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(54) Title: PHARMACEUTICAL MIXTURE EVALUATION

(57) Abstract: A method for obtaining information about a heterogeneous pharmaceutical mixture is disclosed. The method includes beginning to apply an image enhancement agent to the mixture. A plurality of images of the mixture can then be obtained over time, with at least one image being obtained after the step of beginning to apply an image enhancement agent. This allows information to be derived about a distribution of components of the mixture, based on differences between spatial information in different images.

PHARMACEUTICAL MIXTURE EVALUATION

Background of the Invention

It has been recently recognized that the performance of a typical pharmaceutical is not only a function of its chemical composition, but also of its physical makeup. For example, particle sizes and distributions of both the drug and excipients play a role in the final performance of the product. These physical properties can, amongst other things, alter the dissolution profile of a drug, and result in poor or uncontrolled release of the active ingredient into a patient's bloodstream.

Typically, finished pharmaceutical products are a mixture of both the active ingredient and a variety of excipients (lactose, starch, magnesium stearate etc.). During manufacturing these components are physically blended or granulated before being pressed into their final form as tablets. Problems with blending or granulation, such as how well the components have mixed or whether or not there is an agglomeration or preferential association of one or more of the components, can have a significant impact in both the products manufacturability and ability to pass the final quality control tests before product release.

Normally both the active ingredients and the excipients are white powders and visualizing their distribution in either a powder blend, a granulation or a finished product is a challenge. Several analytical approaches are generally taken to assess the heterogeneity of the mixture or finished tablet. These include approaches such as Raman mapping and imaging spectroscopy, as well as infrared and near infrared mapping and imaging. All these approaches produce a map of the distribution of the various chemical components comprising the final product. While these approaches normally result in providing the desired information, they tend to be either slow, expensive, or both. But the information provided is so valuable for understanding an errant manufacturing process that Raman maps are sometimes acquired over a period of several days for a single tablet.

Summary of the Invention

In one general aspect, the invention features a method of obtaining information about a heterogeneous pharmaceutical mixture that includes beginning to apply an image enhancement agent to the mixture. A plurality of images of the mixture are obtained over time, with at least one image being obtained after the step of beginning to apply an image enhancement agent. This allows information to be derived about a distribution of components

of the mixture, based on differences between spatial information in different images, with the differences being caused by the application of the image enhancement agent.

In preferred embodiments, the step of applying can apply a stain as the image enhancement agent. The step of applying can apply a fluorescent stain as the image enhancement agent. The step of applying can apply radiation as the image enhancement agent. The step of applying can apply a stain that is distinguishable in the visible light wavelength range as the image enhancement agent. The step of applying can alter properties of a component in the mixture. The step of applying can alter properties of an inactive component in the mixture. The step of applying can alter properties of an active component in the mixture. The steps of applying, obtaining, and deriving can also be applied to a reference sample. The step of obtaining can obtain images of the reference sample and the mixture at the same time. The steps of applying, obtaining, and deriving can be applied to a pharmaceutical dosage unit that includes active and inactive ingredients. The stain can have an affinity for one or more of the inactive ingredients. The stain can have an affinity for one or more of the active ingredients. The method can also include exposing at least one inner surface of the pharmaceutical dosage unit, with the step of obtaining an image obtaining images of the exposed inner surface. Further steps of exposing inner surfaces of the pharmaceutical dosage unit and further steps of obtaining images of the inner surfaces exposed in the further steps of exposing can be used to develop a three-dimensional data set for the dosage unit. The step of exposing can use a cutting implement. The steps of applying, obtaining, and deriving can be applied to a pharmaceutical tablet. The steps of applying, obtaining, and deriving can be applied to a number of different pharmaceutical dosage units obtained from a process at different times. The step of obtaining an image can obtain images of a plurality of the different pharmaceutical dosage units obtained from the process in a same field of view. The step of deriving can derive a visual presentation of the pharmaceutical dosage unit in which areas affected by the image enhancement agent are presented with a predetermined visual treatment. The steps of applying, obtaining, and deriving can be applied to a number of different samples obtained from a process at different times. The step of obtaining an image can obtain images of a plurality of the different samples obtained from the process in a same field of view. The steps of applying, obtaining, and deriving can be applied repeatedly to pharmaceutical samples from a commercial pharmaceutical process. The method can further include the step of adjusting the process based on information derived from one or more of the steps of deriving. The steps of applying, obtaining, and deriving can

be applied in a sampling regimen sufficient to ensure a predetermined quality objective for the pharmaceutical mixture. The steps of applying, obtaining, and deriving can be performed without stopping the process. The steps of applying, obtaining, and deriving can be performed during an interruption of the process. The steps of applying, obtaining, and deriving can be applied to pharmaceutical samples from an experimental pharmaceutical process. The method can further include the step of adjusting a formulation for the pharmaceutical mixture. The step of deriving can derive statistical information about the distribution of components of the mixture. The step of deriving can derive statistical information about particle size for components of the mixture. The step of deriving can derive statistical information about particle distribution for components of the mixture. The method can further include the step of comparing results from the steps of applying, obtaining, and deriving for a first sample of the pharmaceutical mixture with results from the steps of applying, obtaining, and deriving for at least a second sample of the pharmaceutical mixture. The step of comparing can include deriving statistical information about a number of samples of the pharmaceutical mixture. The method can further include the step of comparing results from the steps of applying, obtaining, and deriving with a predetermined standard. The method can further include the step of providing an indication of origin of the mixture based on the information derived in the step of deriving. The step of providing an indication of origin can be operative to provide a genuine/counterfeit indication. The method can further include the step of providing a cleaning validation indication based on the information derived in the step of deriving. The method can further include the step of determining a root cause of a manufacturing process defect for the mixture based on the information derived in the step of deriving. The step of applying can apply the agent using vapor deposition. The step of deriving can include a step of measuring a rate of change of information, caused by the application of the image enhancement agent, in different ones of the plurality of images. The step of applying can apply heat as the image enhancement agent. The step of deriving can derive spatial information from relative melting points of components of the pharmaceutical mixture. The step of applying can preferentially etch or dissolve part of the mixture.

In another general aspect, the invention features an apparatus for obtaining information about a heterogeneous pharmaceutical mixture that includes an image acquisition system having a field of view operative to acquire images of samples of the pharmaceutical mixture. Also included is an image enhancement detection module optimized to detect portions of the mixture having been exposed to a predetermined image enhancement agent.

An information derivation module is operative to derive information from the image enhancement detection module about a distribution of components of the mixture in the image, based on differences between the portions of the mixture that are caused by the application of the image enhancement agent. In preferred embodiments, the information derivation module can be operative to measure rates of change caused by the image enhancement agent.

In a further general aspect, the invention features an apparatus for obtaining information about a heterogeneous pharmaceutical mixture that includes means for applying an image enhancement agent to the mixture, means for obtaining a plurality of images of the mixture over time, and means for deriving information about a distribution of components of the mixture in the images, based on differences between spatial information in different ones of the plurality of images, wherein the differences are caused by the application of the image enhancement agent.

Systems according to the invention are advantageous in that they can allow information about the physical makeup of a pharmaceutical mixture to be obtained quickly and inexpensively. These capabilities can speed up the development of pharmaceuticals and the process equipment used to manufacture them. They can also reduce the cost of the development and ramp-up of a suitable manufacturing process.

Systems according to the invention can also be very useful as quality assessment and quality control tools. Because of their high speed and low cost, these systems can process large numbers of tablets or other aliquots of a pharmaceutical mixture to monitor a large-scale or ongoing pharmaceutical manufacturing process. This can allow pharmaceutical manufacturers to set and achieve quality standards for the physical makeup of their products.

And because systems according to the invention can operate quickly, they can be deployed in such a way as to monitor a process in real time or near real time. This can allow manufacturers to quickly detect and correct a situation in which a process has developed a defect, reducing the amount of wasted product and catch-up time required to replace that product. Because of the abundance of information that is potentially available, systems according to the invention may even be able to monitor trends in a process and correct them before they result in an error condition in which product must be discarded.

Brief Description of the Drawings

Fig. 1 is a block diagram of an illustrative embodiment of a pharmaceutical mixture quality control system according to the invention;

Fig. 2 is an image of an analgesic tablet that was stained with iodine and acquired in accordance with the invention;

Fig. 3 is a block diagram of an illustrative embodiment of a chemical imaging system employing dual disparate detectors;

Fig. 4 is a flowchart illustrating the operation of the system of Fig. 3;

Fig. 5 is a block diagram of an illustrative embodiment of a system used to monitor pharmaceutical mixing;

Fig. 6 is a cross-section of a window for the system of Fig. 5;

Fig. 7 is a perspective diagram of an alternative sample area arrangement for the system of Fig. 1; and

Fig. 8 is a flowchart illustrating the operation of the system of Fig. 1 with the sample area arrangement of Fig. 7.

Detailed Description of an Illustrative Embodiment

Referring to Fig. 1, an illustrative embodiment of the invention includes an information acquisition system 10 that can be placed proximate a processing device. In this illustrative embodiment, the acquisition operates in concert with a conveyor 14 that transports pharmaceutical dosage units 12, such as tablets. Other types of processing devices could also be accommodated, however, such as hoppers, blenders, or granulators. And other types of pharmaceutical mixtures or dosage units can be provided for, such as bulk powders, capsules, suspensions, or even mixtures of immiscible fluids.

The acquisition system can include an actuator that transports a sample (e.g., 12S) from the processing facility to a sample area. In this illustrative embodiment, the actuator includes a controllable diverter 16 that selectively diverts tablets onto a ramp 18. But one of ordinary skill would of course recognize that other types of actuators can also be provided to obtain samples from a conveyor, such as different types of mechanical actuators, pneumatic nozzles, vacuum fixtures, or electrostatic collectors. The actuator may also be implemented differently depending on the nature of the sampling process required. To extract material from a blender, for example, the actuator can employ a small sampling shovel mounted on a moving carriage.

The acquisition system 10 also includes an imaging enhancement agent applicator 20. In this illustrative embodiment the applicator can include a stain pad similar to an office stamp pad, and an application mechanism to press the pad against the dosage unit. The stain

could also be placed in a sealed package as a disposable (one dose) strip and be applied by pressing the strip to the tablet and then removing. Other types of applicators can also apply a stain to the dosage unit, such as other types of stamping mechanisms, aerosol nozzles, or dipping mechanisms. Vapor deposition is another suitable way of applying a stain. Iodine, for example, can be sublimated and delivered to a chamber in which it condenses on a surface of the dosage unit.

The tablet may be stained with a colorless stain that reacts with one of the components within the tablet to produce a color change. The stain may also be colored, but this would still result in a color change on contact with the tablet. The stain is preferably a visible stain, but it can also be a stain that provides information outside of the visible wavelength, such as an ultraviolet or infrared fluorescence stain. For example, many pharmaceutical active ingredients are aromatic compounds for which a particular visible or fluorescent stain could be identified or explicitly manufactured, while most of the commonly used excipients (e.g., compression/encapsulation aids, disintegrants) are not aromatics. Further, other ingredients, such as starch, could be readily stained using compounds such as iodine. Using an array of stains and fluorophores one, some or all of the components of the tablet could be stained, and then digitally imaged with either a macroscopic or microscopic visible imaging system. The imaging enhancement agent may also take another form, such as a gas, radiation or even heat.

The acquisition system 10 also includes an image sensing system 22. This system can include a camera that is sensitive to visible wavelengths and is equipped with suitable lenses. The imaging system can produce simple RGB type pictures or may be fitted with one or more optical filters to highlight color absorption or fluorescence emission characteristic of a particular stain or tag and therefore of a particular component of the pharmaceutical product. This image can be obtained while the sample is in the staining area, or in another imaging area. The camera may be held at a fixed position, or moved in and out of position.

Tablets may be stained one at a time or in arrays. For example, a plate containing 96 or more tablets may be stained simultaneously before being placed in the field of view of the camera. The entire 96 tablet sample may comprise individual tablets removed from a production line at known time intervals to provide a statistical sampling of the evolution of a process or manufacturing run. Suitable robotic handling machinery to load multi-sample plates is available from, for example, Caliper Life Sciences, of Hopkinton, Massachusetts. Of course, any type of information derived from compound images can also be derived from a series of individual images.

One or more reference samples can also be provided in the field of view of the camera to act as a standard for measurements made on the images. These reference samples could be known-good aliquots of the mixture to be tested, or they may include other reference materials, such as one or more single components of the mixture. A supply of reference samples may be provided such that they are stained along with, or between, some or all of the samples under test. One or more pre-stained reference samples could also be positioned at a fixed position near the sample under test and used repeatedly. The use of a reference sample and other relevant topics are discussed in United States Patent Number 6,690,464, entitled "High-Volume On-Line Spectroscopic Composition Testing of Manufactured Pharmaceutical Dosage Units," issued February 10, 2004, and which is herein incorporated by reference.

As the imaging sensing system 22 acquires image data, it passes them on to an acquisition system 26, which assembles the data into an image. An information extraction module then extracts information about the spatial distribution of stain in the image. This extraction of information can be a relatively simple operation, such as mapping of data into a color image, or it can involve some degree of spectral processing or image processing to enhance the spatial information.

If needed, further processing logic 30 can perform additional operations on the data. The user can use an image processing module 32, for example, to perform further image processing operations on the image. The user can also use a statistical analysis module 34 to derive statistical information about a spatial distribution within a particular sample, or to derive information about trends within a series of samples.

The statistical analysis module 34 can provide its output in a variety of forms, including raw numbers, graphs, or images that can be presented on an output device, such as a display or printer. It can derive and analyze the relative frequency distribution of concentration for one or more substances. It may also calculate a mean, skew, and/or kurtosis for the distribution. The mean provides an indication of the overall concentration or amount of an item or substance analyzed. In the case of a pharmaceutical dosage unit, for example, the mean provides a measure of its dosage. The standard deviation can provide for a measure of the range of variation of certain properties, such as film thickness. Skew and kurtosis both provide an indication of non-uniformity of mixing or non-normal statistical distribution in a sample. These quantities can be evaluated as absolute numbers or in comparison with earlier results. The statistical analysis logic can also perform its analysis on more than one chemical component or property, and it can detect and analyze overlapping distributions, such as by

curve fitting. The application of statistical techniques to particular images and other relevant topics are disclosed in published PCT Application No. WO03060443, which is entitled "Spectrometric Process Monitoring" and corresponds to U.S. Serial Numbers 60/343,449, 60/343,691, 60/394,053, and 60/394,053. All five of these documents are herein incorporated by reference.

It is also possible to make more than one measurement for each sample by exposing inner surfaces of the sample and staining them. Suitable techniques for this type of operation and other relevant topics are described in U.S. Application No. 10/684,965, which is entitled "Volumetric Spectral Imaging" and was published under Publication No. 20040135086. This application is herein incorporated by reference. Staining and other processes pertinent to this disclosure are also discussed in published PCT Application No. WO2006044861, which corresponds to U.S. Application Nos. 60/619,569, 60/627,793, 60/643,837, 60/645,098, and 11/265,796, all of which are herein incorporated by reference.

The system can also include process feedback logic 36, which allows the spatial distribution information to be fed back into the process. This feedback logic can be configured to provide recommendations for changes to the process or it can automatically issue signals to a process device. For example, the feedback logic could provide limits on statistical particle distribution parameters above which a signal would be sent to a blender to adjust one of its operating parameters, such as blend speed or blend time. The feedback logic may also alert an operator or indicate when an entire batch should be discarded.

The system can be used outside of quality control/quality assurance and process monitoring context. It may be used as a development tool in drug development and formulation. It may also be used to establish the root cause of manufacturing problems as they may arise. It may be used for cleaning validation to ensure that one process does not affect a subsequent one that is run using the same equipment. And it may even be used outside of the manufacturer's facilities altogether in the in the identification of recalled, counterfeit, or gray market products.

A single tablet could be multiply stained or multiple tablets can be used, each with a single chemical marker. One stain could be specific to different polarities corresponding to chemical components of the tablet, for example, and another could be specific to their different hydrophobicities. The multiple images collected from such a series of optical filters or multiple stains may be further processed using standard image processing methods or other mathematical algorithms such as univariate or multivariate statistical methods. While the

tablet being stained would likely be contaminated and lost to the manufacturing process, the speed of the technique might facilitate its use near a pharmaceutical manufacturing line where it might sample 1 in 100 or 1 in 1000 tablets actually manufactured. These stained tablets would be discarded, but would provide a good statistical representation of a finished tablet, a granulation or a powder blend. Additionally, using digital image processing techniques, discrete or continuous sample statistics may be collected for a particular manufacturing process which could potentially identify emerging problems before a process goes out of control. Using particle statistics to measure the area of the tablet stained and the intensity of the light absorption or emission, an estimation of the composition may be obtained in addition to the physical information returned on the particle size and distribution statistics provided by the image.

Each of the operations described above can be performed manually, or they may be fully or partially automated. It may make sense in some circumstances, for example, to use an automated sampling mechanism to obtain an appropriate set of samples, but to then manually stain them, position them in the field of view of the camera, and evaluate the resulting images. Or it may be appropriate in some instances to sample, stain, and obtain images manually, but then to rely on an automated software assessment of the results.

In one embodiment, the system is based on the so-called IBM-PC architecture, with the image acquisition interface 26 and image processing module 32 being implemented in hardware as plug-in boards occupying expansion slots on the system bus, and remaining functionality being implemented in software. Of course, other structures can be used to implement systems according to the invention, including various combinations of dedicated hardware and special- purpose software running on general-purpose hardware. In addition, the various elements and steps described can be reorganized, divided, and combined in different ways without departing from the scope and spirit of the invention. It should also be noted that not all of the items presented in the discussion of the illustrative embodiment will be required for all implementations of the invention.

There is considerable interest in measuring not only the potency and purity of a pharmaceutical product but also interest in determining the chemical 'structure' of the product. Most solid-dosage pharmaceuticals are spatially heterogeneous materials comprising mixture of powders. These powders are typically pressed into a finished product which can be a tablet. Because of the disparate nature of the various components there can occur non-uniform distribution of components in the final product. These can be the result of aggregation of one

or more components and or the preferential association of components. These inhomogeneities can be the result of physical forces imparted on the product during the manufacturing process or the result of other factors such as electrostatic charge, hydrophobicity, particle size and de-mixing etc. In either case while the exact composition of the entire tablet may be well characterized the physical distribution of the components may not. In other words pharmaceutical companies may know what and how much of each component is in the tablet but do not always know where it is or how it is distributed.

The concept of staining biological tissue to reveal structural detail at the cellular level is a well established technology. Stains are also used to study dissolved pharmaceutical compounds under either visible or ultraviolet light. In the latter case the method proceeds by dissolving a tablet and extracting the active ingredient with chromatographic techniques such as thin-layer chromatography (TLC). Detection techniques that may include staining are then used to visualize the presence of the active ingredient as spots on a TLC plate. In the latter case no structural information about the tablet is available and the excipients (non-active ingredients) are normally not measured and considered unimportant to the quality of the product. The entire process is designed to only measure the presence of the drug and to give an indication of the amount and/or purity. These are principal parameters determined by the USFDA for determining the quality of the finished product and its fitness for release to the public.

Presented here is the concept of physically staining and imaging a finished and intact pharmaceutical product with a variety of materials that are selective for the different components that comprise a typical drug product. These stains can determine component blending and particle size and particle size distribution of both excipients and active pharmaceutical ingredient(s). These images can be used as an additional and critical measurement of product quality. This spatial information may be a critical component in how a particular product behaves when ingested. For example, these physical factors may affect the dissolution characteristics and cause the product to release the drug into the blood stream either too quickly or too slowly. In another situation the performance of the product may not be impacted, but the manufacturability might be. Lack of optimum blending characteristics may result in tablets that stick in the tablet press or tablets that crack chip or break easily resulting in loss of production time or products that cannot be sold for aesthetic reasons. In another situation the spatial distribution of components in a tablet may be a design element such as in a time-release or sustained release product. In another situation a product may be a

drug product containing two or more ingredients designed to be delivered to the patient in succession and not simultaneously. In these situations the physical composition of the tablet is a critical design parameter and one for which there is little current technology to address, especially in a manufacturing setting. Another use of the technology may be in the visualization and discovery of counterfeit pharmaceutical products. These products are likely to be produced using different manufacturing processes and while the active ingredient may be correct the different process may result in a different distribution and size distribution of the components. This pattern would be the 'fingerprint' of the original and counterfeit products.

The stains may be observed in the ultraviolet, visible or near-infrared part of the optical spectrum. The stains may be simple absorption stains or fluorescent or bio-luminescent stains. The preferential component staining can be achieved with stains that either preferentially bind with one or more components or that react with one or more components to achieve a color change or preferential color localization. For example, Sudan Red (a stain for wax) or others stains such as Furaptra(AM) or Indo-Mag(AM) may be used to preferentially visualize the distribution of Magnesium Stearate. Stains that are specific for Sodium, Magnesium of Calcium may be used to visualize the distribution of excipients such as calcium phosphate, sodium phosphase or magnesium stearate. Iodine may be used to visualize starch or the active ingredient. A myriad of highly selective stains are available and can be used to 'stain' for different functional groups. They may be used singly or in combination to highlight the distribution of one or more components. As another example a pH indicator may be used to preferentially visualize materials in the matrix with slightly or grossly varying pH values. In another mode the tablet may just be subjected to a chemical etching technique where it is subjected to selective dissolution by suitable solvents. In this mode some of the crystals for one or more components in the tablet would be dissolved and the tablet effectively etched. The etching process would serve to reveal the location of these species in the subsequent imaging step.

Finished tablets may be visualized using this technique but it is also useful to apply the technique to other parts of the manufacturing process. Tablets may be stained and examined before or after coating. Pharmaceutical granules from a granulation process may be imaged before being pressed into the final tablet form. A powder blend may be stained and examined for homogeneity of mixing. The technique could be used during manufacturing or during formulation development to determine the distribution properties of the individual

components. The technique could also be used in a trouble-shooting or root-cause analysis mode and these imaging instruments may be used either in a laboratory or in a manufacturing environment. They may be used in an in-line, at-line or near-line capacity to support quality assurance or quality control measurements. The technology is rapid and will also have utility in the new USFDA PAT initiative. The technology may also be employed in a 'field' mode and used to support efforts to determine counterfeit pharmaceutical products as they pass through international borders, ports or airports.

The visualization process may take the form of simply looking at the stained product with the naked eye or through a microscope to visualize the more minute structures and particles. Preferably the data is recorded digitally with a camera, CCD or focal-plane array detector. These data can be stored and subjected to further more quantitative image analysis. Simple color (RGB) type cameras may be used but more sophisticated spectral imaging approaches may also be used. These methods would take images of the samples at multiple wavelengths to provide enhanced discrimination of the various components which may be preferentially stained by one or more of the 'stains'. In addition, a wavelength filter in conjunction with a high dynamic range camera such as a CCD would provide much more accurate color depth information than a simple RGB camera or viewing with the naked eye. This information would provide a much more accurate assessment and discrimination of the different chemical species. The wavelength selection filters may be simple color filters used singly or in combination but may also be more sophisticated filter wheel arrangements or even tunable filters such as AOTFs or LCTFs. The filters may be narrow bandpass optical filters, broad bandpass optical filters or short and/or longpass optical filters. The filters may be used to filter the incident light and also to filter the reflected or emitted light. The samples may be illuminated with narrow band light (lasers etc.) or broad band light. The samples may be illuminated with visible light, ultraviolet light or infrared light. For example, the samples may be illuminated with broad band ultraviolet light and measured by capturing emitted visible light. The physical phenomena by which spatial contrast is derived from the various components may be by absorption or fluorescence emission.

The method by which the stains may be applied to either a finished product or intermediate may be varied. The device may be a chamber into which one or more tablets are placed for the application of the stain by an aerosol system or other means of producing a means of uniformly applying the stain in a non-contact mode. The device may include a pad or adhesive strip containing a stain or other such contact type applicator. The stain applicator

may also be of a type similar to the inkjet deposition technology currently used in printers or some other autopipetting technology. In either case the applicator may be refillable or disposable providing a continuing revenue stream. The stain applicator may be able to apply a stain of only a single type of may be configured with one or more applicators to be able to apply different stains and/or multiple stains. For example, a stain applicator might have one or more inkjet type cartridge locations which may be swapped out for different cartridges or replacement cartridges. The device may also contain one or more solvent applicators for the removal of excess stain from the tablet or for cleaning the various applicators. The device may be capable of staining single tablets, granules or tablet blends but may be also capable of staining multiple tablets, granules or multiple powder samples simultaneously. The system may operate continuously, semi-continuously or in a 'static' laboratory type mode. For example, tablets may be able to move continuously through the system in a manner analogous to a car wash for a fully automated manufacturing application but may also be hand-loaded for near-line or laboratory type applications. The staining system may be manually operated on single samples while the imaging system may be automatic and allow multiple samples to be loaded. The staining system may be automatic while the imaging portion could be done manually or both be automatic or both be manual. Indeed the entire system may be integrated such that staining and imaging are done with a single piece of apparatus. Clearly the staining device might be sold separately or in conjunction with the imaging system and the staining system might be used in conjunction with a standard microscope of other digital imaging system. The device may also come equipped with a timer and other measuring systems for ensuring the correct application of the stain but may also be able to time a staining process to ensure that a particular reaction has completed. It may also include a heater, or light source which may be used in conjunction with the staining process to finish the tablet preparation before being imaged. For example, after the application of a stain a solvent may need to be evaporated before the imaging process should begin. These issues can be automatically controlled by this device. The device may also be connected to an air and solvent handling system for the proper collection and disposal of any toxic materials associated with the staining process. It is also possible that the stain applicator may take the form of a simple 'marker pen' type format for field use.

In both laboratory and manufacturing or quality control applications the technology may be used in conjunction with other well-established analytical methods such as HPLC, near infrared spectroscopy, Raman spectroscopy, mid-infrared spectroscopy. These other

techniques would provide the additional potency and purity data necessary to fully characterize the product. The technique may also be used in conjunction with existing chemical imaging systems such as near-infrared, mid-infrared or Raman imaging systems. These systems may also be imaging systems of the mapping variety. These auxiliary spectroscopic measurements may measure the samples in either a macro or micro mode. In a macro mode the chemical composition of the whole product is measured in conjunction with the imaging data. In the microscopic mode individual locations within the product may be determined from the stained image for further analysis by a NIR, Raman or mid-infrared spectrometer. For example, a particle that stains a particular color or has a particular visible spectral distribution as determined by a tunable filter configuration can be measured by a standard analytical spectrometer to absolutely identify it. The stained image may then be interpreted on the basis of this information. In other words all crystals stained the same color or with the same visible spectral distribution may be interpreted as being of the same chemical composition as the crystal measured by the spectrometer. Other stained crystals may be similarly assessed. Abundance (quantitative) estimates of the total composition may be determined from measuring the area of coverage of a particular stained component. A tablet may also be crushed and spread onto a surface before staining and imaging. While any spatial information would be lost, in some cases this may give a better estimation of the total composition of the finished product.

A staining system may comprise just the imaging device, just the staining device or a combination of the two. It may further include one of the aforementioned spectrometers. In another configuration this type of staining and imaging system may be tied directly to existing HPLC or spectroscopic equipment and/or microscopes from other manufacturers.

In another configuration a system may be assembled expressly for attaching to a pharmaceutical manufacturing apparatus such as a blender, granulator, tablet press or blister packaging machine. For example, in the blending configuration an automated system for retrieving small (unit dose) quantities of the mixture from the blender may be interfaced with a staining and imaging unit. In operation the sample is retrieved and quickly pressed into a tablet or wafer format. The stain is applied and the wafer imaged. The data can be analyzed to determine the distribution of one or more components before the wafer is discarded. The system can stain multiple wafers at discreet time intervals as the blending process progresses. In this manner the blending process may be terminated when optimum mixing statistics are determined. In a manner described previously the multiple stains can be applied to multiple

or single wafers to determine the distribution of multiple components of interest. Also this type of imaging system may be used singly or in combination with another on-line measurement technology such as near-infrared spectroscopy, Raman spectroscopy or mid-infrared spectroscopy. Similar approaches may be used for monitoring a granulation process and the component distribution and stoichiometry of a granulation process. In another configuration a tablet may be retrieved from a tablet press at different time intervals to monitor the distribution of one of more components and determine the uniformity of a coating process. One tablet in 100 or one tablet in 1000 may be retrieved. These tablets would of course, once stained, be lost to the manufacturing process.

Image processing methods for analyzing the image contrast may be both qualitative and quantitative. Individual images may be analyzed using standard techniques to enhance contrast and segment the images. The images may be analyzed using particle statistics to measure particle size and distribution of one or more components. The statistics may be visualized as histograms or other graphical means to represent mixing or particle distributions. The statistics can return information on mean values as well as deviations from the mean which might indicate a manufacturing or quality control problem. Multiple images derived from multi-wavelength filter based approaches may be analyzed using multivariate statistics in a manner similar to conventional chemical imaging data. One or up to three of these images for single or multiple stains may be combined in a simple RGB image, or multiple stains visualized in a binary stack motif where single colors in an image represent a single chemical species. The distribution of multiple chemical species may be determined using either multiple or single stains and the data processed to segment each component and highlight its distribution.

Imaging of pharmaceutical products is of interest because it is now realized that in addition to the chemical composition, the spatial relationship and size of the chemical domains comprising a complex formulation can also play a role in the ultimate performance and/or quality of a pharmaceutical product.

This application describes a system that combines the ability to obtain either simultaneously or in quick succession both chemical and spatial information from a single pharmaceutical product. Existing systems to accomplish this use sophisticated chemical imaging techniques such as infrared, Raman or near-infrared spectral imaging or mapping instruments. These are typically expensive, complex and in some cases slow. This concept stems from recognizing that the issue of spatial information and chemical information within

a pharmaceutical formulation, tablet or mixture can be separated by using two different non-invasive analytical protocols. Proposed in this application is a single instrument that combines visible or fluorescence imaging with a single point infrared, near-infrared or Raman instrument to provide spatial information in the former and chemical information in the latter. For example, a tablet may be placed in an instrument and simultaneously probed by an optical beam to collect a single mean infrared, Raman or near-infrared spectrum while a second optical beam in a different wavelength range can be used to image the sample using fluorescence excitation. These two data streams may be combined to derive a single metric that describes both the spatial and chemical content of the tablet. In another instance the molecular spectroscopy probe may immediately proceed the imaging of the tablet since the imaging may require the addition of a contrast enhancement agent that would affect the prior spectral measurement, as described in Application Serial No. 60/619,569, filed October 15, 2004, and Application Serial No. 60/627,793, filed November 12, 2004 and both entitled "Pharmaceutical Mixture Evaluation," which are herein incorporated by reference. In another instance the fluorescence or other type of imaging may precede the spectral/chemical measurement and be used to identify regions of interest to subsequently probe with a microbeam from the molecular spectroscopy instrument (Raman, IR, NIR). The imaging and spectroscopic measurement can also be performed simultaneously.

The proposed instrument design can use an imaging technique (fluorescence, or visible absorption) that has less chemical specificity that those methods currently used (Raman, IR or NIR). However, its performance can be enhanced by using multispectral or hyperspectral approaches. For example, a tablet may be subjected to incident UV or visible radiation at a series of wavelengths and imaged at each separate excitation wavelength or may be excited at a single visible or UV wavelength and imaged at a series of emission wavelengths using one or more optical bandpass filters, or a tunable optical filter such as an AOTF or LCTF. Changes to the excitation and emission selectivity can of course also take place simultaneously, such as in the case of a synchronous or 2-dimensional fluorescence measurement. An interferometer may also be used as a means of producing a modulated excitation radiation or as a means of measuring emission radiation. In either case one of more images of a sample may be produced which can be subjected to further qualitative and quantitative analysis to determine particle sizes and particle size distributions which may be used to infer the quality of performance of a pharmaceutical product or manufacturing process. In the case of hyperspectral or multispectral fluorescence or visible absorption measurements

the derived digital data can be compared and contrasted to fluorescence or visible absorption spectra of pharmaceutical excipients or active pharmaceutical ingredients previously measured and stored in a spectral library. These comparisons or matches may be done using a variety of univariate or multivariate mathematical approaches. In another example a near-infrared, infrared or Raman chemical imaging data set of a particular tablet, granule or pharmaceutical blend may be collected and the same tablet subsequently imaged using visible staining or fluorescence imaging. Both data sets may be combined to produce a correspondence table, which can be a 'one-to-one' lookup table such that the chemical identity of the particle or spatial location is derived from the infrared, Raman or near-infrared data and stored with the corresponding visible/fluorescence spectrum. For subsequent tablets, granules or powder blends of the same product measuring the fluorescence or visible imaging data and use of the pre-determined 'look-up' table will enable the location of the various chemical components to be derived using this simpler, quicker and less expensive approach.

For the fluorescence measurements one or more UV and/or visible light emitting diodes (LEDs) or laser diodes may be used to perform the imaging measurements at different excitation wavelengths, as described in PCT application WO 01/61293, published August 23, 2001, entitled "Multi-Source Spectrometry" and herein incorporated by reference . This imaging technique alone or in combination with another single-point spectroscopy such as infrared, Raman or near infrared in addition to providing quality assurance and quality control tools for pharmaceutical manufacturing can also provide a rapid and simple method for determining counterfeit pharmaceuticals.

Referring to Fig. 3, a chemical imaging system 40 according to this aspect of the invention includes an image detector 52, and a point detector 54 of a type different from the image detector. In one embodiment, for example, the image detector is a camera sensitive to visible and ultraviolet radiation emitted by fluorescence, and the point detector is a near-infrared single-point detector. This combination of detectors can be coupled with one or more sources 56 that can be tuned to selected fluorescence excitation frequencies. Other combinations of different types of image and point detectors can also be provided, such as visible image detectors sensitive to the color of a predetermined dye or mid-infrared point detectors.

An advantage of this type of arrangement is that it can obtain chemical image information less expensively than may be possible with other prior art arrangements. Using a relatively inexpensive NIR single-point detector can allow for the detection of chemical

information for a whole sample, for example, while the use of an inexpensive visible camera can allow for the detection of the spatial distribution of the chemical components in the sample. Combining the output of these two instruments can provide chemical imaging information that might otherwise only be obtainable using significantly more expensive NIR imaging systems.

In one embodiment, the chemical imaging system 40 uses a synthesis module 44, which is operatively connected to a reference library 42. The synthesis module is operatively connected to outputs of the image detector 52 and the point detector 54 and may also have control outputs operatively connected to inputs of the one or more sources 56. The one or more sources are positioned to illuminate the sample 60 to be imaged, as well as one or more optional reference samples 62. The image detector and point detector are positioned to receive radiation back from the sample(s) and/or reference sample(s). The instrument can be arranged to receive reflectance or transmission measurements.

The synthesis module 44 can access the library 42 to determine how the spatial information from the image detector should be interpreted. This library can include entries for a series of known ingredients, for example, which will allow the instrument to detect how these ingredients are distributed throughout the sample. The use of a library can allow a relatively insensitive image detector to provide spectral-spatial information that it might not otherwise be able to resolve. And if the synthesis and control module is equipped with a series sources having different excitation wavelengths, further spectral-spatial information may be obtained.

In one embodiment, the point detector 54 is kept at a fixed location and optics are provided to enable it to receive radiation from a whole sample area or pharmaceutical tablet. The point detector can also be arranged such that it views a smaller part of the sample. It may even be made to be moveable, such that it can sample or scan regions of interest that may become apparent from the use of the image detector 52.

Referring also to Fig. 4, operation of the system 40 can begin with the population of the library 42 (step 101). Although other techniques could also be used, this population can be performed using an NIR imaging instrument such as the "Sapphire" instrument available from Spectral Dimensions, Inc. An image and a point measurement can then be acquired, either simultaneously or one before the other (steps 102 and 104). The synthesis module can process the resulting data (step 106). The result can then be conveyed to the user, such as by displaying a chemical image of the sample or by providing a go/no-go indication (step 108).

In one embodiment, the system is based on the so-called IBM-PC architecture, with the synthesis module 44 and user interface 46 being implemented in software. Of course, other structures can be used to implement systems according to the invention, including various combinations of dedicated hardware and special- purpose software running on general-purpose hardware. In addition, the various elements and steps described can be reorganized, divided, and combined in different ways without departing from the scope and spirit of the invention. It should also be noted that not all of the items presented in the discussion of the illustrative embodiment will be required for all implementations of the invention.

Referring to Figs. 5 and 6, it is often desirable to use a spectrometer 102 to monitor the homogeneity of bulk pharmaceuticals while they are held in a processing vessel 106, such as a mixing vessel, conduit, or storage container. In these situations, the vessel is usually outfitted with a window that is transparent to the wavelength used to monitor homogeneity. In the case of an NIR spectrometer, for example, the window can be made out of sapphire, which is highly transparent to infrared radiation.

Unfortunately, the results of such experiments are not always satisfactory, because some of the ingredients used in pharmaceutical mixtures, such as magnesium stearate, may adhere to the vessel's window. This effect may be enhanced when the spectrometer is used in connection with one or more high intensity sources 104. A simple "non-stick" material window 108 can prevent this problem. This type of window includes a material that is transparent in the spectral region of interest, but it does not adhere to the pharmaceutical mixture.

The window 108 can be made entirely of the non-stick material, or it can be part of a compound structure in which a non-stick material is associated with another material. For ultraviolet or infrared imaging, for example, a window made of a structural sapphire portion 110 adjacent a polytetraflouoroethylene non-stick portion 112 can be used. The sapphire in this compound window gives it strength, while the polytetraflouoroethylene prevents degradation of results due to adherence of material on the window. Both materials exhibit very good UV and NIR transparency.

The non-stick portion can be made of a number of different materials that resist adherence by pharmaceutical ingredients. For example, fluoropolymers such as polytetraflouoroethylene can be used. These fluoropolymers can be used in any appropriate form, such as in the form of a coating or film. Flouropolymers are available, for example,

from DuPont (e.g., Teflon®). The material in the structural portion of the window can be sapphire, low-OH quartz, CaF2, or other optical grade materials that transmit in the wavelength region of interest. These materials are available from a number of sources, such as the Newport Corporation of Irvine California.

The system can also acquire information about how characteristics of a sample change over time. Referring to Fig. 7, for example, the sample 122 and one or more optional references 124A, 124B, ... 124N can be placed in a vapor deposition chamber 120, and then supplied with one or more vapors from one or more vapor sources 126A ... 126N. The vapor sources can be derived from solid, liquid or gaseous materials, which can be heated, sputtered, reacted, atomized, or otherwise processed to provide a vapor.

Other types of image enhancement treatments can also be applied to the sample, such as heat or radiation treatments. With the application of heat, for example, the relative melting points of different components can be exploited to derive spatial information about the mixture. This approach may be particularly helpful in identifying different polymorphic forms of a substance. In some instances, the chamber may be evacuated through an evacuation outlet 128 before vapor is supplied.

In operation, referring to Fig. 8, the system can first begin the application of an image enhancement treatment (step 140). This treatment will change characteristics of one or more components of the sample over time. The system can thus acquire information about the sample by acquiring images of the sample over time (step 142). It can then extract the information (step 144) and put into a form suitable to the user's objectives.

The rate of change of a characteristic of the sample can be used to derive information about the sample, such as information about its composition or molecular structure. This rate of change can be measured through multivariate methods applied to the pixels in a set of successive images. The result can be a rate-of-change map data set that expresses a rate of change of a characteristic at each pixel. These pixel values can then be compared with one or more known rates to identify a component, or a property of the component. For example, one treatment may be known to cause a first component of a pharmaceutical tablet to darken within a two-minute time frame. If the system detects any pixels that change at a rate that, within a tolerance range, matches the known rate, those pixels can be mapped to the first component.

If a treatment, or a succession of treatments, has a different effect on more than one component, such as a different rate of stain darkening, each pixel can be tested for the

different effects. Pixels that match a fist rate of stain darkening can be mapped to a first color, for example, and pixels that match a second rate of stain darkening can be mapped to a second color. These two rates of darkening can be caused by a single treatment in which components have differing affinities or responses to a treatment. Changes can also result from a succession of treatments, such as one that first targets hydrophobic components and then targets hydrophilic components.

The images in a series can be acquired according to different acquisition schedules. They can be acquired at regular intervals, for example, with the rate of acquisition being selected according to the anticipated rate of reaction. If there are several successive reactions, the rate can be varied over time in accordance with different rates associated with the reactions. The rate can even be adaptive, with acquisition changing or stopping when a particular condition is reached. Alternatively, images can be acquired to simply confirm that the different reactions have taken place. If a reaction is sure to be over at time t_1, and another at time t_2, for example, the system can acquire an image after t_1 and another after t_2.

The system preferably assembles a full set of acquired data into an image data cube before extracting information, although it could also begin the extraction process as soon as images begin to be acquired. Information extraction can involve a variety of univariate or multivariate methods. Successive images can be subtracted, for example, to show where samples have changed. Rates of change can also be measured, as discussed above. And characteristics of areas of the sample can be compared to, or correlated with, other sample areas or the reference(s). The results can be presented in any suitable form, such as a set of numerical values, a component identification flag, or a map of components or component properties.

The present invention has now been described in connection with a number of specific embodiments thereof. However, numerous modifications which are contemplated as falling within the scope of the present invention should now be apparent to those skilled in the art. Therefore, it is intended that the scope of the present invention be limited only by the scope of the claims appended hereto. In addition, the order of presentation of the claims should not be construed to limit the scope of any particular term in the claims.

What is claimed is:

CLAIMS

1. A method of obtaining information about a heterogeneous pharmaceutical mixture, comprising:

beginning to apply an image enhancement agent to the mixture,

obtaining a plurality of images of the mixture over time including at least one image obtained after the step of beginning to apply an image enhancement agent, and

deriving information about a distribution of components of the mixture, based on differences between spatial information in different ones of the plurality of images, wherein the differences are caused by the application of the image enhancement agent.

2. The method of claim 1 wherein the step of applying applies a stain as the image enhancement agent.

3. The method of claim 1 wherein the step of applying applies a fluorescent stain as the image enhancement agent.

4. The method of claim 1 wherein the step of applying applies radiation as the image enhancement agent.

5. The method of claim 1 wherein the step of applying applies a stain that is distinguishable in the visible light wavelength range as the image enhancement agent.

6. The method of claim 1 wherein the step of applying alters properties of a component in the mixture.

7. The method of claim 1 wherein the step of applying alters properties of an inactive component in the mixture.

8. The method of claim 1 wherein the step of applying alters properties of an active component in the mixture.

9. The method of claim 1 wherein the steps of applying, obtaining, and deriving are also applied to a reference sample.

10. The method of claim 9 wherein the step of obtaining images obtains images of the reference sample and the mixture at the same time.

11. The method of claim 1 wherein the steps of applying, obtaining, and deriving are applied to a pharmaceutical dosage unit including active and inactive ingredients.

12. The method of claim 11 wherein the step of applying applies a stain that has an affinity for one or more of the inactive ingredients.

13. The method of claim 11 wherein the step of applying applies a stain that has an affinity for one or more of the active ingredients.

14. The method of claim 11 further including the step of exposing at least one inner surface of the pharmaceutical dosage unit, and wherein the step of obtaining images obtains images of the exposed inner surface.

15. The method of claim 14 further including further steps of exposing inner surfaces of the pharmaceutical dosage unit and further including steps of obtaining images of the inner surfaces exposed in the further steps of exposing to develop a three-dimensional data set for the dosage unit.

16. The method of claim 15 wherein the step of exposing employs a cutting implement.

17. The method of claim 11 wherein the steps of applying, obtaining, and deriving are applied to a pharmaceutical tablet.

18. The method of claim 11 wherein the steps of applying, obtaining, and deriving are applied to a number of different pharmaceutical dosage units obtained from a process at different times.

19. The method of claim 18 wherein the step of obtaining images obtains images of a plurality of the different pharmaceutical dosage units obtained from the process in a same field of view.

20. The method of claim 11 wherein the step of deriving derives a visual presentation of the pharmaceutical dosage unit in which areas affected by the image enhancement agent are presented with a predetermined visual treatment.

21. The method of claim 1 wherein the steps of applying, obtaining, and deriving are applied to a number of different samples obtained from a process at different times.

22. The method of claim 21 wherein the step of obtaining images obtains images of a plurality of the different samples obtained from the process in a same field of view.

23. The method of claim 1 wherein the steps of applying, obtaining, and deriving are applied repeatedly to pharmaceutical samples from a commercial pharmaceutical process.

24. The method of claim 23 further including the step of adjusting the process based on information derived from one or more of the steps of deriving.

25. The method of claim 23 wherein the steps of applying, obtaining, and deriving are applied in a sampling regimen sufficient to ensure a predetermined quality objective for the pharmaceutical mixture.

26. The method of claim 23 wherein the steps of applying, obtaining, and deriving are performed without stopping the process.

27. The method of claim 23 wherein the steps of applying, obtaining, and deriving are performed during an interruption of the process.

28. The method of claim 1 wherein the steps of applying, obtaining, and deriving are applied to pharmaceutical samples from an experimental pharmaceutical process.

29. The method of claim 28 further including the step of adjusting a formulation for the pharmaceutical mixture.

30. The method of claim 1 wherein the step of deriving derives statistical information about the distribution of components of the mixture.

31. The method of claim 30 wherein the step of deriving derives statistical information about particle size for components of the mixture.

32. The method of claim 30 wherein the step of deriving derives statistical information about particle distribution for components of the mixture.

33. The method of claim 1 further including the step of comparing results from the steps of applying, obtaining, and deriving for a first sample of the pharmaceutical mixture with results from the steps of applying, obtaining, and deriving for at least a second sample of the pharmaceutical mixture.

34. The method of claim 33 wherein the step of comparing includes deriving statistical information about a number of samples of the pharmaceutical mixture.

35. The method of claim 1 further including the step of comparing results from the steps of applying, obtaining, and deriving with a predetermined standard.

36. The method of claim 1 further including the step of providing an indication of origin of the mixture based on the information derived in the step of deriving.

37. The method of claim 36 wherein the step of providing an indication of origin is operative to provide a genuine/counterfeit indication.

38. The method of claim 1 further including the step of providing a cleaning validation indication based on the information derived in the step of deriving.

39. The method of claim 1 further including the step of determining a root cause of a manufacturing process defect for the mixture based on the information derived in the step of deriving.

40. The method of claim 1 wherein the step of applying applies the agent using vapor deposition.

41. The method of claim 1 wherein the step of deriving includes a step of measuring a rate of change of information, caused by the application of the image enhancement agent, in different ones of the plurality of images.

42. The method of claim 1 wherein the step of applying applies heat as the image enhancement agent.

43. The method of claim 42 wherein the step of deriving derives spatial information from relative melting points of components of the pharmaceutical mixture.

44. The method of claim 1 wherein the step of applying preferentially etches part of the mixture.

45. The method of claim 1 wherein the step of applying preferentially dissolves part of the mixture.

46. An apparatus for obtaining information about a heterogeneous pharmaceutical mixture, comprising:

an image acquisition system having a field of view operative to acquire images of samples of the pharmaceutical mixture,

an image enhancement detection module optimized to detect portions of the mixture having been exposed to a predetermined image enhancement agent, and

an information derivation module operative to derive information from the image enhancement detection module about a distribution of components of the mixture in the image, based on differences between the portions of the mixture that are caused by the application of the image enhancement agent.

47. The apparatus of claim 46 wherein the information derivation module is operative to measure rates of change caused by the image enhancement agent.

48. An apparatus for obtaining information about a heterogeneous pharmaceutical mixture, comprising:

means for applying an image enhancement agent to the mixture,

means for obtaining a plurality of images of the mixture over time, and

means for deriving information about a distribution of components of the mixture in the images, based on differences between spatial information in different ones of the plurality of images, wherein the differences are caused by the application of the image enhancement agent.

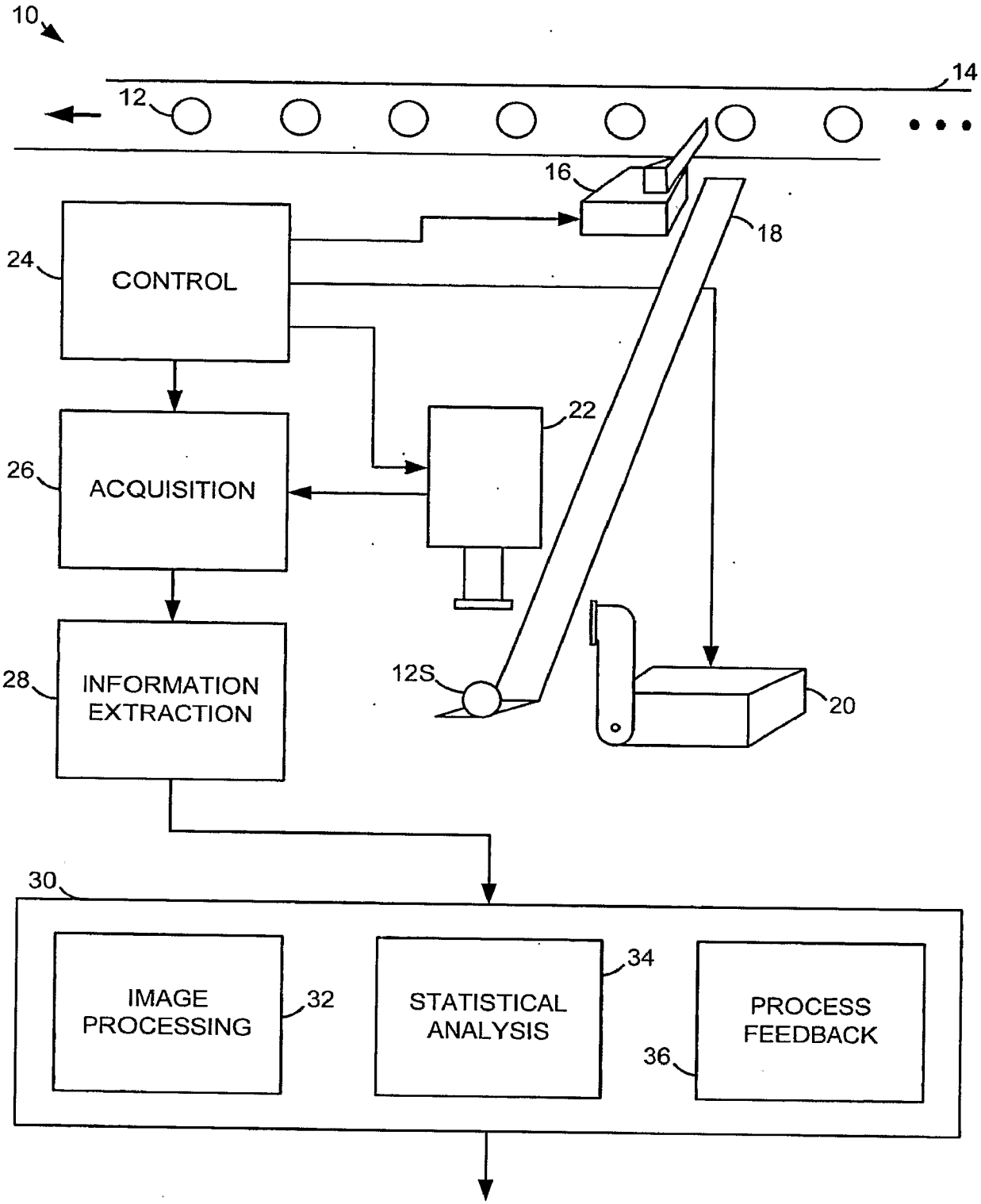
10
14
12
16
18
24
CONTROL
22
26
ACQUISITION
28
INFORMATION EXTRACTION
12S
20
30
IMAGE PROCESSING
32
STATISTICAL ANALYSIS
34
PROCESS FEEDBACK
36

FIG. 1

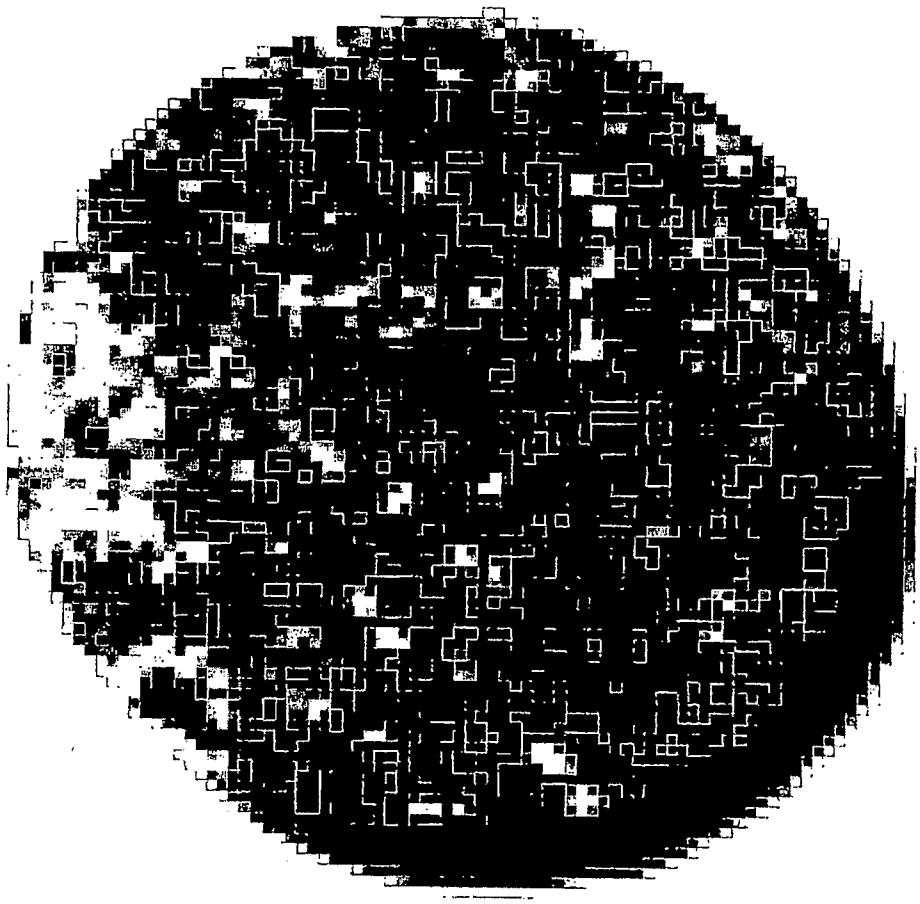

FIG. 2

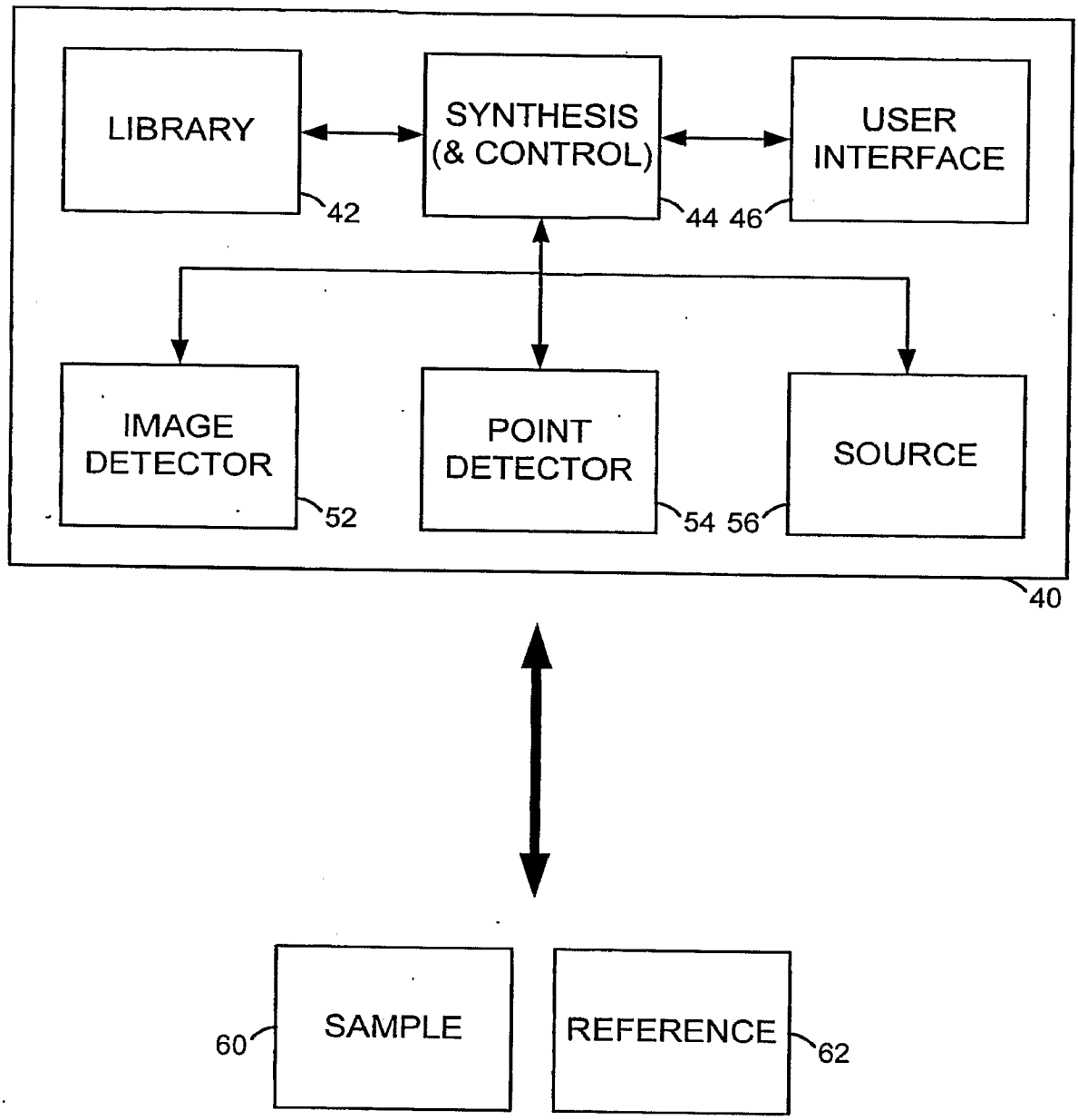
LIBRARY
42
SYNTHESIS
(& CONTROL)
44
USER
INTERFACE
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IMAGE
DETECTOR
52
POINT
DETECTOR
54
SOURCE
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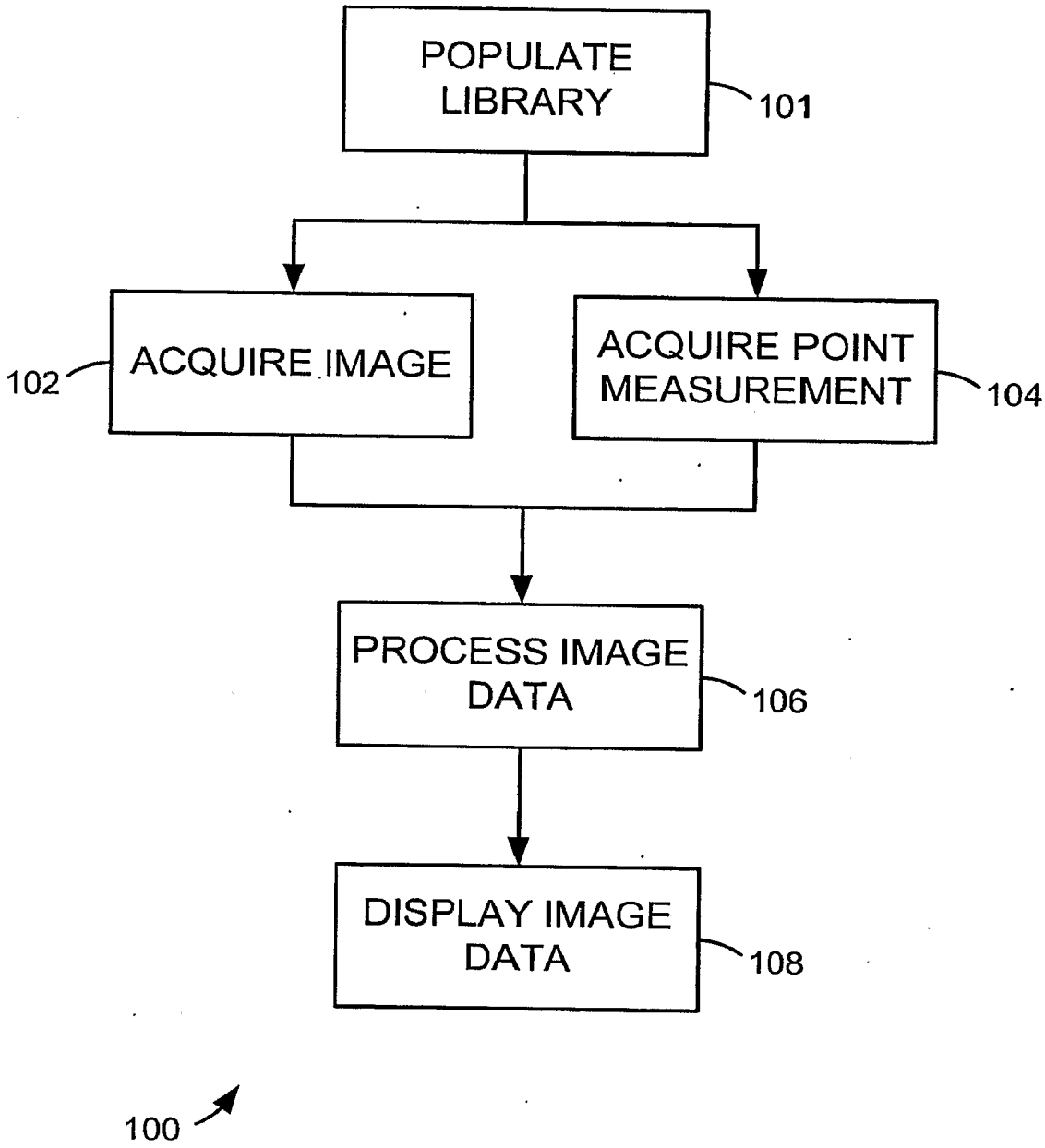
SAMPLE
REFERENCE
62

FIG. 3


POPULATE LIBRARY
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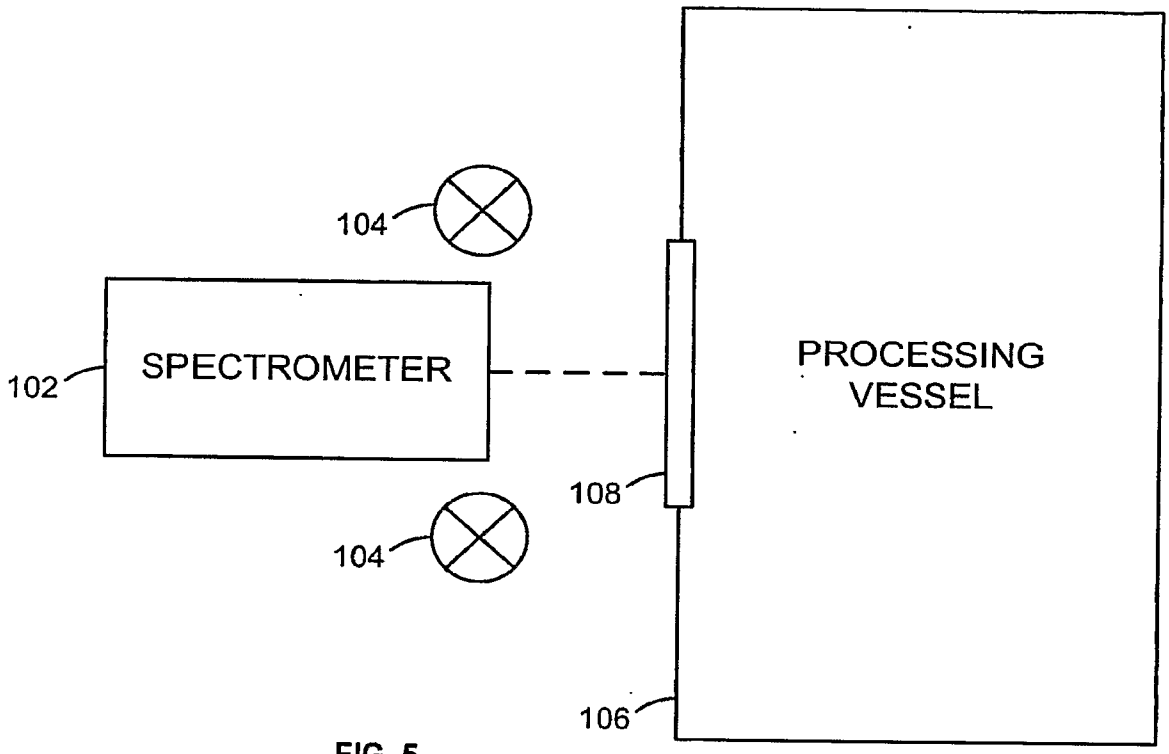
ACQUIRE IMAGE
102
ACQUIRE POINT MEASUREMENT
104
PROCESS IMAGE DATA
106
DISPLAY IMAGE DATA
108
100

FIG. 4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SPECTROMETER
102
PROCESSING VESSEL
108
104
106

FIG. 5

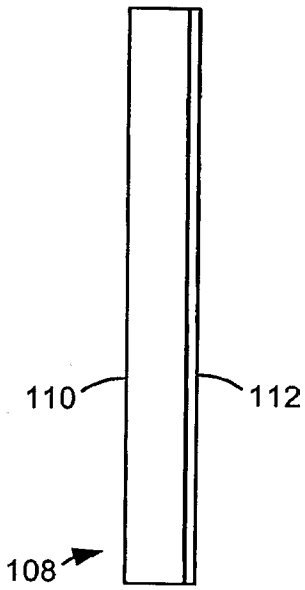
110
112
108

FIG. 6

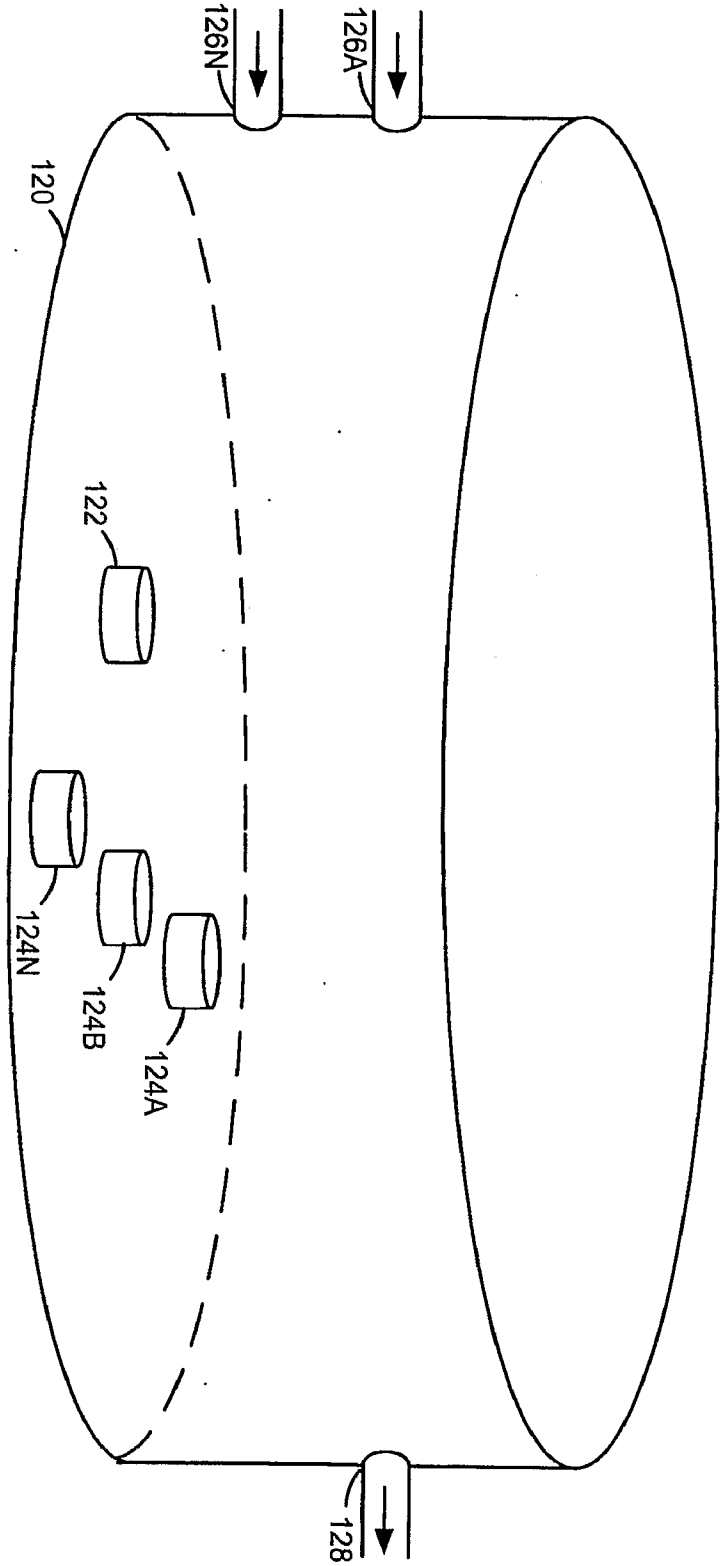

FIG. 7

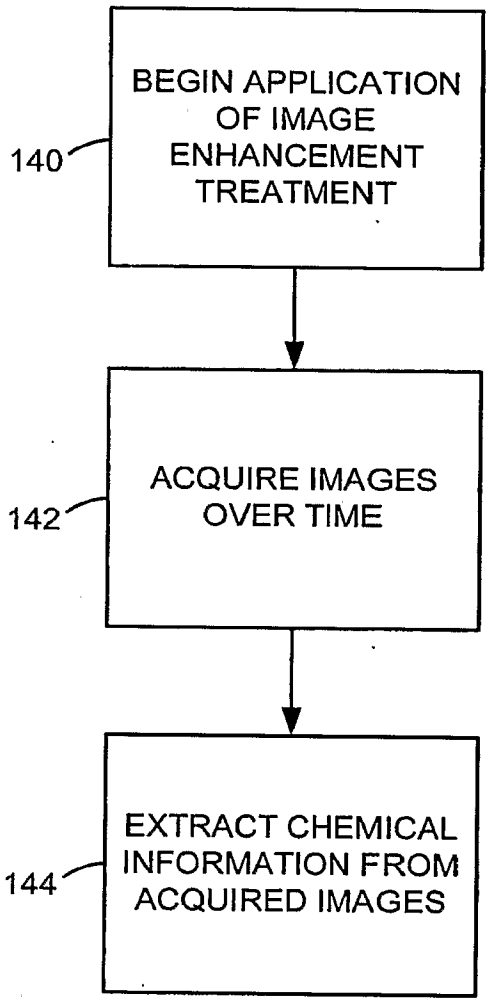
BEGIN APPLICATION OF IMAGE ENHANCEMENT TREATMENT
140
ACQUIRE IMAGES OVER TIME
142
EXTRACT CHEMICAL INFORMATION FROM ACQUIRED IMAGES
144

FIG. 8