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(54) **Apparatus for mixing and detecting on-line homogeneity.**

(57) This invention relates to an apparatus for mixing compositions of matter into a homogeneous mixture and detecting on-line the homogeneity and potency of the mixture, and a method for using the same. More particularly, this invention relates to an apparatus for mixing the components of a pharmaceutical composition into a homogeneous mixture and detecting on-line the homogeneity and potency of said pharmaceutical composition.

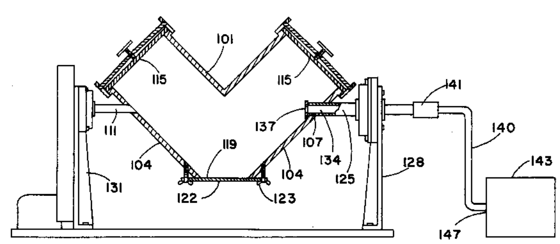

FIG. I

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TECHNICAL FIELD

This invention relates to an apparatus for mixing compositions of matter into a homogeneous mixture and detecting on-line the homogeneity and potency of the mixture, and a method for using the same. More particularly, this invention relates to an apparatus for mixing the components of a pharmaceutical composition into a homogeneous mixture and detecting on-line the homogeneity and potency of said pharmaceutical composition.

BACKGROUND OF THE INVENTION

The mixing of pharmaceutical compositions is a crucial step in processing an active drug into a form for administration to a recipient. Pharmaceutical compositions usually consist of five (5) or more separate components, including the active drug, which must be mixed into a homogeneous mixture. It is critical to determine the concentration of the active drug in a pharmaceutical mixture. It is also advantageous to determine the concentration of the other non-active components within the final homogeneous mixture. The assurance that the pharmaceutical composition is homogeneous is necessary in order to ensure the appropriate dosage of the active drug is delivered to a recipient.

The concentration of the non-active components in a pharmaceutical mixture is also important because it determines the physical properties of the mixture. For example, the non-active components of pharmaceutical compositions are known as excipients. An example of an excipient is a disintegrant. Disintegrants determine the rate of dissolution of a tablet in a recipient's stomach. Therefore, if the disintegrant is not homogeneously distributed in the pharmaceutical mixture, then the resulting tablets may not dissolve at a uniform rate. This could give rise to quality, dosing and bioavailability problems.

Typically, homogeneity of a pharmaceutical composition referred to the distribution of the active drug in the pharmaceutical composition. Potency of a pharmaceutical composition referred to the amount of the active component in a pharmaceutical composition. Traditionally, the determination of the potency and homogeneity of a pharmaceutical mixture has been time consuming. In addition, traditional methods measure the potency and homogeneity of only the active component in a pharmaceutical composition and gives no information concerning the homogeneity of the non-active components.

The traditional methods typically involve using a conventional blender such as a core blender, a ribbon blender, a "V"-blender or the like, to mix the components of a pharmaceutical composition. When the mixture is thought to be finished, the blender is stopped and usually nine or more samples of the mixture are removed from various locations in the conventional blender. The blender remains shut down while the samples are taken to a laboratory and analyzed for potency. The samples are typically analyzed using High Performance Liquid Chromatography (HPLC). The HPLC analysis determines the concentration of only the active component in each of the samples. The measurements determine whether the active component is uniformly dispersed or homogeneous in the mixture and present at an appropriate concentration level. This information reflects the potency of the mixture and if the potency of each of the samples is the same, then the mixture is considered to be homogeneous. HPLC analysis does not establish the concentration of the non-active components of the mixture. Homogeneity of all the components of a pharmaceutical mixture is important because the dispersion of certain components will ultimately affect the physical properties of the final form of the pharmaceutical composition, as discussed hereinabove. The traditional analysis can take from 24 to 48 hours to complete.

Another time consuming aspect of the traditional method is the hit or miss approach to determine when the mixture is homogeneous. Typically, the blender is run for a predetermined amount of time. The blender is stopped and the samples are taken to be tested. If the mixture is not homogeneous then the blender is run again and the testing procedure is repeated. Further, the mixture may reach homogeneity at a time-point before the predetermined set time for blending. In the first case more testing is carried out than is required, and in the second case valuable time is wasted in blending beyond the end-point. It is also possible that over blending can cause segregation of the components. Therefore, the time that is wasted in both cases and the possible risk of segregation due to over blending can be avoided by an apparatus which could detect on-line the potency and homogeneity of the pharmaceutical mixture. The term on-line means that the blender does not have to be turned off in order to take the measurements to determine homogeneity and potency.

For the foregoing reasons, there has been a long felt need in the art for an apparatus which can blend the components of a pharmaceutical mixture and detect on-line the potency and homogeneity of all the components of a pharmaceutical mixture. There is currently no apparatus in the art which can blend a pharmaceutical composition and detect on-line the homogeneity and potency of a pharmaceutical mixture.

SUMMARY OF THE INVENTION

This invention is directed to an apparatus for mixing compositions of matter into a homogeneous mixture and detecting on-line the homogeneity and potency of a mixture during the mixing process. The apparatus comprises a mixing means for mixing compositions of matter. The mixing means has a container for holding the compositions of matter to be mixed, preferably, said container rotates about an axis of rotation during the mixing process. The container has an aperture covered and sealed by a pellucid sealing means. In close proximity to, preferably abutting, the pellucid sealing means is a detection means for detecting the on-line spectroscopic characteristics of the mixture of compositions of matter.

In a preferred embodiment of this invention, said aperture is sealed by an arbor (a hollow shaft). A detection means for detecting the on-line spectroscopic characteristics of the mixture of compositions of matter is rotatably mounted through said arbor. A means for detecting the rotational position of said container is attached to the mixing means. The means for detecting rotational position relays to a data acquisition and control computer the rotational or angular position of said container. The data acquisition and control computer synchronizes the taking of spectroscopic data, by the detection means with a predetermined single rotational position or multiple rotational positions of said container of the mixing means. The taking of spectral data at a consistent predetermined point in the rotation of the container assures a greater degree of accuracy in determining the homogeneity of the mixture being mixed.

Another aspect of this invention is directed to a method for mixing compositions of matter into a homogeneous mixture and simultaneously detecting on-line the homogeneity and potency of the mixture of compositions of matter. The method comprises the steps of charging the mixing means with the individual compositions of matter to be mixed; mixing the compositions of matter; simultaneously detecting on-line the spectroscopic characteristic of the mixture with a detection means; optionally, synchronizing the detecting on-line of the spectroscopic characteristic of the mixture by a detection means with a predetermined single or multiple rotational position of a container which rotates about an axis of rotation, of a mixing means; and either manually shutting off the apparatus of this invention or automatically shutting off the apparatus of this invention utilizing a data acquisition and control computer when the spectroscopic characteristics of said mixture reach a predetermined homogeneity and potency end point as compared to a spectra of a known homogeneous mixture or until the variance in the spectroscopic characteristic converge.

This invention, therefore, allows spectra of a mixture to be collected while the mixing means is in motion, thereby, avoiding the down-time and over-shooting or under-shooting the end point which is characteristic of the traditional process for mixing and determining the potency of a mixture.

Other features and advantages of this invention will be apparent from the specification and claims and from the accompanying drawings which illustrate certain embodiments of this invention.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** illustrates a side view of an exemplary apparatus of this invention, with a cross sectional view of the container **101** and first axle **125**.

FIG. **2** illustrates a top view of the apparatus depicted in FIG. **1**.

FIG. **3** illustrates an enlarged view of FIG. **1**, broken away to illustrate a portion of the container and its attachment to the spectroscopic means.

FIG. **4** illustrates a side view of a transflectance probe attached to an axle.

FIG. **5** illustrates a representational side view of a conventional blender which has internal mixing means (e.g., ribbon blender or a core blender).

FIGS. **6a** to **6d** are cross sectional views taken along line **5a** showing the blender aperture and illustrate different means of connecting the detection means to the blender apparatus.

FIG. **7** illustrates an enlarged cross sectional view of an embodiment of the container, arbor and the various inserts within the arbor.

FIG. **8** illustrates another embodiment of the apparatus of this invention having a means for detecting rotational position of the container.

DETAILED DESCRIPTION OF THE INVENTION

Different types of blenders are currently used in the art for mixing pharmaceutical compositions. One type of blender is exemplified by the "V"-blender which mixes compositions of matter, such as powders or liquids by rotating the container which holds the compositions of matter about an axis of rotation. Therefore, one of the embodiments of this invention is a modified "V"-blender, which is illustrated in FIG. **1**.

According to FIG. **1** and FIG. **2** container **101** holds the compositions of matter to be mixed. Container **101** has a general "V" shape which is formed from a first hollow leg **201** open to a second hollow leg **204** which converge with each other at an angle, thereby giving it the V" shape. Container **101** has an outward facing surface wall **104**, which is the outside surface of the longer portion of legs **201** and **204** of container **101**. Aperture **107** is disposed through outward facing surface wall **104**. The aperture position is fixed by the position of second axle **111** and said second axle's connection with second hollow leg **204**, which is described hereinbelow.

Openings **115** at the top of container **101** are used for either charging container **101** with the individual compositions of matter which are to be mixed or discharging the finished homogeneous mixture. Openings **115** are covered and sealed during the mixing process by top covers **207**. Top covers **207** are secured to container **101** by top clasps **208**. Opening **119** at the bottom of container **101** is used for either charging container **101** with the individual compositions of matter which are to be mixed or discharging the finished homogeneous mixture. Opening **119** is covered and sealed during the mixing process by bottom cover **122**. Bottom cover **122** is secured to container **101** by bottom clasps **123**.

First ballbearing pillow block **210** has a lateral hole through it, preferably at its center. Ballbearing pillow blocks are well known in the art; they have bearings in them which allow for free rotation of an axle which is disposed in the hole and they also function as supports. These features of the ballbearing pillow block are more fully explained below. First support **128** has a lateral hole through it, disposed at its top end. First ballbearing pillow block **210** is disposed between container **101** and first support **128** and is attached, usually by bolts, to the side of first support **128** so that the hole of first ballbearing pillow block **210** and the hole of first support **128** are aligned.

Second ballbearing pillow block **213** has a lateral hole through it, preferably at its center. Second support **131** has a lateral hole through it disposed at its top end. Second ballbearing pillow block **213** is disposed between container **101** and second support **131** and is attached, usually by bolts, to the side of second support **131** so that the hole of second ballbearing pillow block **213** and the hole of second support **131** are aligned.

Second axle **111** has a first end and a second end, it is attached by its first end to container **101**. The second end of second axle **111** is rotatably mounted through the aligned lateral holes of second ballbearing pillow block **213** and second support **131** and connected to a means for rotation **216**, such as a motor. The motor can be connected directly to second axle **111** or it can be connected by a drive mechanism **219**, such as a chain or a belt. Motor **216** rotates container **101** thereby mixing the individual compositions of matter into a homogeneous mixture.

According to FIG. **3**, first axle **125** has a first end and a second end. First axle **125** is attached by its first end through aperture **107** to container **101** in such a manner so that a portion of the first end of first axle **125** protrudes into container **101**. A portion of the first end of first axle **125** has to protrude into container **101** enough so that the compositions of matter which are being mixed come into contact with the portion of the first end of first axle **125** during the mixing process. The second end of first axle **125** is rotatably mounted through the aligned lateral holes of first ballbearing pillow block **210** and first support **128** so that first axle **125** is aligned with second axle **111** to form a level and horizontal axis of rotation. The horizontal axis of rotation must be high enough up the legs of container **101** so that container **101** can freely rotate 360° about the axis of rotation formed by said first and second axles.

As shown in FIG. **1**, first axle **125** has a bore **134** therethrough. Bore **134** is covered at the first end of first axle **125** by a pellucid sealing means **137**, such as a pellucid window or a transflectance probe. Said pellucid window can be made from glass, quartz or sapphire, depending upon the wavelength region of the radiation issuing from the spectroscopic means which is discussed hereinbelow. In the present embodiment a pellucid window is preferred as the pellucid sealing means and quartz is the preferred material for pellucid window **137**.

Alternatively, bore **134** is covered at the first end of first axle **125** by transflectance probe **400**, shown in FIG. **4**. According to FIG. **4** transflectance probe **400** is comprised of housing **405**, pellucid lens **410**, reflector **415** and has a void **420**.

Examples of conduction means for conducting radiation **140**, are light pipes, optics and a fiber optic bundle. The fiber optic bundle is the preferred conduction means for this embodiment. According to FIGS. **1** and **3**, fiber optic bundle **140** has a first end and a second end. The first end of the fiber optic bundle **140** runs through and is covered by sleeve **141**. Sleeve **141** housing fiber optic bundle **140** is removably disposed inside bore **134** so that the first end of fiber optic bundle **140** is in close proximity to pellucid window **137** so that the radiation emanating from said fiber optic bundle passes through pellucid window **137** at an essentially horizontal level and without distortion from outside sources of interference which may disrupt the source radiation. Preferably said fiber optic bundle abuts said pellucid window. The second end of fiber optic bundle **140** is removably attached to spectroscopic means **143** through opening **147** in spectroscopic means **143**. Opening **147** is where the radiation from spectroscopic means **143** emanates and the diffusely reflected radiation or reflected radiation from the mixture via fiber optic bundle **140** is admitted. The following are examples of preferred spectroscopic means: infrared spectrophotometer; ultraviolet-visible spectrophotometer; near infrared spectrophotometer; mid-range infrared spectrophotometer and raman spectrophotometer.

Fiber optic bundle **140** contains two sets of optical fibers. The first set of optical fibers convey radiation emanating from spectroscopic means **143** to the mixture inside container **101**. Pellucid window **137** allows the radiation emanating from fiber optic bundle **140** to pass through to the mixture without distortion.

If the mixture is a solid then the radiation signal is analyzed by reflectance. The radiation hitting the solid mixture is diffusely reflected. The second set of optical fibers collect the diffusely reflected radiation from the mixture and convey it back to spectroscopic means **143.**

If the mixture is a liquid then the radiation is analyzed by transflectance. For a liquid mixture transflectance probe **400** is fitted onto the first end of axle **125** in place of pellucid window **137**. The radiation emitting from the first set of fibers of fiber optic bundle **140** passes through pellucid lens **410** and through the liquid mixture that is in void **420** between reflector **415** and housing **405**. Pellucid lens **410** is made out of the same types of material as enumerated for pellucid window **137** and serves the same function as pellucid window **137**. The liquid mixture distorts the radiation, the distorted radiation is then reflected back by reflector **415** to fiber optic bundle **140**, where the second set of optical fibers collect the reflected radiation and convey it to spectroscopic means **143**.

Spectroscopic means **143** stores and analyzes the diffusely reflected or reflected radiation; or spectroscopic means **143** can further transmit the spectral data to a computer which then analyzes it.

The particularly preferred spectroscopic means is the NIRSystems model 6500 spectrophotometer (a near infrared spectrophotometer), available from NIRSystems Inc., 12101 Tech Road, Silver Spring, MD, 20904. The computer which analyzes the data can be any personal computer such as the Zeos 33 MHz 80846DX PC with 8 Mb of RAM. The data is collected in the computer using Near infrared Spectral Analysis Software (NSAS), which is the instrument control package provided with the spectroscopic instrument from NIRSystems. The data is then analyzed in Matlab (software package) available from The Mathworks Inc. (The Mathworks Inc., Cochituate Place, 24 Prime Park Way, Natick, MA, 01760).

FIG. **5** is a generic representation of another type of conventional blender used for mixing compositions of matter. This other type of conventional blender does not require the blender's container to be rotated about an axis of rotation to mix the individual compositions of matter into a homogeneous mixture. Instead, this other type of conventional blender relies upon agitators inside the container, such as blades or stirrers, to mix the compositions of matter into a homogeneous mixture. A ribbon blender is an example of a conventional blender which utilizes blades. A core blender is an example of a conventional blender which utilizes stirrers. In addition to mixing powders and liquids these blenders can also mix compositions of matter for salves and creams.

According to FIG. **5**, the rectangular box designated by **500** represents any stationary conventional blender which relies upon internal agitators to mix compositions of matter into a homogeneous mixture. Blender **500** has an aperture **502** in one of the blender's walls **501**. However, more than one aperture can be present in any one or more of the blender's walls. The aperture must open into the inside of the container portion of blender **500** so that the detection means will be able to convey the radiation from the spectroscopic means to the mixture inside the container of the blender and the reflected or transflected radiation can be collected and analyzed.

FIG. **6a** illustrates an embodiment of aperture **502**, blender wall **501** and conduction means **140** wherein blender wall **501** is dimpled inward into the container of blender **500**. Aperture **502** in blender wall **501** is covered and sealed by pellucid barrier **503**. Pellucid barrier **503** is made out of the same types of material as enumerated for pellucid window **137** and serves the same function as pellucid window **137**. The first end of conduction means **140** is in close proximity to, preferably abutting, pellucid barrier **503** and the second end of means for conducting radiation **140** is removably attached to spectroscopic means **143** as illustrated in FIG. **1** and discussed hereinabove.

FIG. **6b** illustrates another embodiment of aperture **502**, blender wall **501** and conduction means **140**. Aperture **502** is covered and sealed by attaching conduction means **140** to blender wall **501** through aperture **502**. Conduction means **140** protrudes into the container of blender **500**. The end of conduction means **140** protruding inside the container is covered by pellucid barrier **503**. Alternatively, transflectance probe **400**, discussed hereinabove, can be interchanged for pellucid barrier **503**.

FIG**. 6c** illustrates an embodiment of aperture **502**, blender wall **501** and spectroscopic means **143**. In this embodiment pellucid barrier **503** covers and seals aperture **502** in blender wall **501**. Spectroscopic means **143** is placed next to blender wall **501** so that opening **147** in spectroscopic means **143**, from which the radiation emanates and is admitted, is in close proximity to, preferably abutting, pellucid barrier **503**.

FIG. **6d** illustrates a further embodiment of aperture **502**, blender wall **501** and conduction means **140**. In this embodiment pellucid barrier **503** covers and seals aperture **502** in blender wall **501**. Conduction means **140** is placed so that its first end is in close proximity to, preferably abutting, pellucid barrier **503**.

FIGS. **6a**, **6b** and **6d** show certain preferred embodiments in which a conduction means **140** can be combined with blender **500** in order to employ on-line acquisition of spectral data of the mixture being mixed so that the potency and homogeneity of a pharmaceutical mixture can be determined. The acquisition of spectra is accomplished in the same manner as is discussed hereinabove for the exemplary embodiment represented by the modified V-blender.

In an embodiment wherein said conduction means **140**, shown in FIGS. **6a**, **6b** and **6d** is a fiber optic bundle, the fiber optic bundle **140** contains two sets of optical fibers. The first set of optical fibers convey radiation from spectroscopic means **143** to the mixture. Pellucid barrier **503** allows the radiation emanating from the first set of optical fibers of fiber optic bundle **140** to pass through to the mixture of compositions of matter without distortion. The radiation contacting the mixture is diffusely reflected in case of solid mixture or transflected in the case of liquids. The second set of optical fibers collect the radiation that is diffusely reflected or reflected from the mixture and convey it back to the spectroscopic means **143**. Spectroscopic means **143** analyzes the radiation or spectroscopic means **143** can further convey the data to a computer which will then analyze it.

FIG. **6c** illustrates an embodiment of this invention which does not require a conduction means **140**, instead a spectroscopic means **143** can be placed directly next to blender **500**. The exchange of radiation from spectroscopic means **143** and the diffusely reflected radiation from the mixture passes through opening **147** without the aid of a conduction means **140**.

In a preferred embodiment, according to FIG. **7**, aperture **107** is occlusively sealed by arbor **180**. Arbor **180** has a tunnel **182** therethrough and said arbor has a first end and a second end. Hollow pipe **151** has a first end and a second end; said first end of hollow pipe sealed by an optically transparent sealing means **152**, such as a lens or a transflectance probe **400**. A lens which is used as an optically transparent sealing means **152** is made of the same materials as enumerated for pellucid sealing means **137**. The inside diameter of arbor **180** is larger than the outside diameter of hollow pipe **151** so that said hollow pipe may be removably disposed in said arbor. The first end of arbor **180** extends into container **101** so that it will come into contact with the compositions of matter being mixed in the container. The second end of arbor **180** is rotatably mounted through the aligned lateral holes of first ballbearing pillow block **210** and first support **128** so that arbor **180** is aligned with second axle **111** to form a level and horizontal axis of rotation. The horizontal axis of rotation must be high enough up the legs of container **101** so that container **101** can freely rotate 360° about the axis of rotation formed by arbor **180** and second axle **111**. Said fiber optic bundle **140** is disposed inside of hollow pipe **151** with said first end of said fiber optic bundle **140** abutting lens **152** or pellucid lens **410** if the first end of hollow pipe **151** is sealed by transflectance probe **400**. Hollow pipe **151** is removably disposed within tunnel **182** of arbor **180** with the first end of hollow pipe **151** preferentially disposed, but not necessarily, beyond the first end of arbor **180**. A self-lubricating seal **185** such as TEFLON® (TEFLON® is a registered trademark of E.I. DuPont de Nemours and Co.), is occlusively disposed between the first end of hollow pipe **151** and the first end of arbor **180** in order to prevent leakage of the compositions of matter being mixed in container **101** into tunnel **182** of arbor **180**. Seal **185** is self-lubricating and it rotates with arbor **180** and, hence, seal **180** rotates around the first end of hollow pipe **151** and, therefore, hollow pipe **151** remains stationary.

In another preferred embodiment of this invention, according to FIG. **8**, a means for detecting rotational (angular) position **150** of container **101** is incorporated into the mixing means. Some examples of means for detecting rotational position are an absolute digital shaft encoder, a pulse encoder, an optical encoder and an analog encoder, the foregoing list is not exhaustive and is not intended to exclude any other possible means for detecting rotational position. A brace **155** has a general "U" shape and has a first leg and a second leg, the first leg of brace **155** is attached to means for detecting rotational position **150**. The second leg of brace **155** is attached to second support **131**. Further, FIG. **8** shows a first connecting shaft **160a** and a second connecting shaft **160b**. The first connecting shaft **160a** has a first end and a second end. The second connecting shaft **160b** has a first end and a second end. The first end of first connecting shaft **160a** is attached horizontally and in-line to second axle **111** so that it turns with the rotation of second axle **111**. The second end of first connecting shaft **160a** is flexibly and fixedly connected to coupling **165**. The first end of second connecting shaft **160b** is flexibly and fixedly connected to coupling **165** so that the second end of first connecting shaft **160a** and the first end of second connecting shaft **160b** are facing end to end but do not touch each other.

The second end of second connecting shaft **160b** is attached to the means for detecting rotational position **150**. Coupling **165** transmits the rotational force from first connecting shaft **160a** to second connecting shaft **160b** so that both first connecting shaft **160a** and second connecting shaft **160b** turn simultaneously with the rotation of second axle **111**. Further, coupling **165** flexibly and fixedly holds first connecting shaft **160a** and second connecting shaft **160b** in order to reduce the rotational stress, during the rotation of second axle **111**, between first connecting shaft **160a** and second connecting shaft **160b**. The means for detecting rotational position **150** is interfaced by a first set of communication wires **170** to a relay box, where said relay box is interfaced with data acquisition and control computer **163** by a second set of communication wires. The second set of communication wires relays information from the relay box to data acquisition and control computer **163**. In an embodiment wherein the means for detecting rotational position **150** is an absolute digital encoder, the relay box interprets the digital signal from the absolute digital encoder to an ASCII number, the ASCII number represents the rotational position of container **101** in degrees. The ASCII number is transmitted to data acquisition and control computer **163** by the second set of communication wires. Data acquisition and control computer **163** is interfaced to spectroscopic means **143** by a third set of communication wires **173**. As container **101** rotates, the rotation of second connecting shaft **160b** is detected by the means for detecting rotational position **150**, which relays the rotational position of container **101** to the relay box through the first set of communication wires **170**. The relay box then relays the information to data acquisition and control computer **163** through the second set of communication wires. Data acquisition and control computer **163**, using a control software such as Labview® (commercially available from National Instruments, Austin, Texas 78730), synchronizes the collection of spectroscopic data by spectroscopic means **143** with a predetermined position of the means for detecting rotational position **150** which translates to a rotational position of container **101**, so that spectroscopic data is consistently collected at the predetermined rotational position of container **101**. One or more predetermined rotational position points of container **101** may be selected to collect spectral data. The collection of spectroscopic data by spectroscopic means **143** is executed by software programs such as Microsoft Windows® 3.1 (commercially available at most computer supply stores) and WINSAS® (commercially available from NIRSystems Inc. Silver Springs, Maryland). The WINSAS® program is instructed as to when to start collecting the spectroscopic data by a control software program such as Labview® via Dynamic Data Exchange (DDE is a feature that is innate to Microsoft Windows® 3.1). Further, data acquisition and control computer **163** is interfaced by a fourth set of communication wires to said relay box. Means for rotation **216** may be controlled manually or means for rotation **216** may be controlled by said relay box. The interface of data acquisition and control computer **163** to the relay box, allows the data acquisition and control computer **163** to turn on or off means for rotation **216** when the data acquisition and control computer determines, by the mathematical analysis described below, that the compositions of matter being mixed has reached the homogeneous end-point. The homogeneous endpoint is determined by transferring the spectroscopic data collected by WINSAS® to another software program such as InStep® (commercially available from Infometrix Inc., Seattle, Washington) via DDE, the spectroscopic data is then analyzed using pre-calculated models which were developed using a software program such as Pirouette® (commercially available from Infometrix Inc., Seattle, Washington). Means for rotation **216** may be stopped at desired time intervals before the compositions of matter being mixed reaches a homogeneous end-point so that samples may be taken from container **101** for analysis, or means for rotation **216** may be stopped for any other reasons contemplated by a user. The aforesaid sets of communication wires are any device capable of transmitting optical or electrical signals.

The data acquisition and control computer used in the present embodiment is the Toshiba T6400DX, 33 MHz, 486DX with 16 Mb of RAM, however, the data acquisition and control computer can be any computer with similar or more advanced capabilities.

The initial spectra of the mixture will be closest to the spectrum of each of the individual components of the mixture. As the mixing apparatus begins to mix the compositions of matter, the spectra of the mixture will appear less like the spectra of the individual components and more akin to the spectra of a homogeneous mixture. Eventually the spectra will converge to that of a homogeneous mixture. Utilizing this analytical method the distribution of each of the components in the mixture, the active component as well as the inactive components, can be measured. Thus, enabling the apparatus of this invention to determine the total overall homogeneity of the mixture.

Calculations are performed to estimate when all components of the mixture are homogeneous by measuring the change in a group of spectra as a function of time. For example, a group of 50 spectra are taken at one minute intervals. The standard deviation of the wavelengths of spectra 1-5, followed by 2-6, and 3-7 ... etc. are calculated. The resulting standard deviation spectra shows which regions of the spectra were changing the most. Calculating the variance in each of the individual deviation spectra would then give a measure of the total variance of the mixture as a function of time. When the total variance has diminished to a constant, the blend is considered homogeneous. Alternatively, a computer can be programmed with a spectrum of a known homogeneous mixture. The mixing is complete when the spectrum of an in-progress mixture matches the spectrum of the known homogeneous mixture.

The embodiments of this invention, which are illustrated in FIGS. **1** to **4** and FIGS. **5**, **6a** to **6d**, **7** and **8**, allow spectra of a mixture of compositions of matter to be collected while the blender is in motion. Therefore, the apparatus of this invention avoids the down-time that is the principal drawback of the traditional process. The apparatus of this invention allows the detection on-line of the homogeneity and potency of the mixture, a feature which is not available in the traditional apparatuses.

The apparatus of this invention can be further modified to accommodate more than one detection means wherein said detection means is a spectroscopic means optionally fitted with a conduction means as described hereinabove. The apparatus of this invention with multiple spectroscopic means can be connected with the same type of spectroscopic means or with different types of spectroscopic means. The exemplary apparatus of this invention, a modified "V"-blender, can be further modified to accommodate two spectroscopic means by using a hollow second axle. A conduction means can be disposed within said hollow second axle in the same manner as described for said fiber optic bundle in said bore of said first axle, described hereinabove.

A conventional blender of the type **500** can be further modified to accommodate multiple spectroscopic means by making as many apertures as required in any desired locations in the blender's walls. Each of the multiple apertures could then be fitted with a conduction means which would be connected to a spectroscopic means as illustrated in FIGS**. 6a**, **6b** and **6d** and described hereinabove; or each aperture could be abutted by a spectroscopic means as illustrated in FIG. **6c** and described hereinabove; or a combination of the embodiments illustrated in FIGS. **6a** to **6d**.

An advantage of using more than one detection means of the same type with an apparatus of this invention is that it would allow for acquisition of spectral characteristics of the mixture from two or more locations of the apparatus of this invention. This embodiment of the invention would further insure that the mixture was homogeneous throughout the container.

An advantage of using different types of detection means with an apparatus of this invention is illustrated in the following circumstance. In a pharmaceutical composition there are various components as described hereinabove. Some of the components may only be detectable by one type of radiation, such as near-infrared radiation. The other components of said pharmaceutical composition may only be detectable by another type of radiation other than infrared, for example visible radiation. In such a situation it would be advantageous to have two spectroscopic means connected to the mixing means. The first spectroscopic means, a near-infrared spectrophotometer, and the second spectroscopic means, a visible spectrophotometer. Each spectrophotometer would then detect the spectroscopic characteristics of the components of the pharmaceutical composition which it can detect.

The apparatus of this invention can also be fitted with an alarm which would signal the operator of the apparatus of this invention when the mixture had reached the homogeneity and potency end point. Alternatively, the system could be automatically triggered to shut off when the mixture reaches the homogeneity and potency end point.

It should be understood that the invention is not limited to the particular embodiments shown and described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

Claims

1. An apparatus for mixing compositions of matter into a homogeneous mixture and detecting on-line the homogeneity of said mixture, which comprises:
(a) mixing means for mixing said compositions of matter; and
(b) detection means 143 for detecting on-line the homogeneity of said mixture.

2. The apparatus according to claim 1 wherein:
(a) said mixing means having a container 101;
(b) said container 101 having an aperture 107; and
(c) a pellucid sealing means 137 for sealing said aperture 107 disposed between said aperture 107 and said detection means 143.

3. The apparatus according to claim 2 wherein said detection means 143 comprises:
(a) spectroscopic means 143 for measuring the spectroscopic characteristics of said

compositions of matter having an opening 147 from which radiation emanates and is received; and

(b) conduction means 140 for conducting radiation to said mixture from said spectroscopic means 143 and then conducting reflected or transflected radiation to said spectroscopic means 143, said conduction means 140 connected to said opening 147 of said spectroscopic means 143.

4. The apparatus according to claim 3 wherein:

(a) said container 101 has an axis of rotation;

(b) means for rotation 216 about said axis of said container 101, said means for rotation 216 connected to said container;

(c) said axis of rotation having a bore 134; and

(d) said conduction means 140 inserted in said bore 134.

5. The apparatus according to claim 4, wherein:

(a) said mixing means has a first support 128 and a second support 131, said first support 128 has a lateral hole therethrough and said second support 131 has a lateral hole therethrough;

(b) said container 101 formed from a first hollow leg 201 open to a second hollow leg 204, said first hollow leg 201 and second hollow leg 204 converging at an angle giving said container a "V" shape, each of said first hollow leg 201 and said second hollow leg 204 has an outward facing surface wall 104;

(c) said container 101 has an aperture 107 disposed through the outward facing surface wall 104 of said first hollow leg 201;

(d) a first ballbearing pillow block 210 having a lateral hole therethrough, said first ballbearing pillow block 210 disposed between said container 101 and said first support 128 and attached to said first support 128, wherein said first ballbearing pillow block's hole is aligned with said first support's hole;

(e) a second ballbearing pillow block 213 having a lateral hole therethrough, said second ballbearing pillow block 213 disposed between said container 101 and said second support 131 and attached to said second support 131 , wherein said second ballbearing pillow block's hole is aligned with said second support's hole;

(f) a first axle 125 having a first end and a second end and having a bore 134 therethrough;

(g) said pellucid sealing means is selected from the group consisting of a pellucid window 137 and a transflectance probe 400, said pellucid sealing means covers and seals said bore 134 of first axle 125 at said first end;

(h) a second axle 111 having a first end and a second end;

(i) said second axle's first end attached to said outward facing surface wall 104 of said container's second hollow leg 204;

(j) said second axle's second end rotatably mounted through said aligned holes of said second support 131 and said second ballbearing pillow block 213 and said second axle's second end connected to said means for rotation 216;

(k) said first axle's first end engaged to said container 101 through said aperture 107, said pellucid sealing means protruding inside said containers first hollow leg 201;

(l) said first axle's second end rotatably mounted through said aligned holes of said first support 128 and said first ballbearing pillow block 210 in alignment with said second axle 111;

(m) said conduction means 140 having a first end and a second end; and

(n) said conduction means 140 removably disposed within said first axle's bore 134, said conduction means first end abutting said pellucid window 134 and said conduction means second end attached to said spectroscopic means' opening 147.

6. The apparatus according to claim 5 wherein:

(a) said container 101 has a plurality of openings 115 and 119 for loading compositions of matter which are to be mixed and discharging the homogeneous mixture;

(b) said conduction means 140 is a fiber optic bundle; and

(c) said means for rotation 216 is an electric motor.

7. The apparatus according to claim 4 wherein said mixing means is a V-blender, a ribbon blender or a core blender.

8. The apparatus according to claim 7 wherein said detection means is a near infrared spectrophotometer, an ultraviolet spectrophotometer, a visible spectrophotometer, a Raman spectrophotometer, or a mid-range infrared spectrophotometer.

9. The apparatus according to claim 1 wherein:

(a) said mixing means having a container 101;
(b) said container 101 having an aperture 107; and
(c) an arbor 180 seals said aperture 107 of said container 101 and is an axis of rotation.

10. The apparatus according to claim 9 wherein said detection means comprises:
(a) spectroscopic means 143 for measuring the spectroscopic characteristics of said compositions of matter having an opening 147 from which the radiation emanates and is received; and
(b) conduction means 140 for conducting radiation to said mixture from said spectroscopic means, and then conducting reflected or transflected radiation to said spectroscopic means 143, said conduction means 140 connected to said opening 147 of said spectroscopic means 143.

11. The apparatus according to claim 10 wherein:
(a) means for rotation 216 about said arbor 180 of said container 101, said means for rotation 216 connected to said container 101;
(b) said arbor 180 having a tunnel 182 therethrough; and
(c) said conduction means 140 removably inserted in said tunnel 182.

12. The apparatus according to claim 11 wherein:
(a) said mixing means has a first support 128 and a second support 131, said first support 128 has a lateral hole therethrough and said second support 131 has a lateral hole therethrough;
(b) said container 101 formed from a first hollow leg 201 open to a second hollow leg 204, said first hollow leg 201 and second hollow leg 204 converging at an angle giving said container 101 a "V" shape, each of said first hollow leg 201 and said second hollow leg 204 has an outward facing surface wall 104;
(c) said container 101 has an aperture 107 disposed through the outward facing surface wall 104 of said first hollow leg 201;
(d) a first ballbearing pillow block 210 having a lateral hole therethrough, said first ballbearing pillow block 210 disposed between said container 101 and said first support 128 and attached to said first support 128, wherein said first ballbearing pillow block's hole is aligned with said first support's hole;
(e) a second ballbearing pillow block 213 having a lateral hole therethrough, said second ballbearing pillow block 213 disposed between said container 101 and said second support 131 and attached to said second support 131, wherein said second ballbearing pillow block's hole is aligned with said second support's hole;
(f) said arbor 180 having a first end and a second end and having a tunnel 182 therethrough;
(g) a second axle 111 having a first end and a second end, said second axle's first end attached to said outward facing surface wall 104 of said container's second hollow leg 204, said second axle's second end rotatably mounted through said aligned holes of said second support 131 and said second ballbearing pillow block 213 and said second axle's second end connected to said means for rotation 216;
(h) said arbor's first end engaged to said container 101 through said aperture 107, said arbor's first end protruding inside said container's first hollow leg 201, said arbor's second end rotatably mounted through said aligned holes of said first support 128 and said first ballbearing pillow block 210 in alignment with said second axle 111;
(i) a hollow pipe 151 having a first end, a second open end, said first end sealed by an optically transparent sealing means selected from the group consisting of a lens 152 and a transflectance probe 400;
(j) said conduction means 140 having a first end and a second end, said conduction means 140 removably disposed within said hollow pipe 151 with said first end of said conduction means 140 abutting said optically transparent sealing means 152 and said conduction means' second end attached to said spectroscopic means' opening 147;
(k) said hollow pipe 151 removably disposed within said arbor's tunnel 182, said hollow pipe's first end extending beyond said arbor's first end;
(l) a seal 185 occlusively disposed between said hollow pipe 151 and said arbor 180;
(m) a brace 155 having a first leg and a second leg, said first leg of said brace 155 attached to said second support 131 and said second leg of said brace 155 attached to a means for detecting rotational position 150;
(n) a first connecting shaft 160a having a first end and second end, said first end attached horizontally and in-line to said sec-

ond axle 111, said second end fixedly and flexibly connected to a coupling 165; and

(o) a second connecting shaft 160b having a first end and a second end, said first end of said second connecting shaft 160b fixedly and flexibly connected to said coupling 165 facing said second end of said first connecting shaft 160a, said second end of said second connecting shaft 160b attached to means for detecting rotational position.

13. The apparatus according to claim 12 wherein

(a) said means for detecting rotational position 150 interfaced to a relay box by a first set of communication wires 170;

(b) said relay box interfaced to a data acquisition and control computer 163 by a second set of communication wires; and

(c) said data acquisition and control computer 163 interfaced to said spectroscopic means by a third set of communication wires 173;

14. The apparatus according to claim 13 wherein:

(a) said container 101 has a plurality of openings 115 and 119 for loading compositions of matter which are to be mixed and discharging the homogeneous mixture;

(b) said conduction means 140 is a fiber optic bundle;

(c) said means for rotation 216 is an electric motor; and

(d) said seal 185 is made of TEFLON®.

15. The apparatus according to claim 14 wherein

(a) said data acquisition and control computer 163 interfaced by a fourth set of communication wires to said relay box; and

(b) said means for rotation 216 is controlled by said relay box.

16. The apparatus according to claim 11 wherein said mixing means is a V-blender, a ribbon blender or a core blender.

17. The apparatus according to claim 16 wherein said detection means 143 is a near infrared spectrophotometer, an ultraviolet spectrophotometer, a visible spectrophotometer, a Raman spectrophotometer, or a mid-range infrared spectrophotometer.

18. A method for mixing compositions of matter into a homogeneous mixture and detecting on-line the homogeneity of said mixture comprising:

(a) placing the compositions of matter to be mixed into a container of a mixing apparatus having an aperture;

(b) mixing the compositions of matter;

(c) detecting on-line the spectroscopic characteristic of the mixture during the mixing process with a detection means for detecting on-line the homogeneity and potency of said mixture until the spectroscopic characteristic of said homogeneous mixture reaches a predetermined end point for homogeneity or until the spectroscopic characteristic converge.

19. The method according to claim 18 wherein said detecting on-line the spectroscopic characteristic of the mixture during the mixing process with said detection means is synchronized with the detecting of the rotational position of said container by a means for detecting rotational position.

20. The method according to claim 18 wherein said detection means comprises a spectroscopic means having an opening from which radiation emanates and is admitted and a conduction means for conducting radiation from said spectroscopic means to said mixture and conducting reflected or transflected radiation back to said spectroscopic means, said conduction means having a first end and a second end and said conduction means connected to said spectroscopic means' opening at its first end and connected to said container's aperture at its second end.

21. The method according to claim 18 wherein said detection means comprises a spectroscopic means having an opening from which radiation emanates and reflected or transflected radiation from said mixture is admitted and said detection means opening abuts said container's aperture.

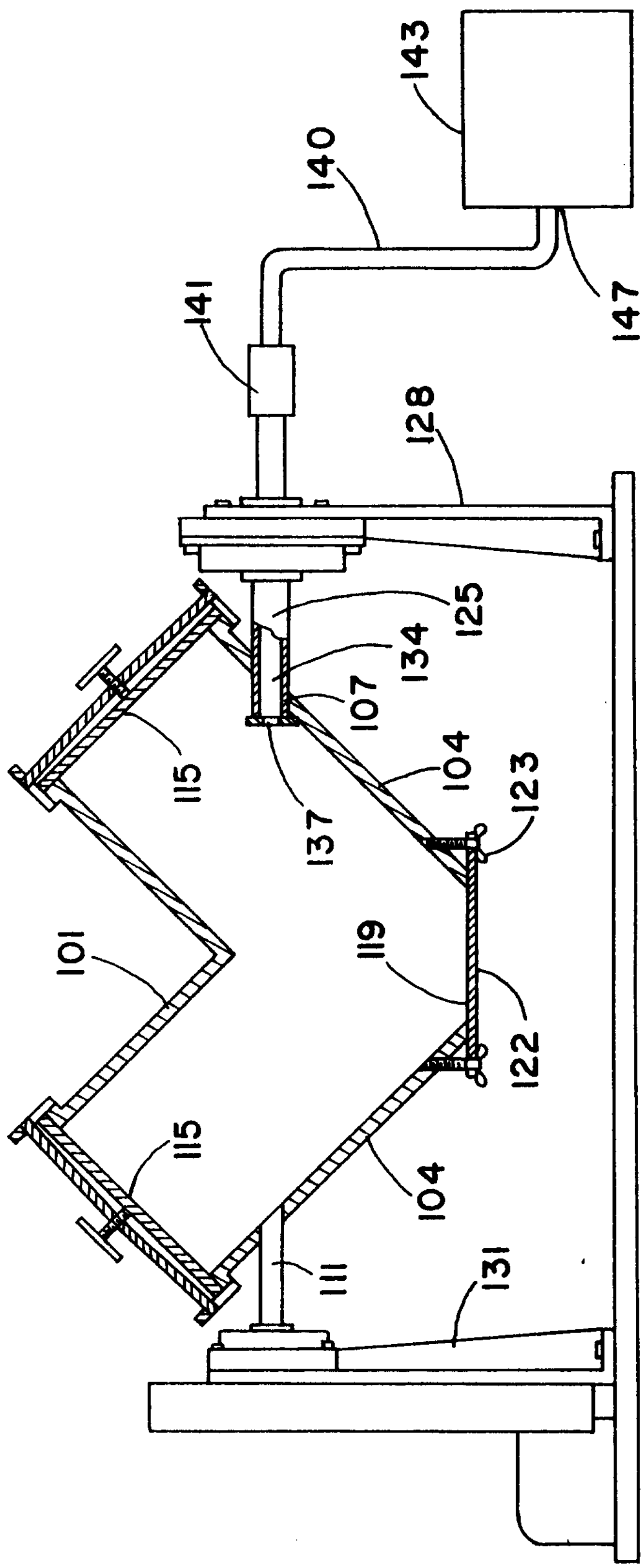
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FIG. 1

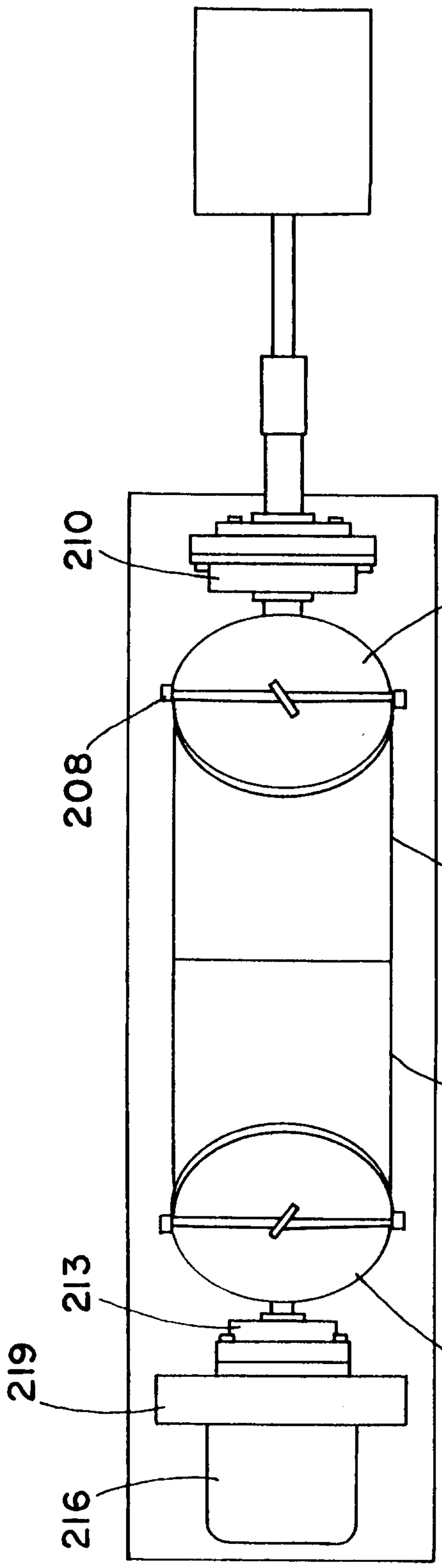


FIG. 2

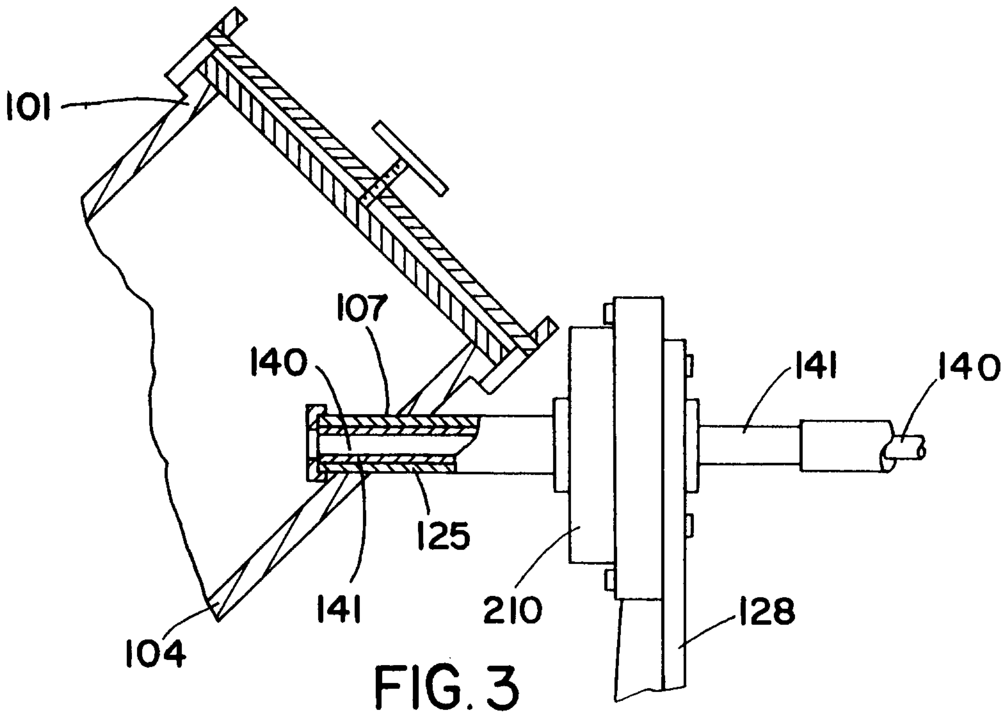


FIG. 3

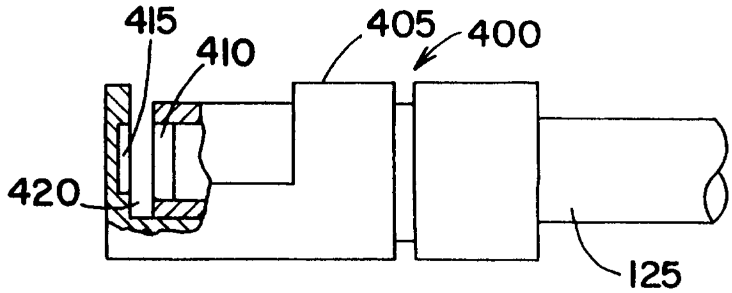


FIG. 4

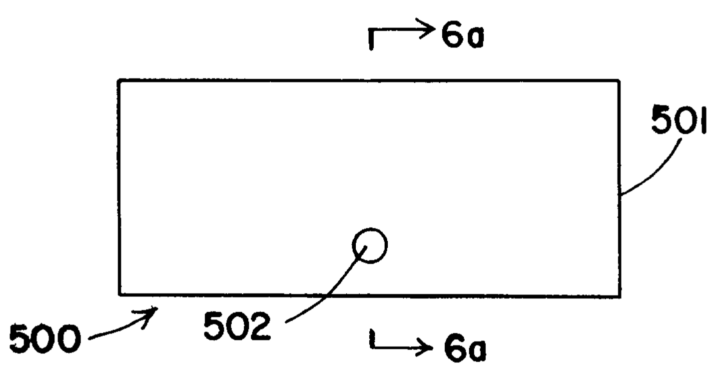


FIG. 5

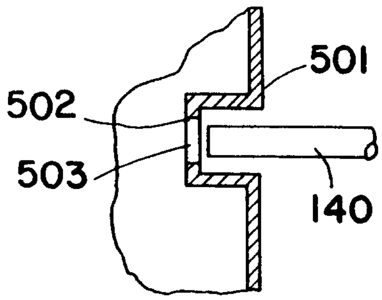
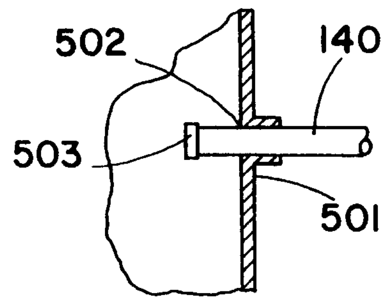


FIG. 6A

FIG. 6B



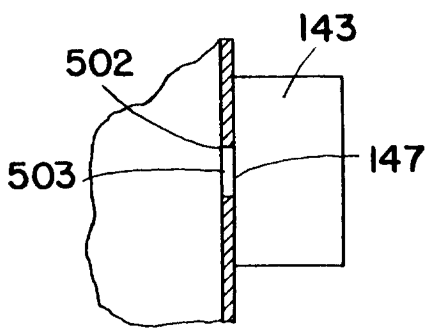


FIG. 6C

FIG.6D

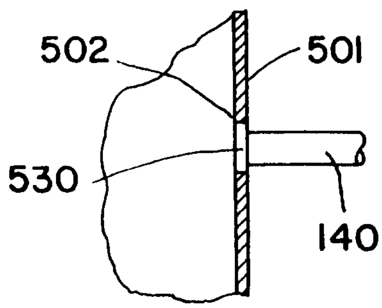
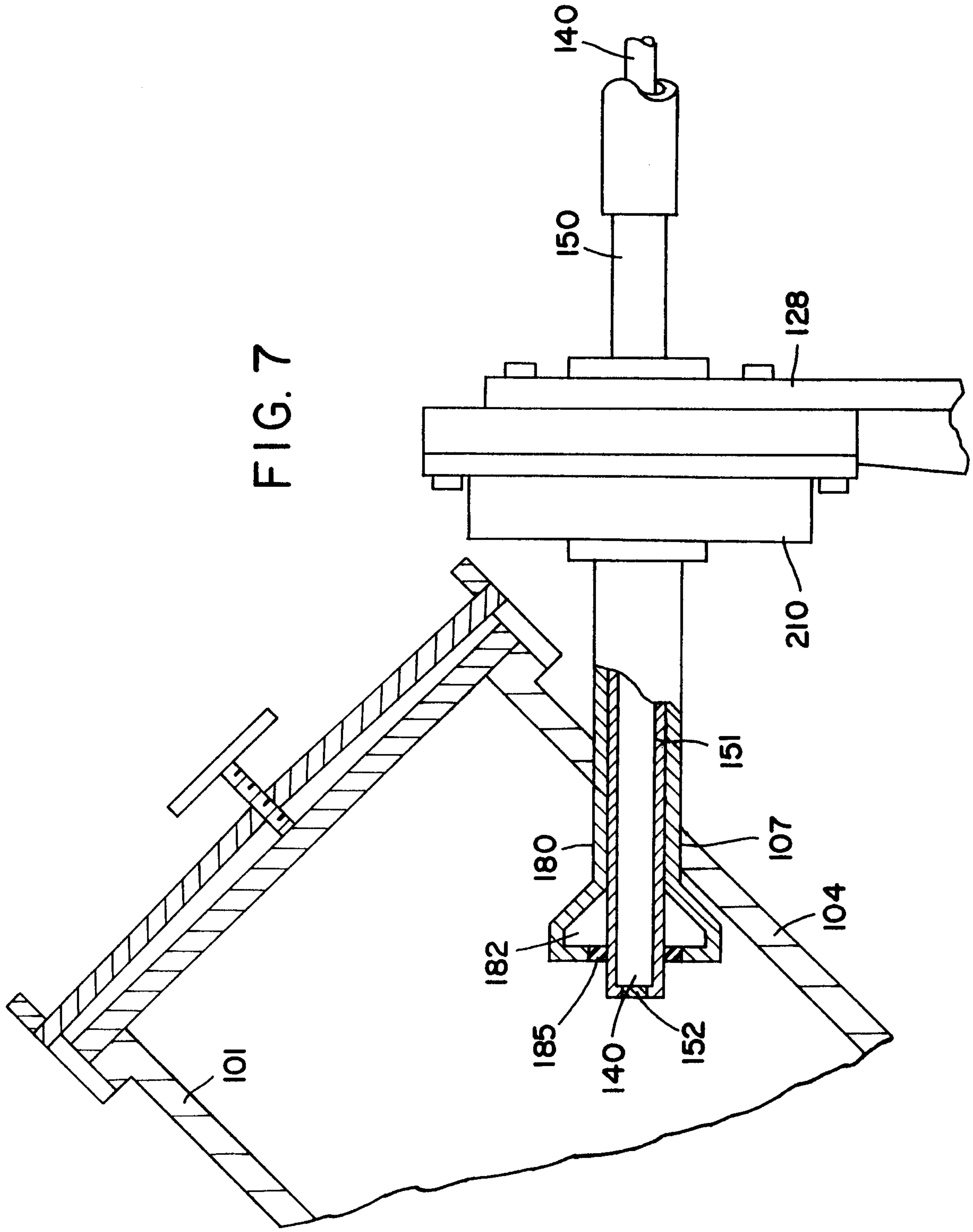


FIG. 7



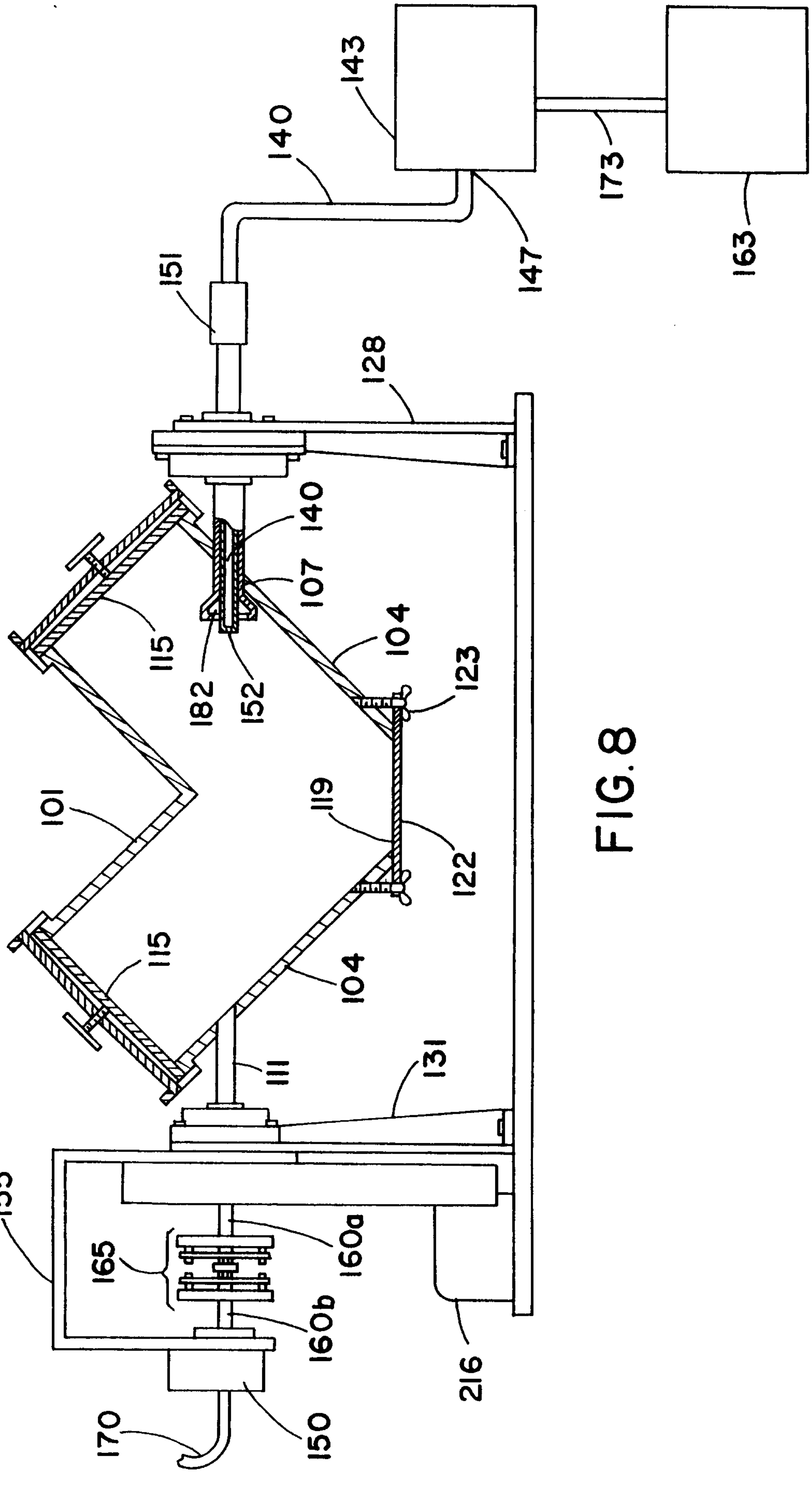

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FIG. 8

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 4010

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	US-A-2 514 126 (FISCHER) ---	1-21	B01F15/00 B01F9/04
Y	SOVIET PATENTS ABSTRACTS Section Ch, Week 8801, 15 February 1989 Derwent Publications Ltd., London, GB; Class J01, AN 89-005879 & SU-A-1 402 856 (IVAN UNIV) * abstract * ---	1-21	
A	JAPANESE PATENTS ABSTRACTS (EXAMINED) Week 9051, Derwent Publications Ltd., London, GB; AN 90-379406 & JP-A-2 273 535 (FUJITSU) * abstract * ---		
A	PATENT ABSTRACTS OF JAPAN vol. 11, no. 75 (C-408)(2522) 6 March 1987 & JP-A-61 230 727 (NIPPON PAINT) * abstract * ---		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	US-A-4 125 327 (MARGOLIS) ---		B01F
A	GB-A-590 441 (TYLER) ---		
A	DE-A-19 05 290 (DYNAMIT NOBEL) ---		
A	GB-A-1 386 312 (INOUE-JAPAX) ---		
A	PATENT ABSTRACTS OF JAPAN vol. 3, no. 151 (M-84)12 December 1979 & JP-A-54 127 065 (KUBOTA) * abstract * ---		
A	DE-A-33 37 403 (SEYD FERTIGBETON) ---		
A	GB-A-2 252 259 (UNILEVER) -----		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	6 September 1994	Peeters, S

CATEGORY OF CITED DOCUMENTS

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