 权利要求1或2的方法，其中所述方法是连续的。

4. 权利要求1或2的方法，其中该方法是连续的，并且其中所述超临界流体选自CO_2、HFC或替代品、丙烷、甲烷及其组合。

5. 权利要求1或2的方法，其中研磨介质是陶瓷、玻璃、钢或聚合物材料。

6. 权利要求1或2的方法，其中，95%的产品颗粒不大于1微米。

7. 权利要求4的方法，其中，CO_2处于液态。

8. 一种磨，包括：

(a) 一个研磨腔，能够在最高2000 psig的压力下容纳物料；

(b) 在所述腔室中的磁性搅拌器；和

(c) 磁驱动。

9. 权利要求8的磨，其还包括：

(a) 到所述研磨腔中的一个或多个口，用于装卸研磨介质、待磨物料和高压下的流体。

10. 权利要求8或9的磨，其中所述研磨腔包含通过密封装置结合在一起的两个或多个部分。

11. 权利要求8的磨，其中所述搅拌器包含连接到轴上的圆盘。

12. 权利要求8或9的磨，其中所述研磨腔含有研磨介质，研磨介质选自陶瓷、玻璃、金属、聚合物材料及其组合。

13. 权利要求8或9的磨，其中高压流体选自CO_2、HFC和替代物、丙烷、甲烷及其组合。

14. 权利要求8的磨，进一步包含用于控制温度、压力和进料速度的控制装置。

15. 权利要求1或2的方法，其中产品中值粒径小于200微米。

16. 权利要求15的方法，其中中值粒径小于100微米。

17. 权利要求1、2、3、4、5、6、15或16的方法的产品。

18. 权利要求17所述的产品，其中该产品不含残余的研磨流体或气体。

高压介质磨

技术领域

本发明涉及高压介质磨(HPMM)及其使用方法。

背景技术

浆料介质研磨对于矿物、油漆、油墨、颜料、微生物、食品和农产品及药物的细磨和超细磨是各种工业中的一个重要单元操作。在这些磨中，进料颗粒在大量小研磨介质之间减小尺寸，这些研磨介质通常是沙、塑料珠、玻璃、钢或陶瓷珠。由于内部搅拌的非常小的研磨介质和液体介质(水基、非水基或其混合物)的作用，可以生产亚微米或纳米颗粒分散产品的较细颗粒，这在以前用传统的磨是做不到的。

超临界流体(SCF)加工技术在食品、营养品(nutraceutical)和化学工业中有许多用途，并且目前作为一种供选择的技术出现在制药工业中，用途涉及颗粒形成、微包封、涂布、提取和提纯。对于制药用途，二氧化碳是最广泛使用的SCF，尽管其它烃气体如乙烷、丙烷、丁烷和乙烯、水、一氧化二氮、氨和三氟甲烷已经报道用于其它用途。已经公开了三种SCF方法。它们是：

1) 超临界溶液快速膨胀(RESS)法，

2) 反溶剂法，和

3) 从气体饱和溶液中获得颗粒法(PGSS)

RESS法限于SCF可溶性化合物，因为它涉及使化合物溶解在SCF中，随后通过喷嘴的快速膨胀形成颗粒。大多数药物化合物在SCF，尤其是超临界CO_2中，溶解度非常低。

反溶剂法使用SCF作为反溶剂，以便用反溶剂结晶法原理从预溶解的溶剂溶液中沉淀颗粒。由Bradford大学在US 5,108,109中开发的方法结合反溶剂和喷嘴膨胀来控制颗粒形成。反溶剂法的局限性是对于给定的化合物必须使用可溶解的溶剂.

Weidner(美国专利6,056,791)公开了一种方法，即在液体或熔融药物或聚合物中溶解CO_2以形成气体饱和溶液，然后减压以形成颗粒。这种方法的一些明显的缺点是：需要较高的温度熔化化合物可能降解化合物，以及熔体的高粘度可能限制产品的颗粒尺寸。

U.S. 5,854,311 公开了 10-40 微米颗粒在粉末涂敷用途中的应用。所公开的方法在不大于 30 psig 下运行。

U.S. 5,500,331 公开用小颗粒研磨材料来粉碎物料。U.S. 5,145,684 公开了表面改性药物纳米颗粒。在这些专利中公开的技术涉及研磨的浆料，而不是干燥的可流动纳米颗粒，因为在该方法中使用液体介质。

Hock S. Tan 和 Suresh Borsadia 在使用超临界流体形成颗粒：制药用途，Exp. Opin. Ther. Patents (2001) 11(5)，Asley Publications Ltd. 综述了使用超临界流体(SCF)加工法用于受控的颗粒形成的一些方法概念。但是，该文章没有描述使用 SCF 产生干燥可流动微尺寸粉末的研磨设备。

本发明，一种高压介质研磨(HPMM)法，把浆料介质磨与超临界流体(SCF)技术结合或与作为研磨介质的挥发性气体结合，以生产处于干燥自由流动粉末形式的微米或纳米颗粒，而不限制溶解度并且不需要有机溶剂或高温。挥发性气体还可以包括冷却成液态的那些气体，如液体 CO_2。该方法具有用于许多材料包括热敏生物活性材料和环境敏感的电子材料的用途。

发明内容

本发明涉及一种研磨方法，其包括以下步骤：a)向高压介质磨中加入研磨介质和待磨材料；b)把磨排气以产生真空；c)向所述磨中加入超临界流体或挥发性气体；d)在所述磨中加压并保压；和 e)运行该磨使得产品颗粒尺寸减小。

该方法还包括附加步骤：向步骤(a)中加入液体或固体材料用于涂敷产品颗粒。

上述方法包括一种实施方案，其中中值产品粒径小于 200 微米，优选小于 100 微米，更优选小于 1 微米。优选的是产品中不含残余的研磨液体或气体。

本发明还包括一种磨，其包括：a)能在最高 2000 psig 的压力下容纳材料的研磨腔；b)在所述腔室中的磁力驱动搅拌棒；和 c)磁力驱动。

本发明还包括上述的磨，其进一步包括：d)引入到所述研磨腔的一个或多个端口用于装卸研磨介质、待磨物料和高压流体。

附图说明

图 1 描述 SC 介质磨的一般设计。

图 2 描述介质磨实验装置的草图。

图 3 表示在 SC 介质磨中 CO_2 的 PT 曲线。

图 4 描述压力密度曲线的计算值。

图 5(a)表示在对 HNO_3 和 KOH 滴定的 KNO_3 中的超临界研磨的 TiO_2。

图 5(b)表示产品的扫描电子显微图像。

图 6(a)表示 NaCl 原料的微观图像。

图 6(b)表示相同材料在研磨后的微观图像。

图 7(a)和(b)表示 19a 中的加工材料的光学显微镜照片。

图 7(c)表示在 19a 上的布洛芬的 SEM 照片。

图 8 表示在试验 19(c)的 kv 加速下布洛芬的 SEM 照片。

发明详述

本文所述浆料介质磨能够进行微米和纳米颗粒浆料生产，并且可以广泛用在大规模操作的化学工业上。SCF 在这里用作低粘度液体介质，以便于研磨过程中更好的分散和能量传递。当在研磨过程后释放 SCF 时，获得分散的、干燥的自由流动粉末作为产品。该方法还不限于使用 SCF。在 T_c(或 $T_{临界}$，临界温度)和 P_c(或 $P_{临界}$，临界压力)下，液体 CO_2 或其它挥发性气体可以用作研磨介质。

相对于现有微米化技术，特别是对于制药用途，这种方法提供了显著的优点。这些优点包括：产生干燥的微米和纳米颗粒，这些颗粒难以通过微米化和其它现有方法产生或根本不可能；在研磨过程中集成了涂敷或包封；用于直接吸入制剂的干燥细颗粒，包括干粉吸入和计量剂量吸入以及口服和非肠道制剂；和来自固体颗粒、细胞、植物等的活性成分的一体化破坏和提取。

本文描述且如图 1 所示的高压介质磨(HPMM)装置是一种介质磨研磨腔室(4)，其用超临界气体加压，例如二氧化碳。尺寸减小、产品颗粒的解团聚和分散所需能量得自机械搅拌器(5)，机械搅拌器(5)控制一组搅拌圆盘(17)，搅拌园盘在磨研磨腔(4)中使研磨珠介质(27)运动。磨的研磨腔(4)具有下部(20)和上部(19)。产品颗粒被捕获在搅拌圆盘(17)之间并暴露于碰撞的研磨珠介质(27)。驱动皮带(28)连接到马达(29)，马达(29)有速度传感器(30)和扭矩传感器(31)。

所述磨在流体（大多数情况下为 CO_2）的超临界压力和温度以上操作，尽管可以使用任何可压缩气体，包括但不限于烃（HFC's）及其替代物、丙烷、甲烷等。压力和温度的选择允许控制流体的粘度和密度，这对磨腔内的流动型式有重要影响，所以对传热和传质有重要影响。

HPMM 特别用于干燥形式的亚微米颗粒的生产。生产干燥的良好分散的粉末是可能的，因为在加工后超临界流体被排出。不需要使用水（例如某些物料如蛋白质在水中是不稳定的）并且省去了干燥步骤。生产流程被简化并且一体化（例如纳米晶材料的表面处理和分散；细胞的研磨、破坏和提取生物组分同时发生而不暴露于空气/氧气），从而通常比分散和研磨的其它方法更便宜。

在图 1 中，介质磨本身的设计是已知的，如上所述。研磨腔是一个压力容器（4），它由下部（20）和上部（19）组成。如图 2 所示，本文中的 HPMM 实验装置通过连接 4 个搅拌圆盘（17）到由磁力搅拌器（5）控制的轴上而组成，磁力搅拌器在该组件的上部（19）中。容器的下部（20）通过密封装置连接到上部。密封装置可以是机械的、磁力的或其组合。螺栓可以与密封装置一起使用或者作为密封装置的一部分。还连接了用于加热和冷却（21 和 22）容器周围的夹套的连接。

安全膜（10）到制动转筒（11）和转筒排气口（25）的管道被连接用于安全性。

去除在上部中的装料口（13）的塞子并使用漏斗来装入研磨介质和待加工固体。用来涂敷颗粒的任何其它液体或固体组分此时通过相同的口加入。该口用塞子封闭并准备装入要使用的超临界流体。

关闭超临界介质磨的全部阀门并打开通过产品收集过滤器（6）的来自真空泵（7）的阀门（14、15 和 16），以便在加工开始之前把全部空气从系统中抽出。该真空用要用在加工中的在天平（24）上的 SC 流体（1）破坏，通过关闭到真空泵（16）的阀门和打开到要使用的 SC 流体钢瓶（2）的阀门来做到这一点。在开始装料前重复这种抽真空和吹扫过程三次。

当容器的最后一次抽真空完成时，记录来自钢瓶天平（24）的重量。打开夹套的冷却水（9），然后把容器装入特定重量的来自钢瓶（1）和阀门（2）的 SC 流体，这通过管道或使用泵（3）进行，然后关闭钢瓶（2）的阀门。记录该流体重量。关闭阀门（14 和 15）使该容器孤立。

打开马达(5)到设定的速度，关闭冷却水(8)并开始加热(9)。对于要运行的所设计设备，加热设定在特定温度。在监视和控制系统(12)上记录数据，包括RPM、扭矩、温度、压力和到夹套的流量(用GPM表示)，直至希望的测试时间完成。

然后停止加热(9)，并开始冷却(8)，当容器的温度低于25℃时，停止马达驱动(5)。当冷却完成时，打开阀门(15)在收集过滤器(6)中收集产品。从过滤器中回收物料供使用。

移开磨的下部(20)，回收在容器中和叶片上残留的所有过量物料，清扫该单元并重新组装用于进一步试验。

启动条件

初始试验涉及磨的装载和卸载、产品收集、温度和功率控制以及数据采集。

在装载SC CO_2之前，该磨需要在真空循环中抽出空气。真空循环应当重复至少3次，以便除去夹带的空气。压力和温度的监测是必要的，因为小的变化可能导致大的压力增大. 监测可以进行SC区域在相图中的定位(图4)。此外，在初始试验后，注意到以下结果:

注意到TiO_2在SC磨中的快速分散。在10分钟内获得一次粒径。聚合物珠碰撞足以破坏TiO_2团聚体。与SEPR相比，聚合物珠减小了磨损率。

磨的装载用天平测量，达到0.65-0.7 g/cc的优选装载量。

操作条件按照图4中所示的相图. 热交换/混合在较低RPM下较差。

可接受的结果在50-70体积%的珠装载量下获得。还注意到磨的内容物的良好循环。

热力学

不同试验的PT曲线表示在图3中。明显看出了排气的影响。很明显，如果用太高的密度开始试验(在SC磨中更大的CO_2质量，如系列5、6)，压力必须增大到4000 psig以达到超临界等温线($T_{临界}$=31.1℃)。

系列1: 仅加热

系列2: 加热+搅拌

系列3: 加热+搅拌试验2

系列4: 加热+搅拌+TiO_2 50 g

系列 5：加热+搅拌+TiO_2 150 g

系列 6：加热+搅拌+TiO_2 150 g 排气 1

系列 7：加热+搅拌+TiO_2 150 g 排气 2

图 4 是“计算的压力-密度曲线”并表示对不同操作温度的计算值（10、27、31、35、50℃）。恒定体积的磨腔装载已知质量的 CO_2。所以，CO_2 密度在试验过程中处于恒定水平。该图用来对于不同操作温度预测 SC 磨腔中的压力，并可以证明获得 SC 条件。

定义

本文使用以下定义：

SC：超临界

SC CO_2：MG Industries, Malvern, PA

杀真菌剂：Famoxadone

SEPR：得自 S.E. Firestone Assoc., Russell Finex Inc., Charlotte, NC 的陶瓷研磨介质

YTZ：得自 S.E. Firestone Assoc., Russell Finex Inc., Charlotte, NC 的陶瓷研磨介质

Poly-Sty：得自 S.E. Firestone Assoc., Russell Finex Inc., Charlotte, NC 的聚苯乙烯研磨介质

Nylon：尼龙粉末，Dupont Co., Wilmington, DE

Silver：用于含银导体的银颗粒，DuPont Company, Wilmington DE

除非另外说明，所有的化学药品和试剂都是按得自 Aldrich Chemical Co., Milwaukee, WI 的原样使用的。

实施例

实施例 1-19

用 HPMM 进行以下实验来探索操作范围（马达速度、压力水平、运行时间）和研究介质装载、介质类型和添加剂的影响。实验条件列在表 1，“试验条件”中。测试了以下（有机和无机）材料。

0 无机 - 在水中不可溶的（TiO_2）

0 有机 - 在水中可溶的（葡萄糖、醋胺酚、布洛芬）

0 有机 - 在水中不可溶的（famoxadone）

0 无机 - 在水中可溶的（NaCl）

此外，测试了含银导电浆料。这些是厚膜组合物，通过丝网印刷涂敷在陶瓷基板和介电组合物上。这些基板然后在输送带炉中在氧化气氛(空气)中烧成，以便在单层和多层微电路中形成互连的线路和焊点。含银导体焊点通常用于无源 SMT 元件用低温共熔 Sn/Pb 焊料或导电环氧粘合剂的连接。

醋胺酚(Paracetamol)用 HPMM 测试，以产生用于吸入器用途的 1-5 微米颗粒。

实施例 19a、19b 和 19c

用 HPMM 的布洛芬

表 1 列出了在 HPMM 上用布洛芬进行实验的条件。布洛芬购自 Spectrum Chemicals。用于试验的流体是 CO_2。

试验 19a：布洛芬在超临界 CO_2 中的介质研磨

在试验 19a 中，温度保持在 35℃。磨腔中的压力为 1550 psi。总试验时间为 2 小时。使用振动筛在卸压后收集产物。

表 2 列出所产生的中值粒径(D50)。颗粒尺寸分布用正向光散射装置(Malvern Mastersizer 2000)测量。尺寸分布向右侧漂移，表明颗粒由于细产物颗粒的团聚和聚集而长大。光学显微镜和 SEM 照片证实了这一点。图 7a 和 b 表示原样的布洛芬的光学显微镜照片(Nikon Optiphot)。图 7c 表示加工后物料的照片(试验#19a)。

图 7c 表示试验 19a 的布洛芬的 SEM 照片，颗粒小到 30 纳米。试验 19a 的操作温度(35℃)高于布洛芬的软化温度，这导致这些颗粒的熔合/聚集。

试验 19b：布洛芬在液体 CO_2 和表面活性剂(SDS)中的介质研磨

本试验的目的是证明通过低操作温度和表面活性剂可以避免/减少团聚。在试验 19b 过程中，温度保持在 10℃，而磨腔中的压力为 600 psi(见表 2)。总运行时间是 30 分钟。35 重量%的表面活性剂(十二烷基硫酸钠，MW=288.38，由 ICN Biomedical Inc. 供给)。

颗粒尺寸从 33.85 微米(原样的)减小到 1.805 微米。图 8 表示试验 19b 的产物的 SEM 照片。

试验 19c：布洛芬在液体 CO_2 和表面活性剂(SDS)中的介质研磨

与试验 19b 中一样，布洛芬在液体 CO_2 中研磨，但是使用 2 重量%的 SDS 表面活性剂。结果表示在表 2 中。

表 1：试验条件

实施例	珠	珠	珠	产物	产物	CO_2	添加剂
	类型	%	尺寸 (mm)	克		克	名称/克
1	SEPR	80	.8-1.0	50	TiO_2	410	
2	SEPR	76	.8-1.0	150	TiO_2	410	
3	SEPR	80	.8-1.0	150	TiO_2	386	
4	SEPR	50	.8-1.0	150	TiO_2	477	
5	SEPR	70	.8-1.0	150	TiO_2	410	
6	Poly-Sty.	70	0.5	150	TiO_2	363	
7	Poly-Sty.	50	0.5	150	TiO_2	454	
8	Poly-Sty.	70	0.5	150	Dextrose	295	
9	Poly-Sty.	70	0.5	150	Dextrose	318	
10	Poly-Sty.	70	0.5	150	NaCl	340	
11	SEPR	70	.8-1.0	150	Dextrose	363	
12	SEPR	70	.8-1.0	150	NaCl	363	
13	Poly-Sty	70	.25/.15	150	Silver	431	
14	Poly-Sty	70	0.5	150	Silver	363	
15	SEPR	70	.8-1.0	150	Famoxadone	363	
16	Nylon	70	.5/.88	150	TiO_2	409	
17	Poly-Sty	70	0.5	150	Silver	363	硬脂酸 0.75
18	Poly-Sty	70	0.5	150	Silver	363	硬脂酸 0.75
19	YTZ	70	0.3	150	Acetominophen	370	
19a	SEPR	70	8-1.0	150	Ibuprofen	370	—
19b	SEPR	70	8-1.0	110	Ibuprofen	370	十二烷基硫酸钠
19c	SEPR	70	8-1.0	150	Ibuprofen	370	十二烷基硫酸钠

过程监测和产品表征

在每个试验过程中，监测 HPMM 中的温度和压力、磨吸收的功率、搅拌器速度。产品用其尺寸、形状、表面形貌和反应性/活性表征。

用 Leeds and Northrop 的 Microtrek UPA 和 Microtrek FRA 测量进料和产物的颗粒尺寸分布（见表 2）。使用 Hitachi S-4700 (Hitachi Instruments, San Jose, CA) 拍摄扫描电子显微图像

(SEM)，粉末样品安置在双面胶带上，对许多样品进行X-射线粉末衍射。粉末衍射研究所用的仪器是Philips X-射线衍射仪PW 3040(Philips Analytical Instruments, Natick, MA)。所用的技术是使用CuKα辐射的粉末X-射线衍射。图6a表示研磨前的实施例12的NaCl的SEM，图6b表示研磨后的相同物料的SEM。可以注意到物料尺寸的减小。

表2：试验结果总结(在1750 rpm进行全部研磨试验)

实施例	总时间	SC时间	净扭矩 (零点=14.6)	瓦	温度	压力	能量	比能量	中值粒径
No.	Hrs.	Hrs.	In-lbs.		摄氏	Psi	KWh.	KWh. /Kg	D50 [micron]
1	2.00	1.80	22.8	472	35	1400	0.94	18.89	0.34
2	1.60	0.50	25.4	526	33	1500	0.84	5.61	0.27
3	1.08	0.50	45.4	940	38	1300	1.02	6.77	0.32
4	0.83	0.50	10.6	220	37	1350	0.18	1.21	0.28
5	0.25	0.17	23.4	485	36	1550	0.12	0.81	0.28
6	0.28	0.17	10.4	215	34	1320	0.06	0.40	0.35
7	0.33	0.10	2.4	50	32	1330	0.02	0.11	0.37
8	0.25	0.17	12.4	257	35	1300	0.06	0.43	173
9	0.50	0.42	17.4	360	36	1400	0.18	1.20	185
10	0.25	0.00	7.4	153	25	570	0.04	0.26	–
11	1.00	0.83	23.4	485	40	1580	0.48	3.23	58
12	1.00	0.83	20.4	422	38	1530	0.42	2.82	4.3
13	1.00	0.75	0.9	19	35	1240	0.02	0.12	23
14	1.00	0.83	2.7	56	37	1300	0.06	0.37	1.8
15	1.00	0.66	20.4	422	33	1550	0.42	2.82	5.4
16	0.50	0.36	6.9	143	37	1375	0.07	0.48	0.33

实施例	总时间	SC时间	净扭矩 (零点=14.6)	瓦	温度	压力	能量	比能量	中值粒径
No.	Hrs.	Hrs.	In-lbs.		摄氏	Psi	KWh.	KWh. /Kg	D50 [micron]
17	1.00	0.95	6.4	133	40	1400	0.13	0.88	1.78
18	1.00	0.83	7.8	162	40	1400	0.16	1.08	28.31
19	4.00	3.70	27.4	583	46	1600	0.16	2.11	5.2
19a	2.00	2.00	5.0	104	35	1550	0.21	1.38	44.68*
19b	0.50	0.50	3.2	66	10	600	0.03	0.30	1.805
19c	2.00	2.00	3.1	61	10	600	0.13	1.11	4.106

* 团聚体

实施例 20-26：TiO_2粉末在 SC 磨中的分散

使用本文所述的 HPMM 研磨 TiO_2，并与标准 TiO_2(R900，得自 E.I duPont de Nemours 和 Co.，Wilmington，DE)比较。为此，如下表 3 中所示，使用许多颗粒表征技术。使用 Matec MBS 8000(Matec Applied Sciences，MA)测定等电点。等电点是 ESV 等于 0 的 pH 值，即与零ζ-电位重合的一点。通过仪器测定电动声波振幅(ESA)的仪器并在搅拌容器中相对于硝酸(降低 pH 值)或氢氧化钾(提高 pH 值)滴定悬浮液来测定等电点，如图 5a 所示。通过在硝酸钾的 10^{-3} mol/dm^3溶液中混合然后在超声波浴中分散 30 秒来制备 SC 产品的悬浮液。超临界研磨产品的等电点与起始原料的等电点不同，表明表面化学状态有某种不同。

在超临界研磨后，在起始物料与产品之间，在颗粒尺寸或表面性质方面没有可分辨的差异。

SC 研磨后的产物的体积密度高达原始物料的两倍。流动性被改善。此外，基于图 5b 和 5c 中所示的 SEM，这些物料看起来是相同的。

HPMM 的功率吸收和加热/冷却是相互作用的，以保持系统在希望的/选择的温度。温度的监测是必要的，因为小的变化会导致大的压力增大。温度和压力的监测允许进行 SC 点在相图中的定位。

在初始试验后，推断出迅速发生 TiO_2在 SC 磨中的分散。聚合物珠碰撞足以破坏 TiO_2团聚体。在研磨 10 分钟内，达到一次粒径。使用天平，磨的装载可以合理地精确。操作条件遵循相图。存在磨内容物的良好循环，尽管在低磨速下热交换和混合较差。50-70 体积%的研磨珠装载量获得了良好的研磨结果。与使用陶瓷小球(SEPR)相比，聚合物珠的使用减小了磨损率。

表3

实施例编号		外观	SEM	等电点	比重瓶法测量的密度	用N₂测量的孔隙体积分布	BET表面积 m2/g	d10, d50, d90, um	XRD, all TiO2. 晶体尺寸
20	原料	成映的白色粉末	进行	7.5	4.22 +/- 0.01	没有微孔	6.2	0.32, 0.60, 1.12	2337
21	原料	细灰色粉末	进行	not enough	3.875 +/- 0.005	没有微孔	40.2	0.20, 0.34, 0.88	610
22	原料	细灰色粉末	进行	5.5	4.086 +/- 0.008	没有微孔	8.9	0.16, 0.27, 0.45	899
23	研磨介质	灰色珠	进行	n/a	n/a	n/a	n/a	n/a	n/a
24	研磨介质	细灰色粉末	进行	not enough	4.130 +/- 0.006	没有微孔	8.2	0.17, 0.32, 0.64	1636
25	研磨介质	细灰色粉末	进行	5.6	4.155 +/- 0.006	没有微孔	8.1	0.16, 0.27, 0.48	1603
26	研磨介质	细灰色粉末	进行	5.9	4.176 +/- 0.004	没有微孔	8.3	0.16, 0.28, 0.44	1573
Comp. B	R900 standard TiO2			9.0					

电动力学结果:

使用 Matec MBS 8000 测定等电点，如上所述。等电点是 ESA=0 的 pH 值。超临界研磨产物的等电点与起始原料的等电点不同，这表明表面化学上有一些差异。

在超临界研磨后，起始原料与产物之间的颗粒尺寸或表面性质方面没有可分辨的差别。SC 研磨后的产物的体积密度高达起始原料的两倍。相对于起始原料，流动性得到改善。

实施例 27-31

沉淀的银颗粒的分散

使用如上所述的高压介质磨研磨银。产物使用扫描电子显微镜表征并且评价颗粒尺寸分布、形状、等电点和润湿性.

表 4

实施例编号	以下全部实验是干银粉	通过 Microtrac 测定的 PSD，d10、d50、d90，微米	扫描电子显微镜，干法安装	润湿粉末所需的 EtOH/水混合物的表面张力
27		1.15、3.09、6.21	具有球形一次颗粒的团聚，其出现在约 0.5-1 微米	>72.6 达因/厘米
28		0.81、1.80、106.8，双峰分布，主峰在 2 微米，另一个峰在 100 微米	较少的规则团聚，约 0.5-1 微米的不规则一次颗粒。板状或硬壳状，也是可见的	<43.7 达因/厘米
29		0.20、0.33、0.59	硬壳状外观，团聚的球形一次颗粒，约为 0.3 微米和更小	n/a
30		0.62、1.78、9.21，通常具有 2 个大肩部	约 0.7 微米和更小的不规则的略有团聚的一次颗粒	<33.6 达因/厘米
31		1.17、28.31、260.1，主峰在 2 附近，然后在更大的尺寸有许多其它峰	具有一些硬壳的团聚不规则颗粒。颗粒尺寸为 1 微米和更小	<33.6 达因/厘米

仅有“原样的”样品润湿到水中并且因此不能评价等电点。与实施例28和29相比，硬脂酸涂层似乎用实施例30和31的更大尺寸表示。

银粉的润湿方面进一步揭示了以下性质。不同的乙醇/水比例产生具有不同表面张力的溶液。这些又将润湿或不润湿所述粉末。银实施例27的起始原料容易被所有的溶液润湿，甚至高达72.6达因/厘米，与对比例C材料一样。这表示在表5中。

表5

% EtOH	校正的 % EtOH	实施例27	实施例28	实施例29	实施例30	实施例31	对比例C	测量的表面，张力 达因/厘米
100	70	0	0	没有样品	2, f	2, f	0	26.7
50	35	0	0		1, f	1, f	0	29.1
75	52.5	0	0		0, f	0, f	0	33.6
25	17.5	0	2, f		99, nw	99, nw	0	43.7
10	7	1	99, f, nw		99, f, nw	99, f, nw	0	54.2
0	0	0	99, f, nw		99, f, nw	99, f, nw	0	72.6

数字=用时间表示的润湿，S（99=在该时间内没有润湿）
nw=沉淀物被润湿
f=在表面形成的薄膜上的未润湿的银

实施例28中所示的产品，其没有添加剂但是已经在超临界磨中处理，表现出明确的疏水特性。需要小于43.7达因/厘米的表面张力来润湿粉末。浸入润湿是相当容易的，可能是由于特殊的粉末密度，但是最显著的问题是在浸渍时在内部润湿粉末团聚体。

已经涂敷硬脂酸的银甚至更不可润湿，要求小于33.6达因/厘米的表面张力来润湿它们。通过使用附加的EtOH/水混合物，可以获得更多的溶解。

在HPMM中加工的银粉不能显著地改变颗粒尺寸，但是表面似乎被改性而变得更疏水。硬脂酸到超临界磨中的添加，然后排出CO_2，似乎留下表面活性剂在颗粒上的有效涂层，其比在没有硬脂酸的SC磨中处理的那些更疏水。这证明这些颗粒实际上在该过程中已经被涂敷。

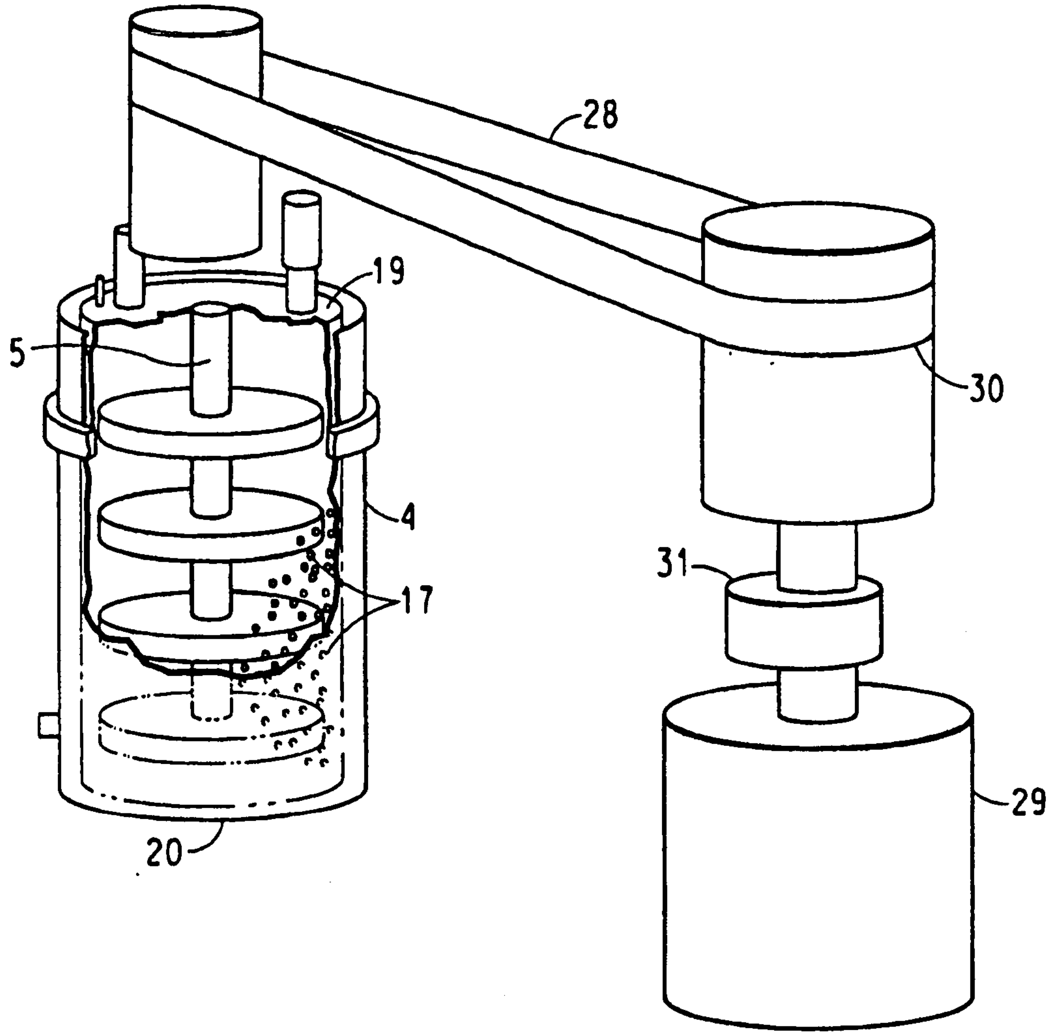

图 1

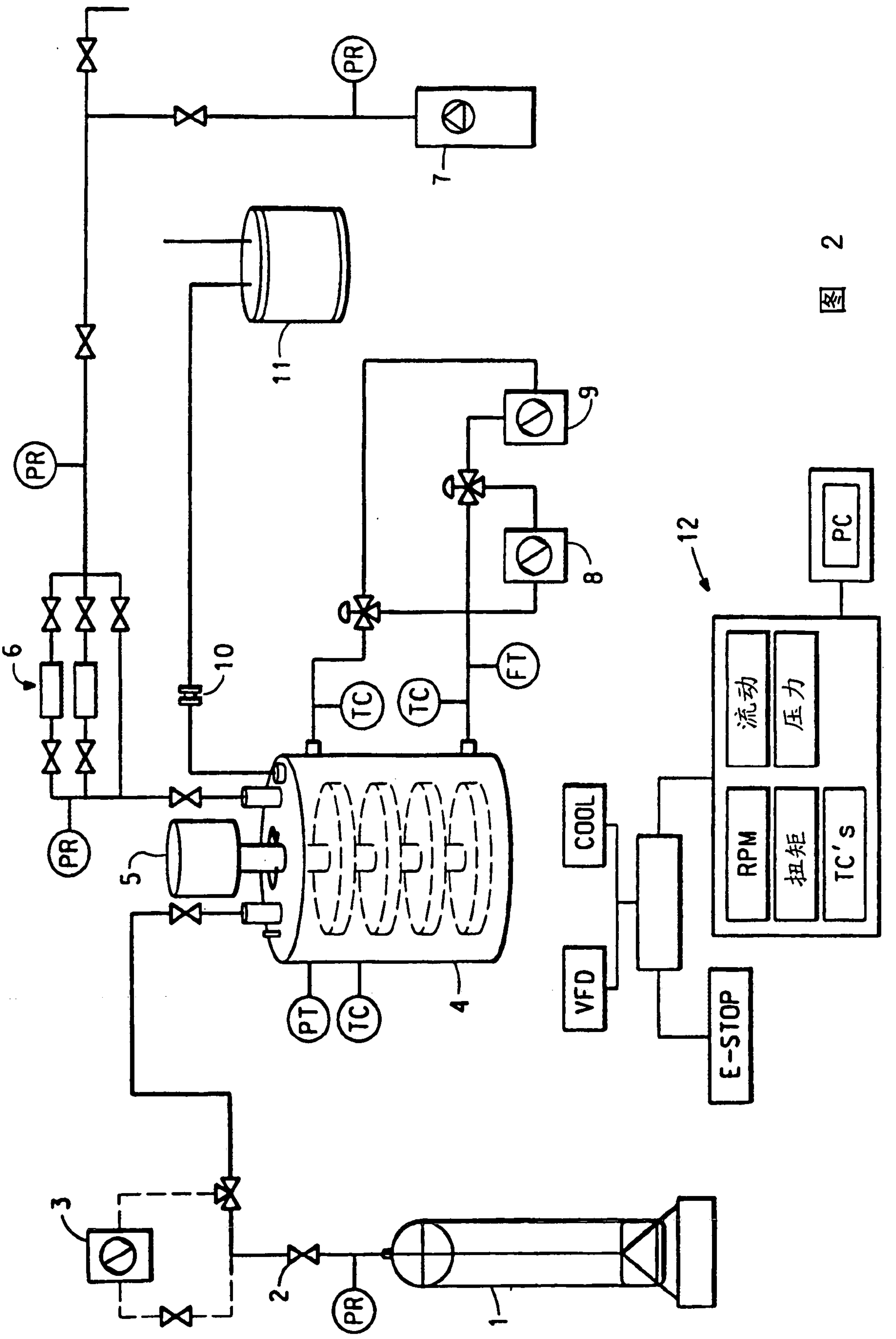
PR
7
11
9
8
12
PC
流动
压力
RPM
扭矩
TC's
COOL
VFD
E-STOP
6
10
TC
TC
FT
PR
5
4
PT
TC
3
2
PR
1

图 2

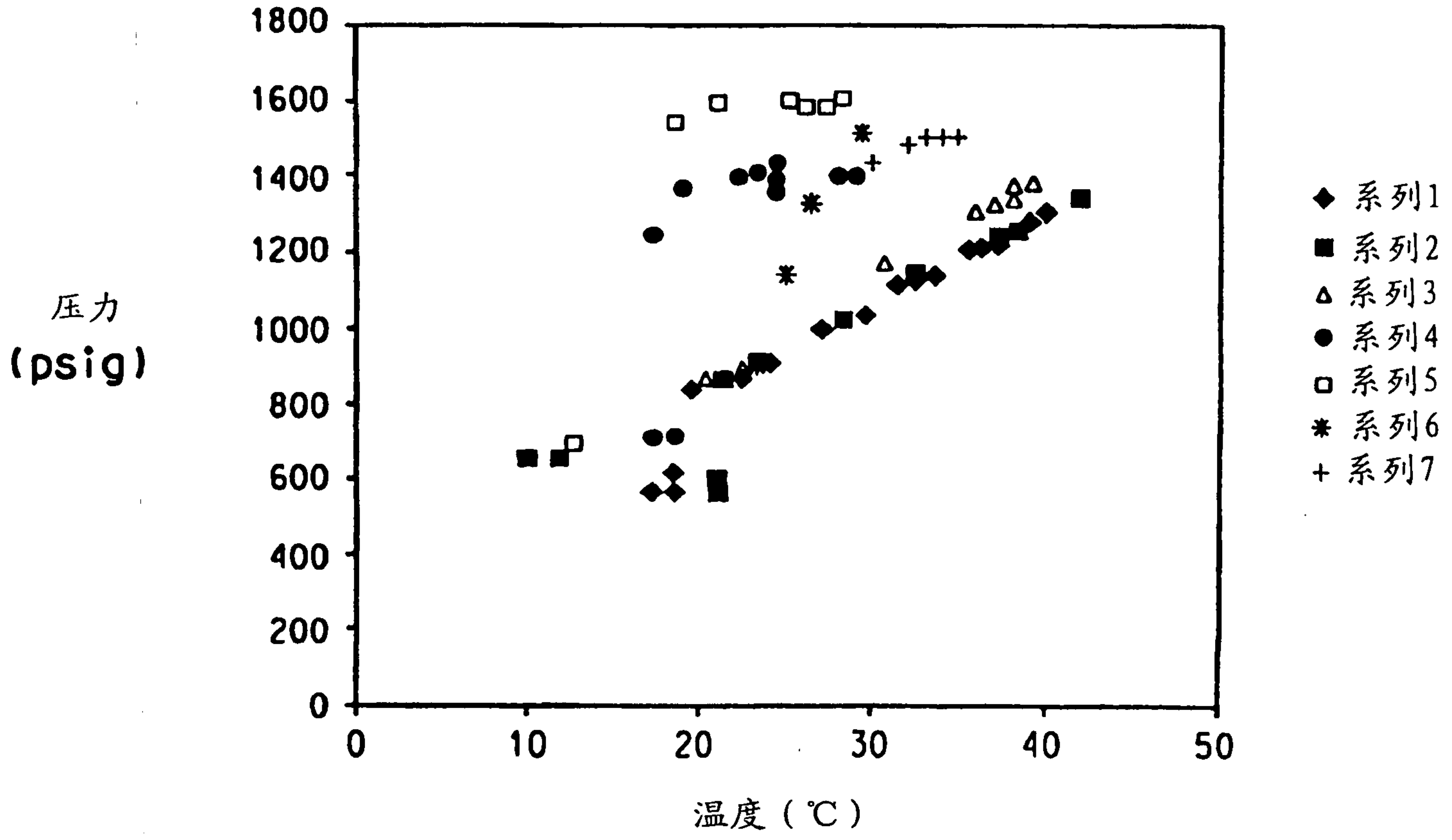
压力
(psig)
1800
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
温度 (℃)
◆ 系列1
■ 系列2
△ 系列3
● 系列4
□ 系列5
✱ 系列6
+ 系列7

图 3

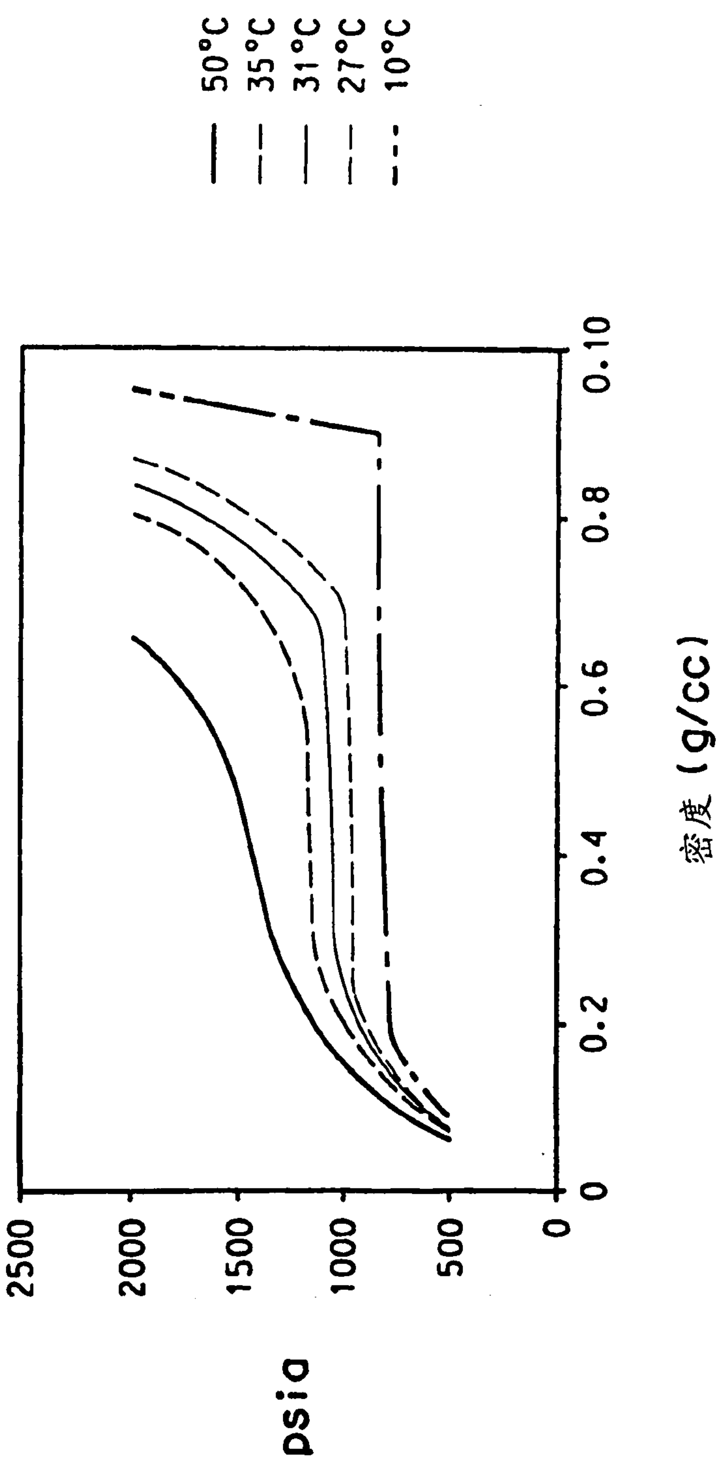
50°C
35°C
31°C
27°C
10°C
psia
2500
2000
1500
1000
500
0
0
0.2
0.4
0.6
0.8
0.10
密度 (g/cc)

图 4

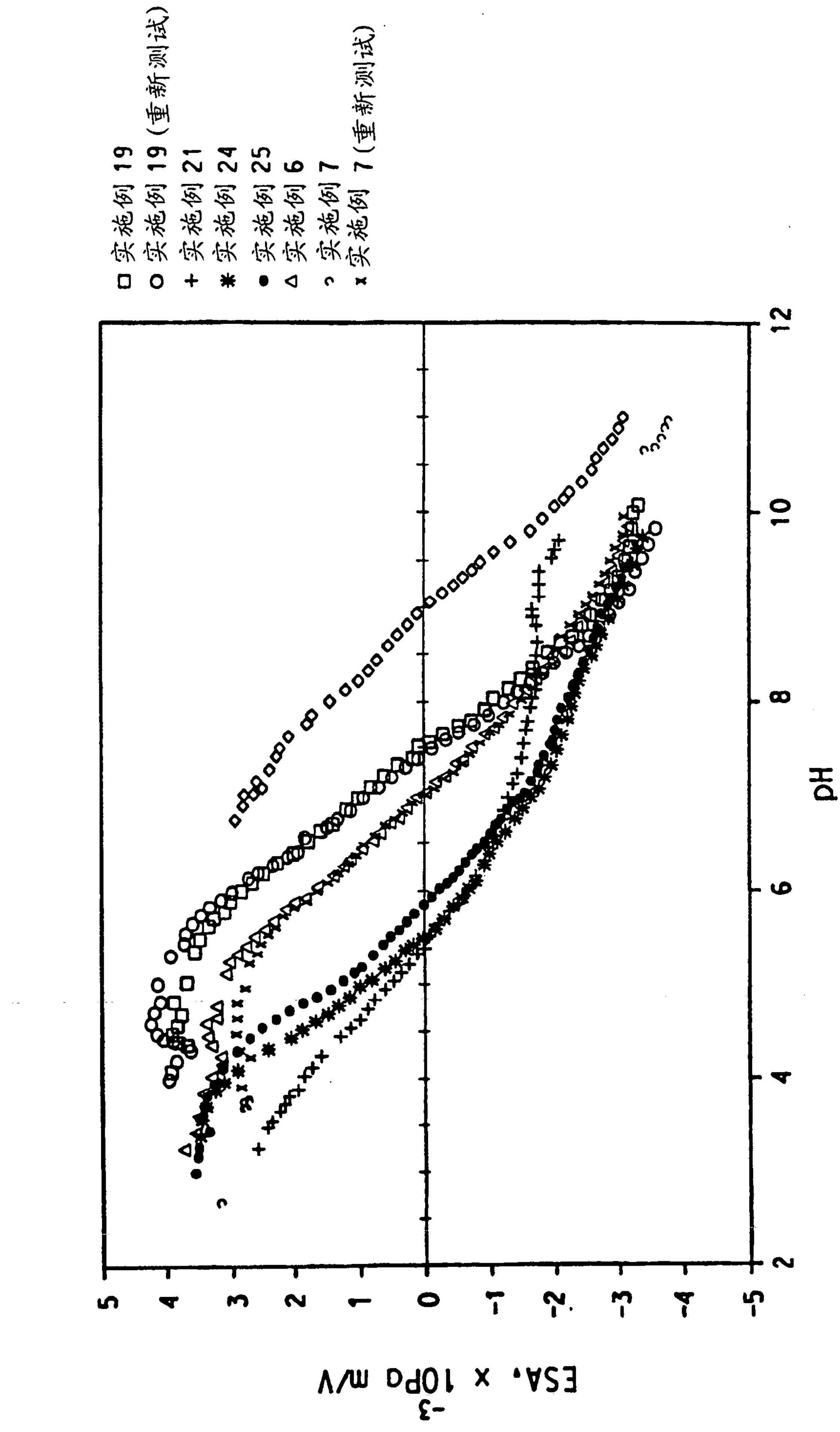
□ 实施例 19
○ 实施例 19（重新测试）
+ 实施例 21
✱ 实施例 24
● 实施例 25
△ 实施例 6
ɔ 实施例 7
x 实施例 7（重新测试）
ESA, x 10^{-3}Pa m/V
5
4
3
2
1
0
-1
-2
-3
-4
-5
pH
2
4
6
8
10
12

图　5A

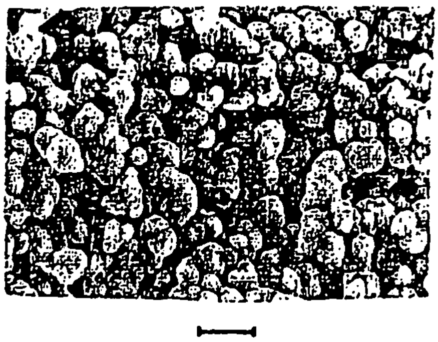

图 5B

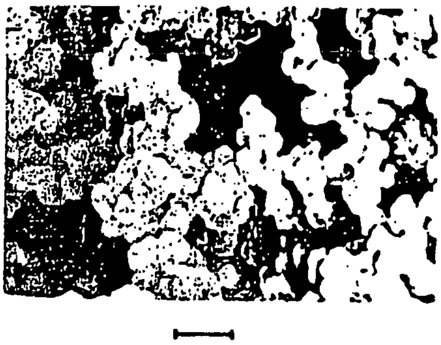

图 5C

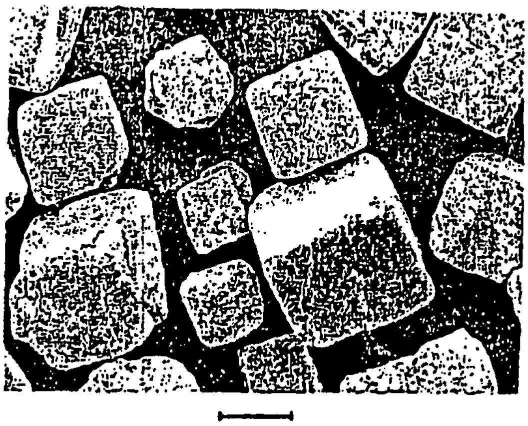

图 6A

图 6B

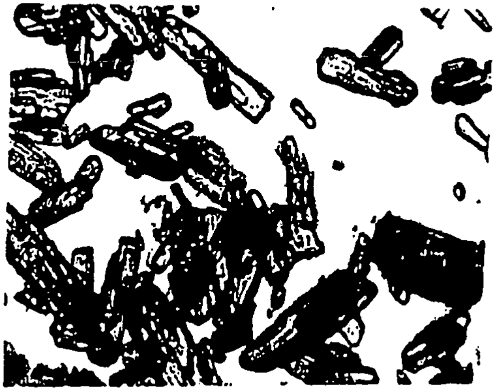

图 7A

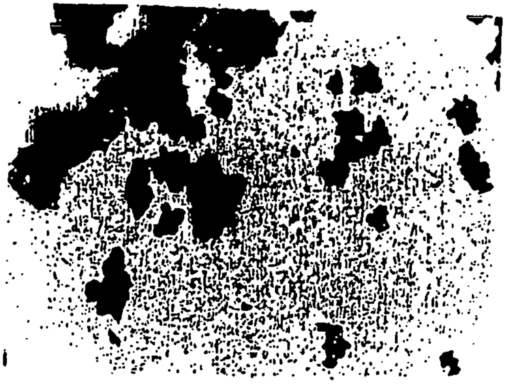

图 7B

图 7C

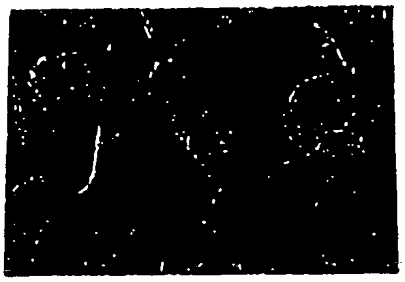

图 8