

- [54] CENTRIFUGAL APPARATUS AND CELL

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- [58] **Field of Search** 233/2, 23 R, 12, 25, 26,
233/3; 210/206, 380, 325; 23/230 R, 253 R,
259, 230 B; 73/61.4; 259/DIG. 46, 72, 57,
58; 241/DIG. 27, 199.7, 199.8

- [56]

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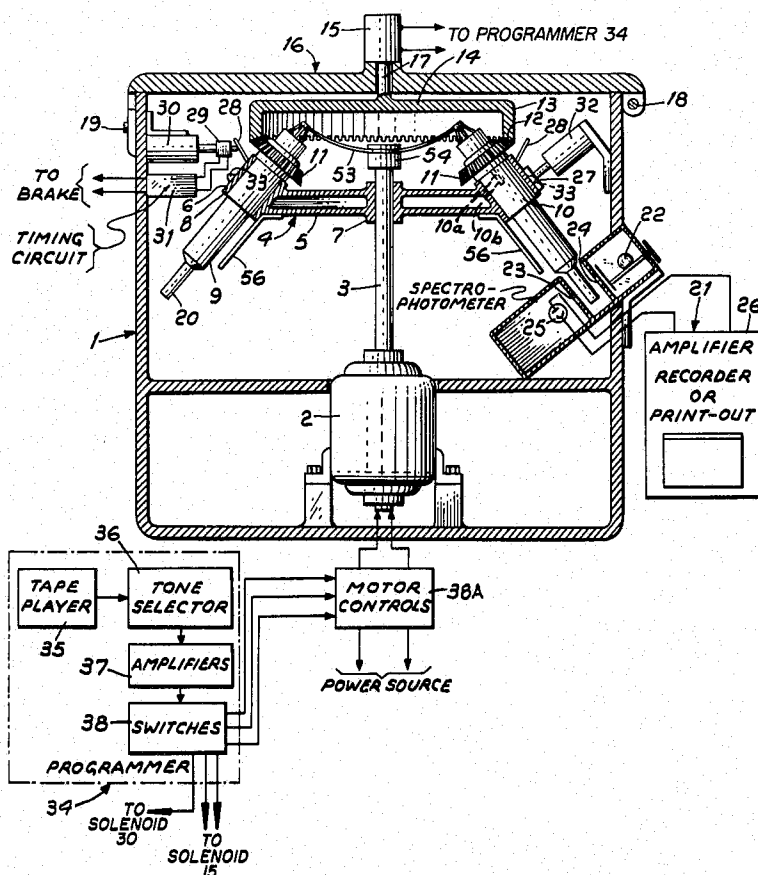
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[57]

ABSTRACT

Centrifuge cells, mounted at an acute angle to the drive shaft, orbit therearound, the resulting centrifugal force driving some of the contents of each cell through successive filters dividing the cell into separate chambers and into a cell cuvette. Each cell also rotates around its own axis when a gear arrangement is engaged, to grind tablets or mix the contents of the chambers. The cuvettes are sequentially examined by a read-out instrument such as a spectrophotometer, colorimeter, etc. A programmer controls successive operations. In one embodiment the chambers, which are separable, are selected for the test or other intended use according to their previously prepared contents, filter or other characteristic and then joined together to form the cell.

11 Claims, 3 Drawing Figures



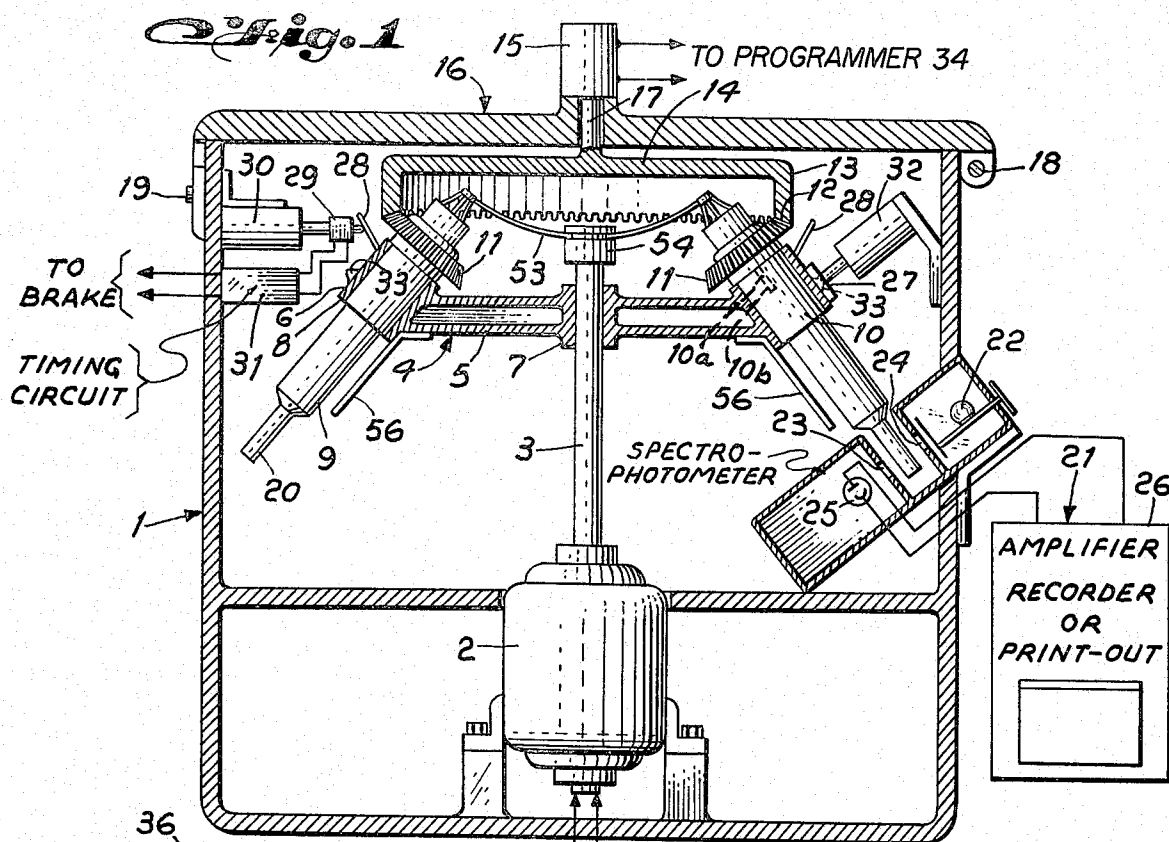
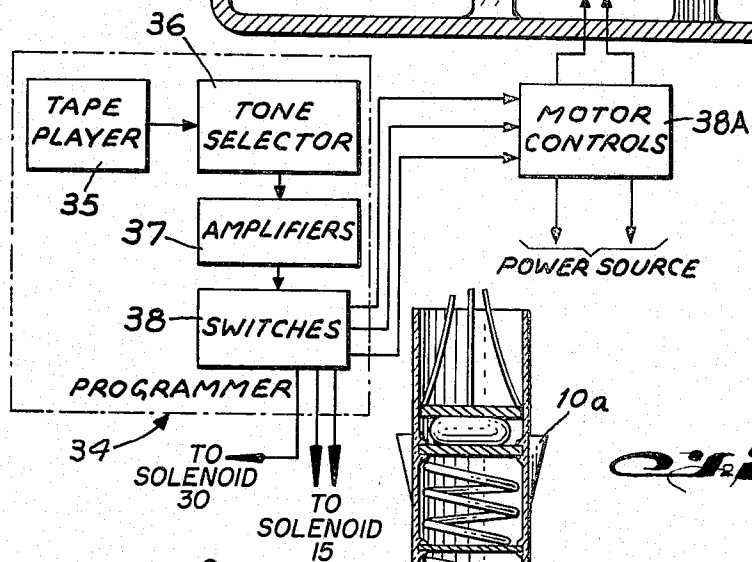
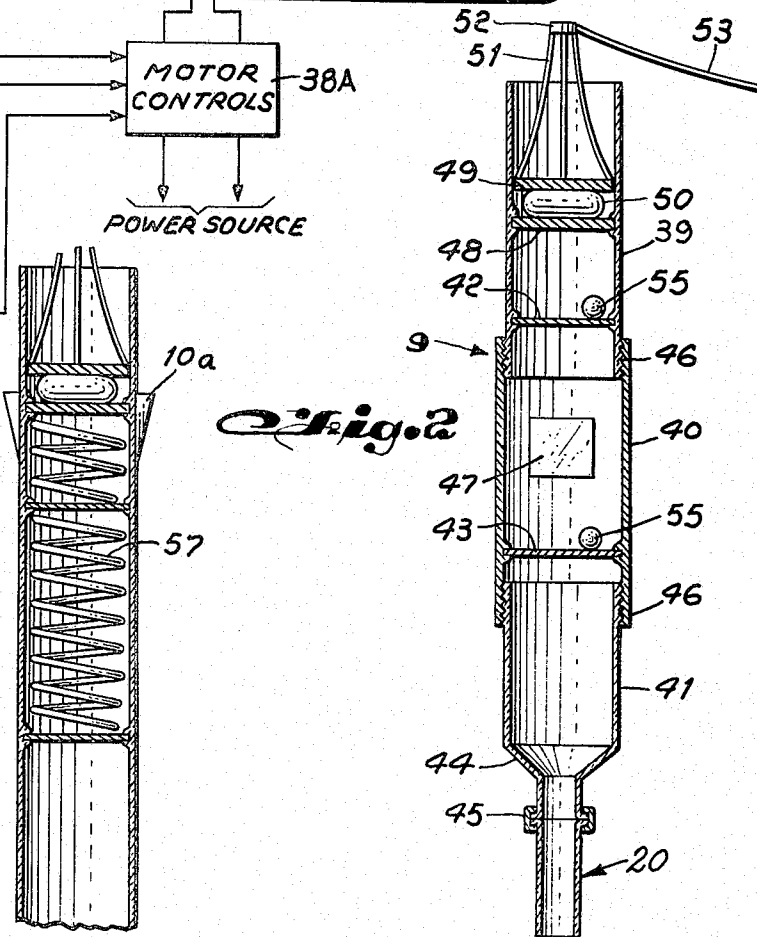


Fig. 2



CENTRIFUGAL APPARATUS AND CELL

This invention relates generally to centrifugal apparatus and to cells adapted for use therewith and particularly relates to automated centrifugal analytic apparatus and to multi-chambered cells which are adapted to be associated therewith.

In making tests for "content uniformity" as is required of the pharmaceutical industry, multiple assays are made of samples (such as tablets or capsules) representative of a batch. If done individually such tests impose a heavy workload on the analytical laboratory. Likewise, where tests are made of a number of substances having similar chemistries or involving similar chemical procedures, as in conducting blood chemistries for medical diagnosis, doing such tests on an individual basis is highly inefficient.

However, while it seems desirable to test a number of samples simultaneously and to automate these tests, suitable equipment for this purpose which is not too expensive, which is versatile and can be employed for different tests, which is adapted to utilize disposable cells, and which is convenient for use, is not readily available.

The use of a centrifuge in association with a number of cells each having a number of compartments or chambers has already been suggested for simplifying simultaneous analysis of a number of samples, as for example in separating particles as a step in blood chemistry. However, the range of uses of such centrifugal apparatus has been limited by the limitations of the equipment itself and the cells employed therewith and has not lent itself readily to simplified and automated procedures.

A general object of the present invention is the provision of an improved centrifuge and an improved cell for use therewith.

A further object of the present invention is the provision of improved equipment which enables chemical testing of a number of samples in a single operation, particularly such equipment which lends itself to, and is adapted for, automated operation.

A feature of the present invention is the provision of a centrifuge which not only applies centrifugal force to one or more cells but in addition rotates the cell(s) around one of the cell's axes for other purposes such as, for example, mixing of the contents of the cell and/or grinding solid samples.

A further feature of the present invention is the provision of cells which may have separable chambers and are prepared in advance for specific tests, as for example by having different reagents in different chambers, and which cells or chambers are intended to be discarded after a single use.

Other and further objects of the present invention will become apparent and the foregoing will be better understood with reference to the following description of embodiments of the present invention taken in conjunction with the drawings in which:

FIG. 1 is a schematic drawing of an automated centrifugal analytic apparatus and its cells;

FIG. 2 is a detailed cross-sectional view of one of the cells; and

FIG. 3 is a similar view of a modified form of said cells.

Referring now to FIG. 1 there is provided within a cylindrical housing 1 a centrally mounted motor 2 having a drive shaft 3 on which is mounted for rotation with

the shaft, a rotatable carrier 4. The carrier 4 is roughly shaped like a thick bowl with a flat bottom 5 and a thick inturred rim 6. At the center of the bottom 5 is an annular flange 7 which surrounds and is attached to the drive shaft 3. The carrier 4 is preferably hollow and made of a light weight non-magnetic material such as aluminum or a strong molded plastic. A plurality of spaced openings or collars 8 is provided in the rim within which collars the cells 9 are inserted, the cells 9 generally being tubular in form as shown in FIGS. 2 and 3. While only two collars 8 carrying cells 9 are illustrated in order to simplify the drawing, it is to be understood that the centrifuge may have many collars for carrying many cells and usually carries more than two, for example, a half dozen or a dozen collars and cells.

For supporting cells 9 within the collars 8 there is provided for each cell or tube a metal sleeve 10 into which the cell fits so that as the sleeve rotates the cell also rotates. One simple arrangement for accomplishing this consists of a pin or key 10a (FIG. 3) provided on opposite points of the cell slipping into a slot or keyway 10(b) provided in the sleeve. Mounted around each sleeve 10 and fastened thereto by any suitable means is a pinion gear 11 which is used in rotating each of the cells 9 about its own central longitudinal axis by the following mechanism which may be termed a planetary gear arrangement. A large annular toothed gear 12 at the edge of annular flange 13 extending from non-rotatable member 14 is moved into engagement with the pinion gear 11 by spring means (not shown) or raised out of engagement by a solenoid 15 mounted on top of the cover 16 of the housing, the shaft 17 of the solenoid extending through the cover and being non-rotatable. To facilitate the engagement of the gear 12 and the pinion gears 11, the teeth of the gears may be tapered towards the points at which they meet. Alternatively a planetary set of beveled gears may be used, tapered for easy engagement. The shaft 17 may be square and pass through a closely-fitting square opening in the cover. The cover 16 is pivoted at one point 18 on the casing 1 and locked at a diametrically opposite point by a spring release catch 19 so that the cover may be opened or locked in closed position.

Each of the cells 9 is provided at its lower end with a cuvette 20 through which radiation, such as light, is passed to a suitable read-out instrument for studying the contents thereof. Instruments for this purpose may include a colorimeter, spectrophotometer, polarimeter, fluorometer and others well known in the art. For this purpose there is shown in FIG. 1 a spectrophotometer and a recorder 21 having a light source 22, whose light is passed through the cuvette 20 via an adjustable light slit 24 which controls the amount of light passing there-through. The light then passes through opening 23 and falls on a photocell 25 whose output is then amplified and recorded on a suitable printout or recording device 26 forming part of the spectrophotometer 21.

A single read-out instrument is provided for all the cuvettes and each cuvette is brought sequentially into registry with the instrument. Where the read-out instrument gives a continuous read-out and can provide an adequate reading as the cuvette passes slowly by, the motor 2 rotates the carrier 4 continuously at a very slow pace. To enable identification of each cell's output reading, a blank cell or its equivalent, providing a reading outside of the range of that provided by the other cells, can be used as a marker and the other cell's

reading can be then identified by a simple count of the number of intervening cells readings.

Where the read-out instrument requires that the cuvette be stopped for a time in order to obtain a satisfactory read-out, a solenoid — actuated quick — acting brake 27 is provided operating, for example, on the rim 6 of the carrier. To actuate the brake, timing pins 28 may be provided spaced around the rim, each of which sequentially trips a microswitch 29 which is inserted, by a solenoid 30, into the path of the pins during the read-out period. The microswitch 29 upon being tripped, operates a timing circuit 31 (or relay or the like) to operate the brake solenoid 32 for the time necessary and the release. After release the carrier moves forward bringing the next cuvette into registry with the read-out instrument. The next actuating pin causes the brake to stop the carrier at this point. To provide for more precise registry, stops 33 may be provided around the rim of the carrier in the path of the brake so that the brake, adjusted for a slight slippage, strikes each stop 33 and halts the carrier at precise points. The motor may either apply a slight torque or be shut off during the time a cuvette dwells at the read-out instrument. The movement of the carrier to bring the cuvettes sequentially into read-out registry may, of course, be done manually or accomplished by other conventional means. For example, a spring-loaded roller may be inserted by a solenoid into a V-shaped indentation in the rim, a plurality of such indentations being spaced around the rim at suitable points. When the roller enters an indentation it forces the carrier to move slightly until the roller is centered in the bottom of the V.

The operation of the equipment may be manually controlled by controlling the various motor switches or switches activating the solenoids, or any suitable programmer 34 may be employed. While this programmer could be a tape or punched card controlled computer, a single programmer is illustrated in FIG. 1 and uses a tape player 35 which preferably may employ cassettes each having magnetically printed thereon at selected points, tone signals of selected frequencies which actuate tone selectors 36 (tuned frequency circuits) and amplifiers 37 which in turn are used to control switches 38 which actuate and select the motor controls 38A. The motor controls 38A start in either forward or reverse, stop the motor and control its speed. The output of amplifiers 37 through switches 38 also controls the solenoid 15 to determine when the stationary gear 12 engages the pinion gear wheels 11 and causes them to rotate the cells as the drive shaft 3 rotates. It also controls the solenoids controlling the brake, the microswitch insertion, etc.

Referring now to FIG. 2, each of the cells 9 is divided into a plurality of chambers or compartments 39, 40 and 41 with adjacent chambers separated by filters 42 and 43. The bottom of each cell comes together and is formed into a neck 44 to which the cuvette 20 may be removably attached by a rubber ring 45 or the like. In certain types of chemical analysis it is desirable that the cuvette 20 be made of quartz or silica and since quartz and silica are relatively expensive while the rest of the cell is intended to be disposable, the quartz or silica cuvette is removed for subsequent reuse.

In the FIG. 2 embodiment, the three chambers 39, 40 and 41 are also separate units held separably together by suitable means such as screw threads 46 or by any other suitable connection such as a bayonet and twist-

lock arrangement. A window 47 (or windows) made of rubber or the like, that permits injecting a fluid into a selected chamber may be provided in the envelope of the cell leading into one or more chambers. The fluid may be injected by syringe and the window should be adequately self-sealing so that an inordinate amount of the contents is not lost during operation of the centrifuge.

Towards the upper end of the top chamber 39 of cell 9 there is provided an arrangement for grinding tablets consisting of a coarse mesh stainless steel screen or porous stainless steel disk 48 which is fixedly mounted in the wall of the cell envelope and a second coarse mesh stainless steel screen or porous stainless steel disk 49 attached to bear down upon a tablet 50. The upper screen 49 is forced down against the tablet or capsule by stiff spring arms 51 which in turn are held together by a ring 52, the ring 52 in turn being pushed down as shown in FIG. 2 by a spring arm 53 held and supported in a nut 54 removably mounted on shaft 3 (see FIG. 1). The nut is attached to rotate with the shaft 3 so that as the shaft turns the whole assembly including the carrier 4 and the cells 9 mounted in its collars together with the nut 54 and spring arms 51 and 53, all rotate around the central shaft 3 simultaneously. However, when large gear wheel 12 engages the small gear wheels 11, each of the cells 9 is also rotated around its own central longitudinal axis causing the screen 49 to rotate with respect to the lower disk 48 and thereby grind down the tablet 50.

Referring back again to FIG. 2, means are provided for mixing the contents of each of the chambers or selected ones thereof and in the embodiment shown in FIG. 2 the mixing means consists of one or more balls 55 of ferromagnetic material each of which may be located in one or more of the separate chambers, each ball preferably having an outer layer of material which is inert to the substances in the chamber and may be for example made of teflon. These balls 55 are held stationary under the influence of elongated straight magnets 56 (see FIG. 1) which extend from the carrier 4 adjacent each cell 9. When a cell rotates around its own axis, it moves with respect to the stationary balls and thus agitates and mixes the contents of the chamber in which the balls are placed.

Another way of mixing the contents of each compartment is shown in FIG. 3 which consists of a spiral 57 formed from and extending from the envelope of the cell so that when the cell rotates the spiral agitates the contents of the compartment and mixes it. This is in addition to any turbulence due to the normal orbiting of the centrifuge cells around shaft 3.

The following is a general description of how the aforescribed apparatus may be used.

To perform any tests, suitably prepared cells must be obtained having the proper reagents, filters, etc. As contemplated by the present invention such cells may be prepared by the user or purchased in ready form from a manufacturer. To increase the versatility of the cells, differently prepared individual chambers may be made by a manufacturer and selected and assembled into cells by the user or provide the characteristics required. Of course, such previously prepared chambers should be protected during transport from loss of material or from contamination, for example, by end caps at either end or a suitable cover.

The prepared cells are inserted into the centrifuge collars. A tablet or solid dosage form is placed between the two porous stainless steel disks of each cell. The programmed sequence is started with the centrifuge running at slow speed and large gear 12 meshed with small gears 11. Each cell together with its lower stainless steel disk 48 is rotated around its own axis while the upper disk 49 is held stationary. The downward pressure of the upper disk 49 applies pressure to the tablet 50 and grinds the tablet into a powder, placing the active ingredients into solution in the first or upper chamber 39. Suitable solvents used in the first chamber include such reagents as chloroform, water or alcohol and the selection of a particular solvent depends upon the sample to be analyzed.

In order to aid the dissolution of the active ingredient into the first solution, the programmer continues with the rotation of the cell which may be simultaneous with the grinding action. The rotation of the cell will cause a vortex in the upper solution aiding in solubility of the active ingredient. At a predetermined time the tablet or its active ingredient will be completely dissolved and the rotation of the cells is terminated by halting rotation of shaft 3 and then disengaging gear 12. The composition of the membrane or filter in the top chamber is of such nature that none of the solution in the top chamber will pass through during the rotational movement. Following termination of the cell rotation the centrifuge is now started by the programmer causing shaft 3 to rotate and orbit the radially spaced cells and causing centrifugal force to be applied to the first solution in the top chamber 39. The solution is forced through the first filter or membrane 42. Part of the solution that does not pass through the filter 42 is the insoluble residue of the tablet and this remains in the chamber 39 on the filter. The solution which passes into the second chamber 40 is mixed with a second solution which may already be in the compartment, or it may be injected via window 47 just prior to the start of the test. The first and second solutions are now together in chamber 40. The purpose of the second solution is to add a reagent for separating or further purifying the active ingredients originally present in the tablet. The nature of the second solution is determined by the sample being analyzed. An example of the second solution is chloroform. The addition by mixture of the solution increases purification and extraction of the ingredients to be assayed. Once the two solutions are together in the second chamber 40, rotation of the cell is then begun causing the blending or mixing of the first and second solutions in chamber 40. The rotation of the cell is terminated after a predetermined time sufficient to ensure that there is proper mixing, for example, of aqueous and non-aqueous solutions. The sample has now been blended or dissolved in the reagent in the second chamber, with the rotating motion of the cell terminated. The centrifuge unit is again started up by the programmer so that the combined solutions in the second compartment are subject to centrifugal force. Filter 43 is of a nature that it would allow only a desired phase, such as the chloroform phase to go through the filter. An example of such a filter would be one that is treated with silicone. This treatment of silicone would allow the solvent to pass through the paper and the aqueous phase would remain on top. It is to be understood that extreme centrifugal forces would not be applied. The analyzer would be traveling at a slow to

moderate speed. An example of this might be 50 to 100 RPM. Speeds higher than that are not necessary to conduct most assays for which this apparatus is intended. The solution which is driven by centrifugal force out of the second chamber 40 into the third chamber 41 is either processed further or goes directly into the cuvette 20. In the latter case, each cell is then sequentially brought into registry with the read-out instrument as heretofore described. The read-out instrument records the results of each test and possibly provides a print-out, depending on the particular instrument employed.

Having described hereinabove a general procedure for using the analytic centrifuge apparatus, a more specific one is next described for salicylates, such a methyl salicylate or Aspirin which is acetylsalicylic acid containing salicylic acid. A colorimetric procedure is here employed. The sample or the tablet is ground down as aforesaid between the upper and lower stainless steel disks. An example of the first solution which would be in the top chamber 39 would be 0.02 normal Nitric Acid in an equal volume of alcohol (SDA 3A). In the next chamber 40, prior to starting the test would be placed a predetermined amount of ferric nitrate crystals. These crystals could be added into the second chamber either during manufacture, or assembly of the cell. After the tablet is ground up, it is dissolved in the 0.02 normal nitric acid and alcohol. Next centrifugal force (with gear 12 disengaged) is used to drive the solution of the salicylate through the filter membrane into the second chamber 40. The filter membrane could be a tight porosity filter paper that would not allow the solution to go through without centrifugal forces that would develop at about roughly 50 or 60 RPM within the centrifuge. After the solution is transferred into the second chamber, the programmer next shifts the centrifuge into its "mixing mode" and a magnetic ball in the second chamber now creates a sufficient degree of turbulence so that the salicylate in 0.02 normal nitric acid and alcohol now reacts with ferric nitrate producing a stable blue colored complex, the color development that is generated in this test for salicylates. The centrifuge is then momentarily stopped while it is changing over to go into its "centrifugal mode". The solution is driven by centrifugal force through the filter 43 on the bottom portion of the second chamber, the colored blue solution now going into the cuvette. The cuvette fills up with the solution and at this point the cell is ready for the actual read-out by the colorimeter and is brought into registry therewith. The colorimeter is preset at the start of the assay at a wavelength which would be the peak absorption wavelength for this material. At this point, the programmer turns on the colorimeter and the signal is picked up by the photo cell, transferred either onto a recorder or a direct print-out type apparatus.

Another example of an analysis would be that using a spectrophotometer rather than a colorimeter read-out as in the assay of chlorpheniramine maleate. This test would be generally applicable to an organic nitrogenous base compounds of which chlorpheniramine maleate is one. The tablet would be dissolved in the first chamber between the fixed and movable stainless steel disks as it was in the colorimetric assay. An example of the solution in the first compartment would be diluted sulfuric acid. The ground-up tablet is placed into solution in the top chamber 39 and the centrifuge then starts its centrifugal mode passing the dissolved

amine salt into the second chamber 40. In chamber 40 there is chloroform. Laying on top of the filter 43 in the second chamber is some sodium hydroxide pellets. The quantity of the pellets should be enough so that they would not only neutralize the diluted sulfuric acid but would make the solution slightly alkaline. This is necessary for the organic nitrogenous base to be released from its salt. The free base is now insoluble in the aqueous phase and soluble in the chloroform which was already in the second chamber. The filter 43 may be silicone treated paper overlayed with a chloroform-insoluble but aqueous-soluble material. An example of this coating is gelatin. The reason for this is that with the chloroform in the second chamber 40 prior to the start of the test, there are centrifugal forces built up within the cell, and to maintain the chloroform in the second chamber the paper would have to be treated with a chloroform-insoluble material. When the aqueous portion is brought down in the second chamber and mixed with the chloroform the aqueous soluble coating that is on the filter paper is now dissolved and this leaves the filter paper in a condition such that under centrifugal force, the chloroform phase, containing the free base (chlorpheniramine), will be allowed to pass through into the third chamber and cuvette. The cuvette in this case is not permanently fixed to the tube because the tube itself is disposable while the cuvette would be made of quartz glass or silica glass and have a rubber or plastic ring collar to attach itself to the neck below the third compartment.

The cells are now brought sequentially into registry with the spectrophotometer. The absorption readings are taken at a lower wavelength, as opposed to the visible region or the blue color development for the salicylates. The method of print-out could vary from a meter reading, a print-out on a recorder or a direct print-out that would be part of the spectrophotometer.

It is to be understood that the foregoing description of specific examples of this invention is made by way of example only and is not to be considered as a limitation on its scope.

What is claimed is:

1. A centrifuge comprising:

a housing,

drive means mounted in said housing and including

a rotatable longitudinal shaft having a central axis,

a rotatable support member mounted on said shaft,

a plurality of cells mounted on said support member at an acute angle to said shaft for centrifugal rotation with said support member about said central axis,

peripheral means secured around each said cell for

rotating each of said cells about its own respective

axis on said support member, each said cell having

a portion adapted for detecting the contents

thereof,

an annular axially movable non-rotatable member selectively engageable with said peripheral means around said cells to rotate said plurality of cells simultaneously about their respective axes,

read out means disposed within said housing adjacent the path of said cells for detecting the contents of said cells, and

control means for sequentially positioning said cells adjacent said read out means.

2. The centrifuge of claim 1 wherein said control means includes brake means for selectively stopping said cells.

3. The centrifuge of claim 2 wherein said control means includes means to selectively move said annular axially movable member into engagement with said cells.

4. The centrifuge of claim 3 wherein said peripheral means and said annular member are gears, and said housing includes a pivotable cover plate, said annular gear member being mounted on the inside of said coverplate, and said control means includes a solenoid mounted on said coverplate to axially move said annular gear member.

5. The centrifuge of claim 3 wherein said read out means includes a light source on one side of said cell and a photocell on the other side within said housing to detect light passing through said cell.

6. The centrifuge of claim 3 wherein said cell portion adapted for detecting said contents is removable.

7. The centrifuge according to claim 3 wherein said cell includes

an envelope;

a filter in said envelope barring the passage of given substances therethrough except under centrifugal force;

and means in said cell for mixing substances therein independently of centrifugal force.

8. The centrifuge according to claim 7 wherein said cell comprises

a plurality of aligned separable connected chambers with a filter in at least one of said chambers.

9. The centrifuge according to claim 8 in which said mixing means includes a magnetic element in each said cell movable about the axis of said cell upon rotation of said cell about its own axis, and a magnet mounted adjacent each said cell.

10. The centrifuge according to claim 8 further including spring biased grinding means responsive to rotation of the cell about its own axis for grinding solid substances.

11. The centrifuge of claim 8 wherein one of said chambers includes a window for insertion of substances there through.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,882,716
DATED : May 13, 1975
INVENTOR(S) : Elliott Beiman

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

On the cover sheet, Item 76, "305-A White Ave. Northvale, N.J. 07646" should read --- 12 Dorotockeys Lane, Old Tappan, New Jersey 07675 ---.

Signed and Sealed this

Twenty-fifth Day of September 1979

[SEAL]

Attest:

Attesting Officer

LUTRELLE F. PARKER

Acting Commissioner of Patents and Trademarks