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(54) **FLUID-JET MEDICAMENT DELIVERY**

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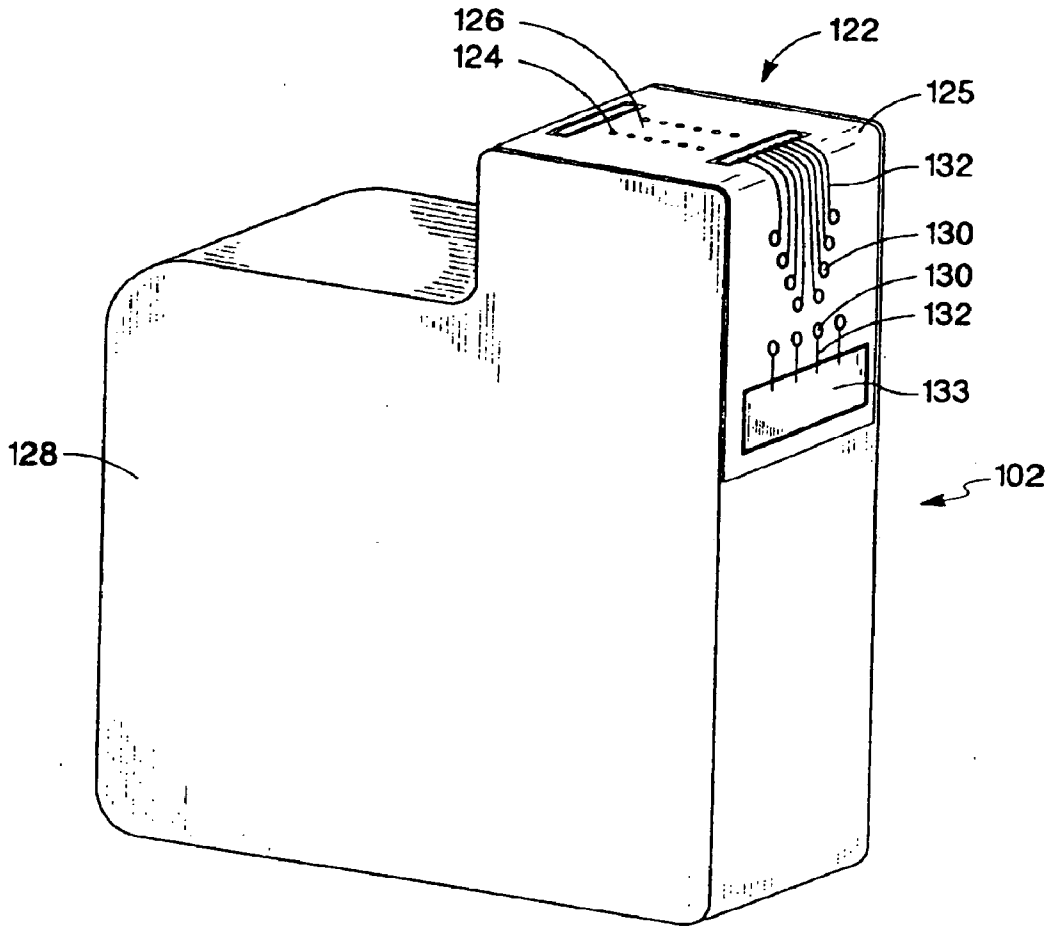
B67D 7/06 (2010.01)

(52) **U.S. Cl.** **222/1**; 222/23

(57) **ABSTRACT**

A method of applying an orally-ingestible medicament to an orally-ingestible carrier comprising the steps of controlling a relative position between a fluid ejector and the carrier, and ejecting a plurality of drops of solution onto the carrier, wherein the plurality of drops includes a desired therapeutic quantity of the orally-ingestible medicament.



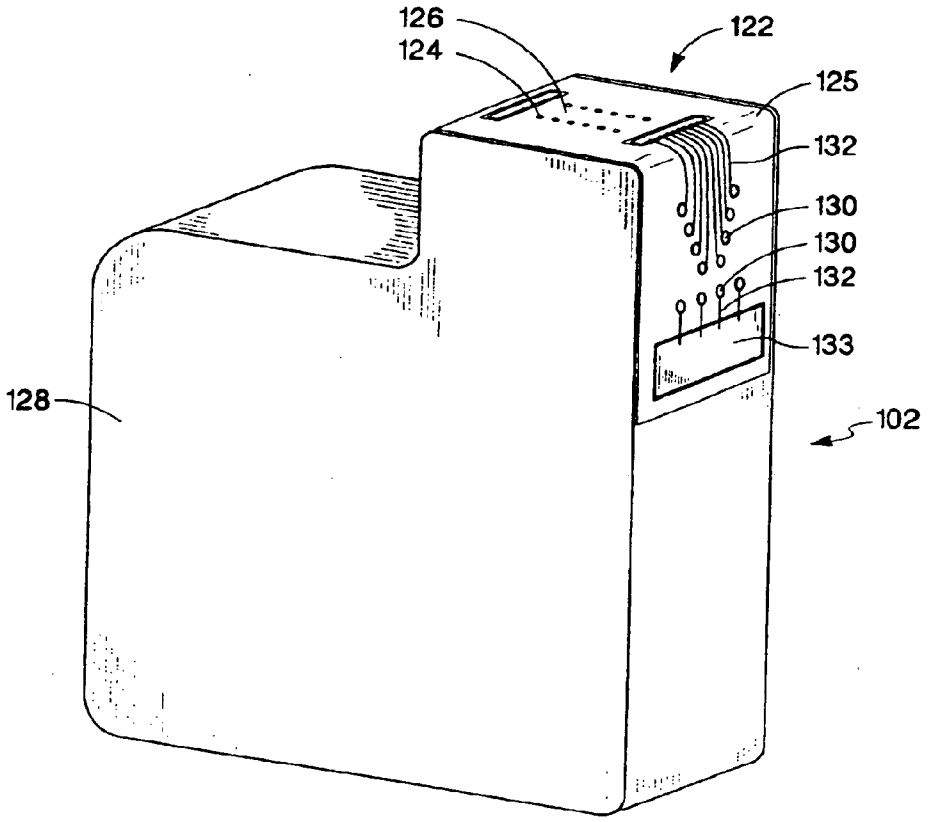


Fig. 1a

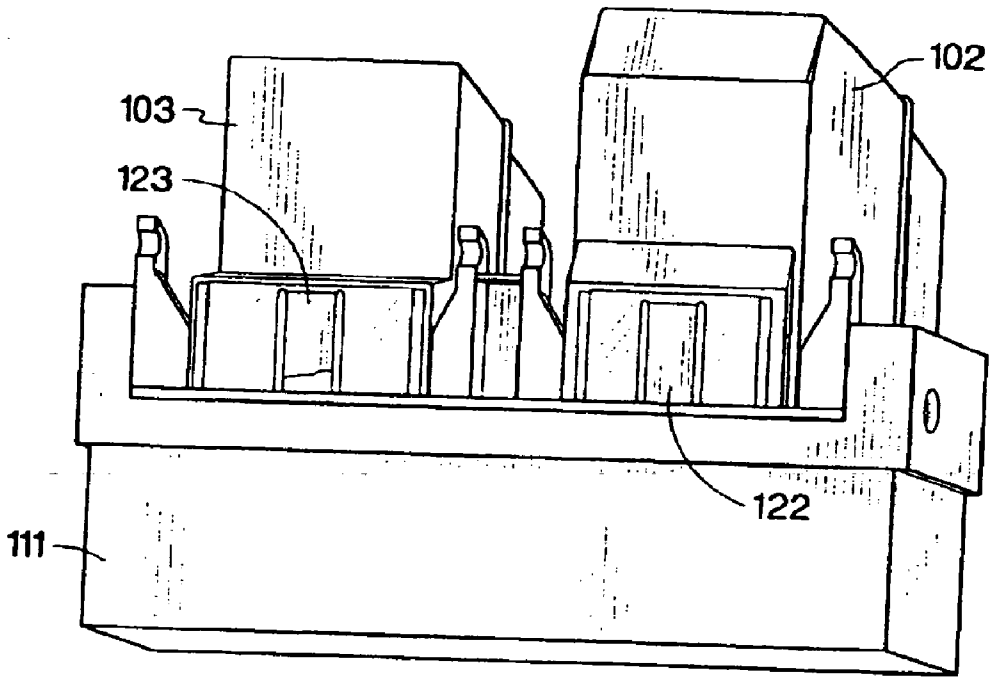


Fig. 1b

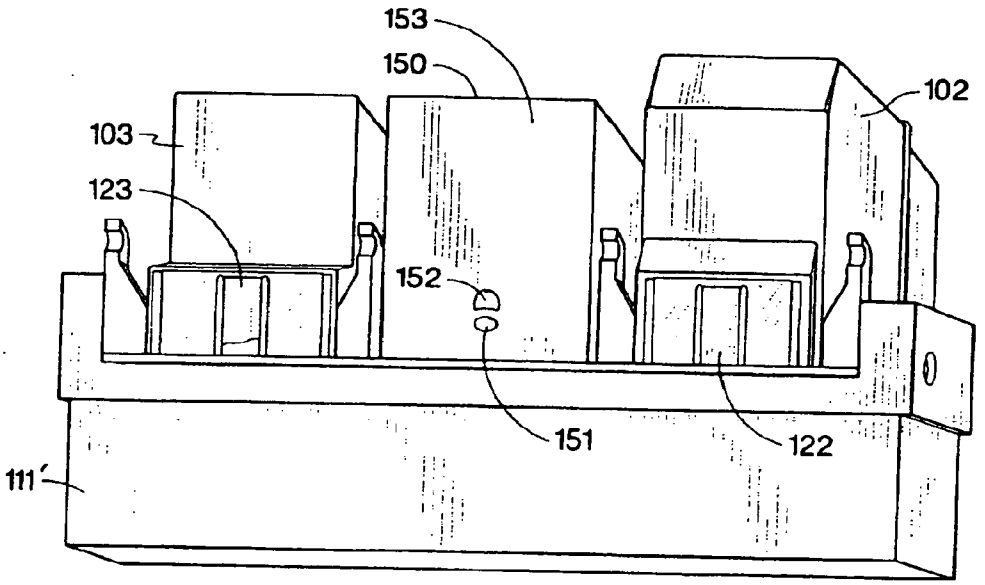
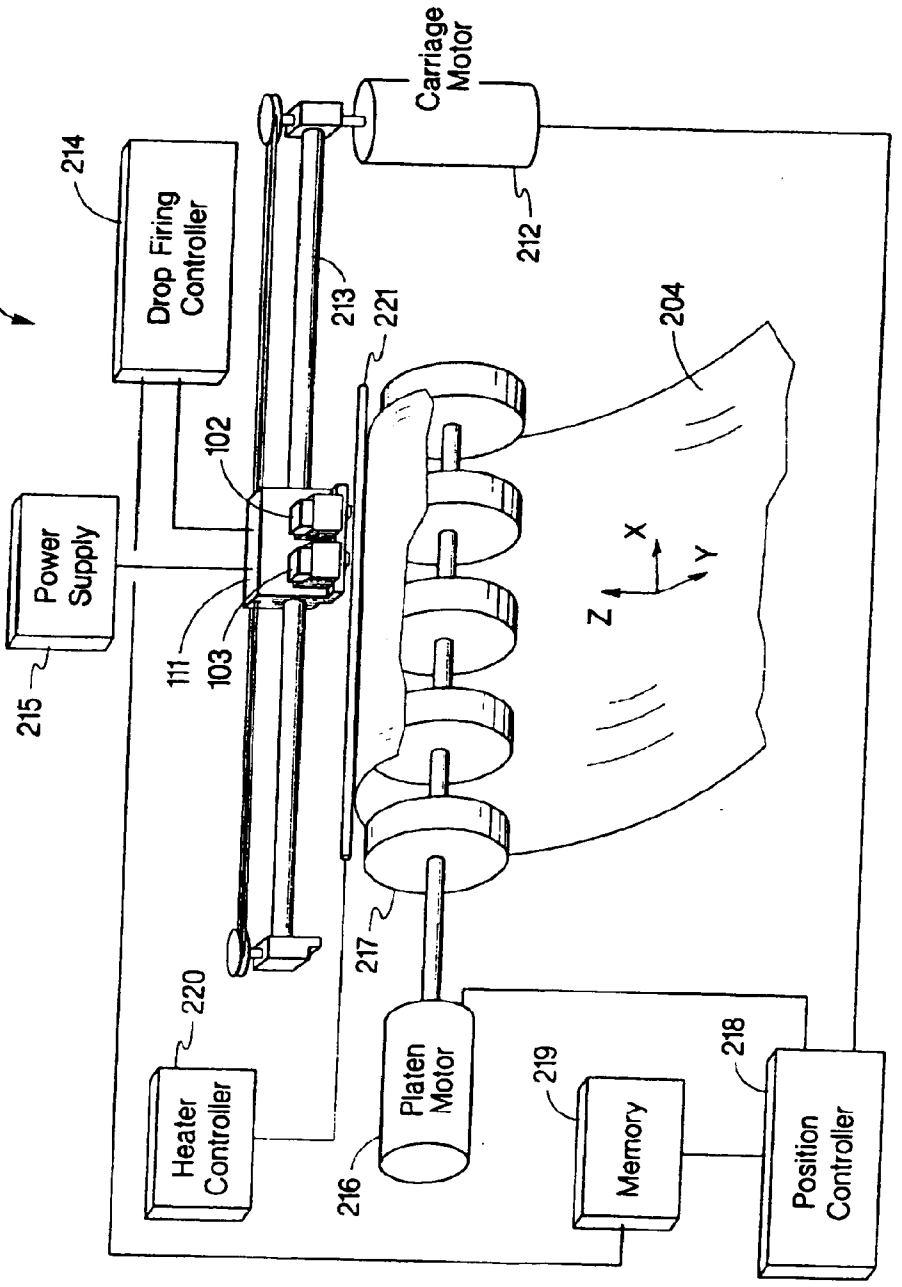


Fig. 1c


200
214
Drop Firing Controller
Carriage Motor
212
213
221
204
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Power Supply
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111
103
X
Y
Z
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Heater Controller
Platen Motor
216
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Memory
218
Position Controller

Fig. 2a

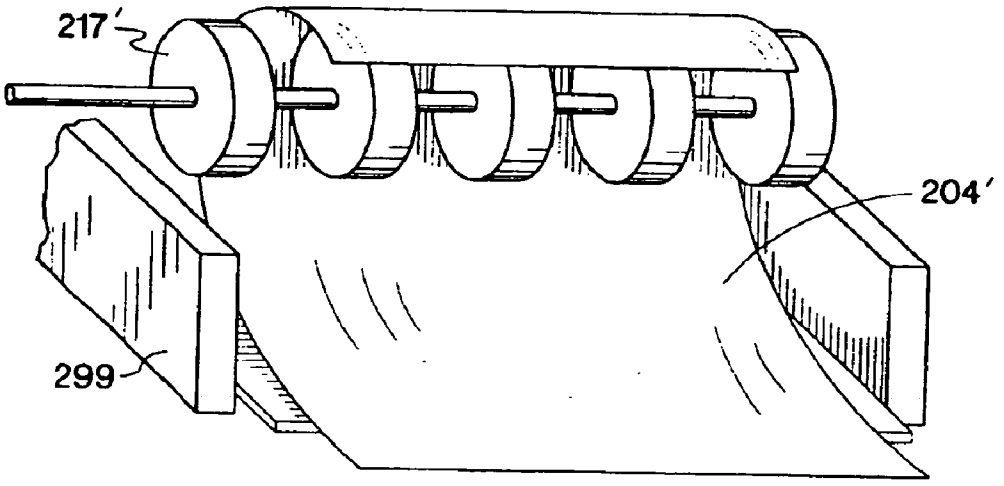

Fig. 2b

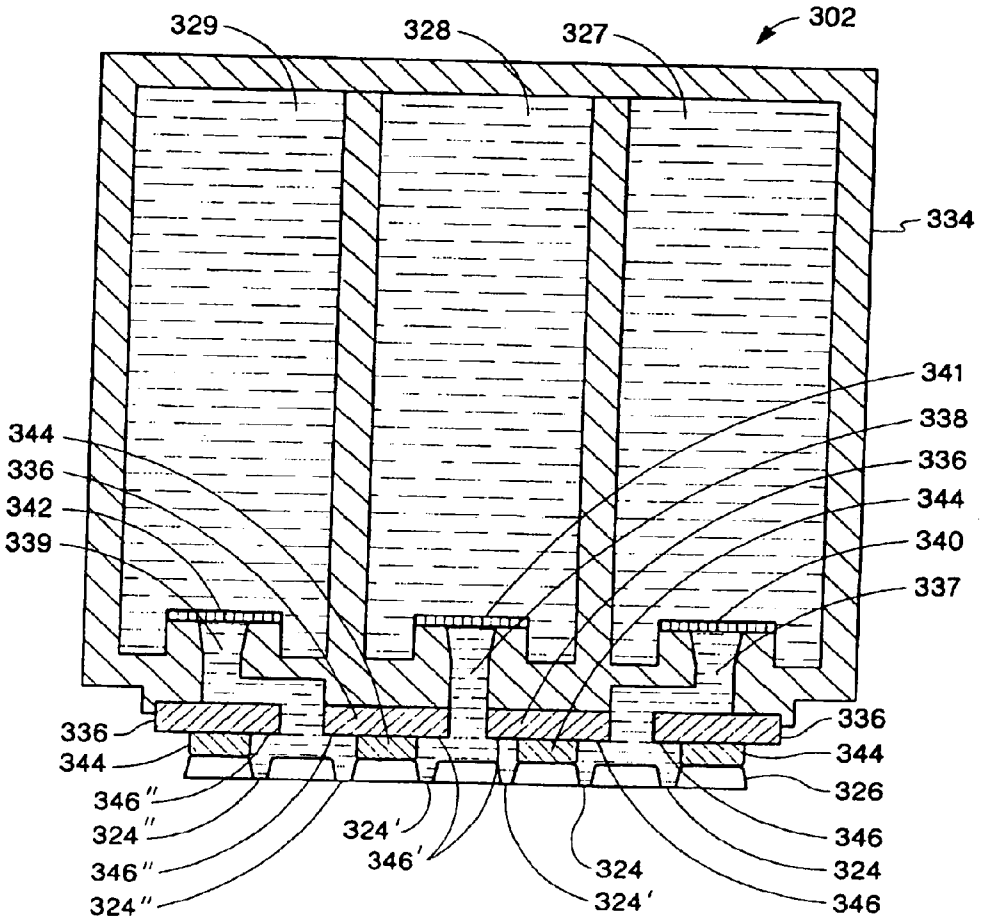
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Fig. 3

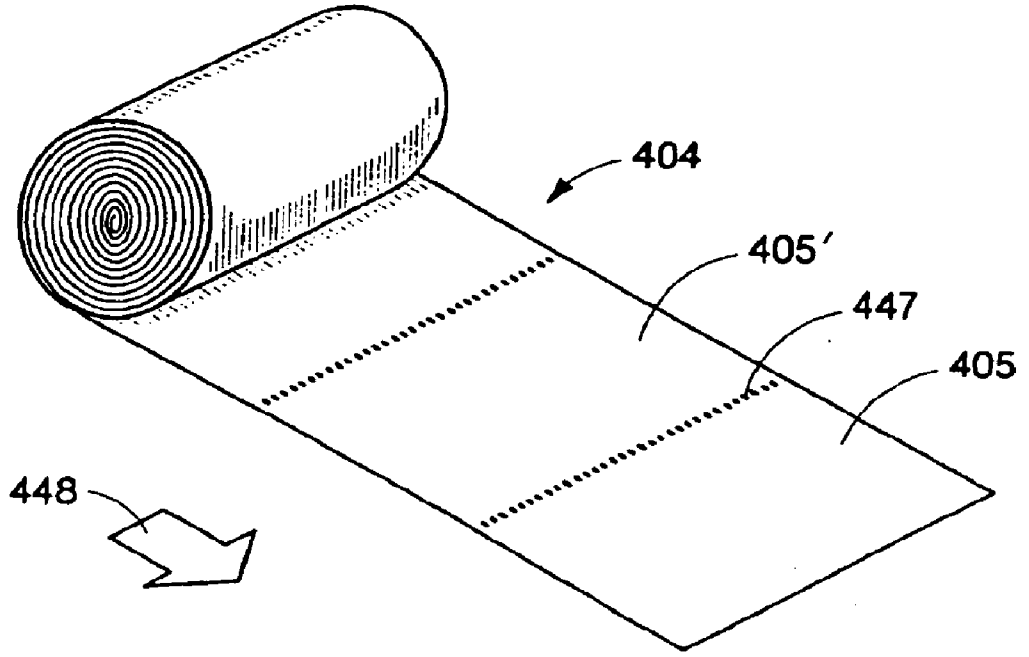

Fig. 4

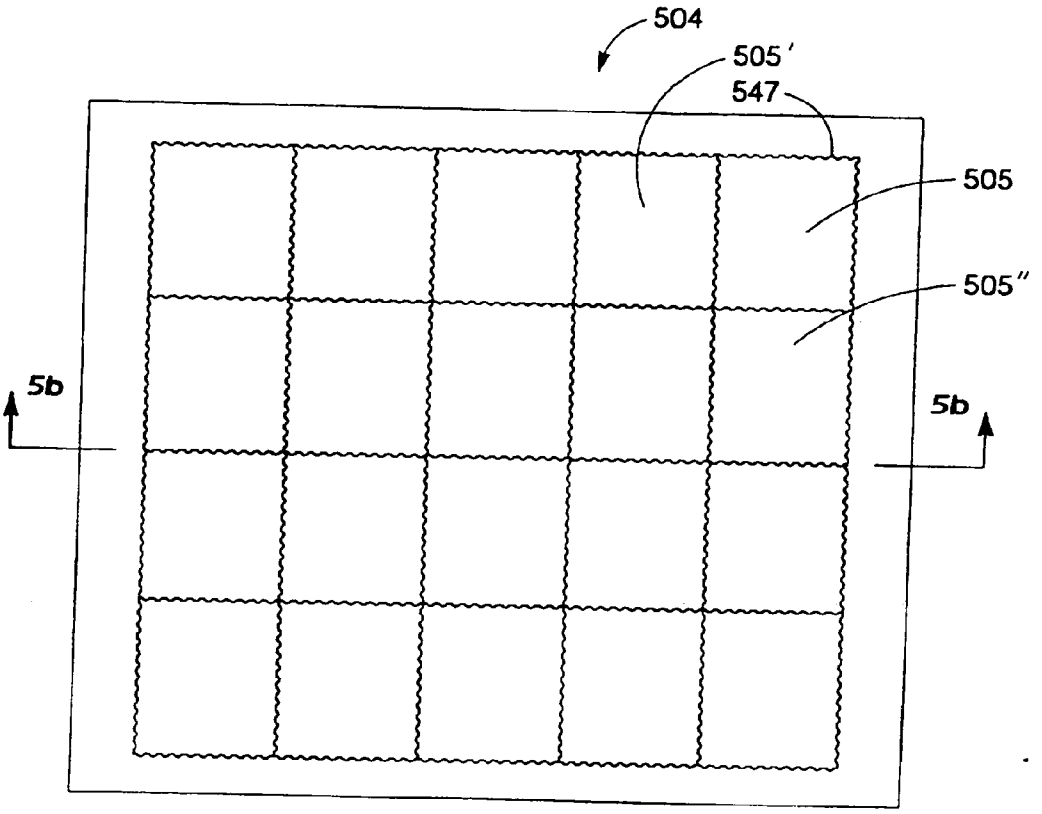

Fig. 5a

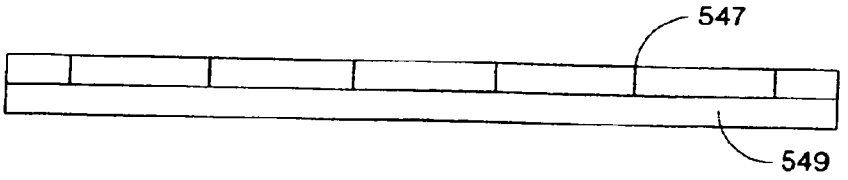

Fig. 5b

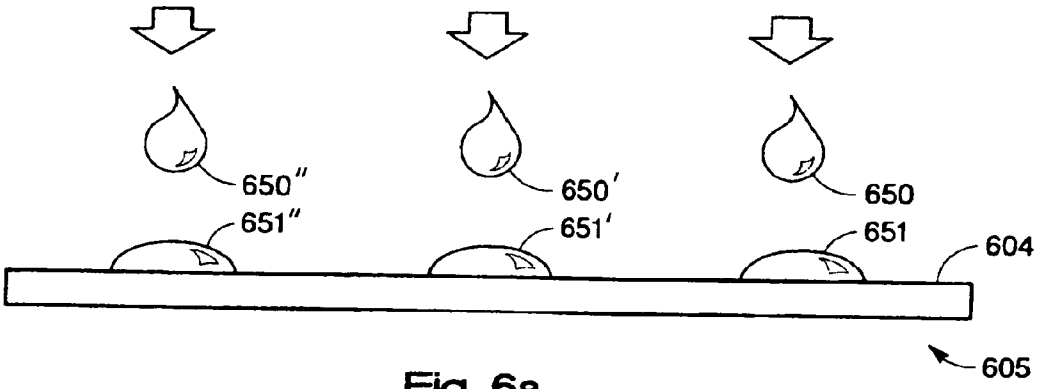

Fig. 6a

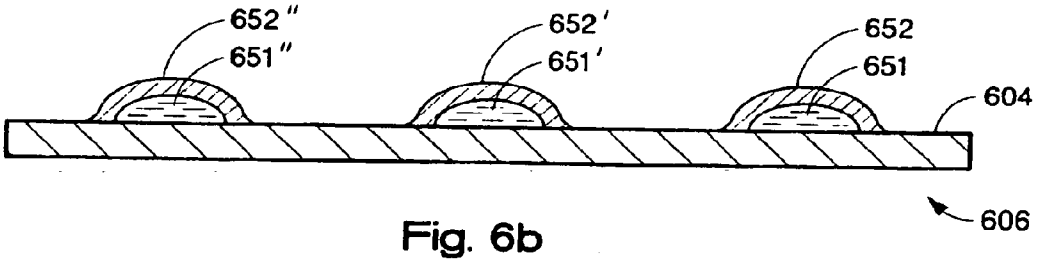

Fig. 6b

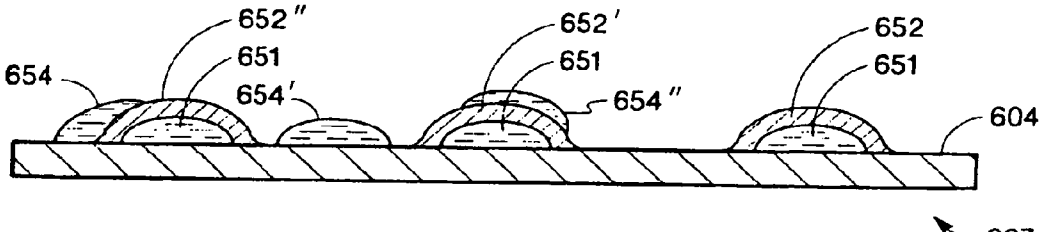

Fig. 6c

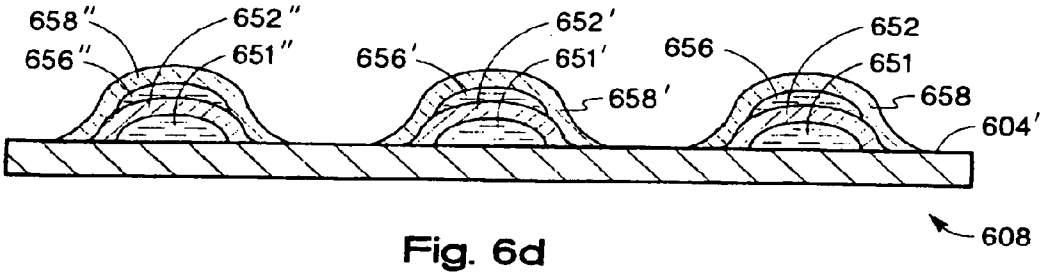

Fig. 6d

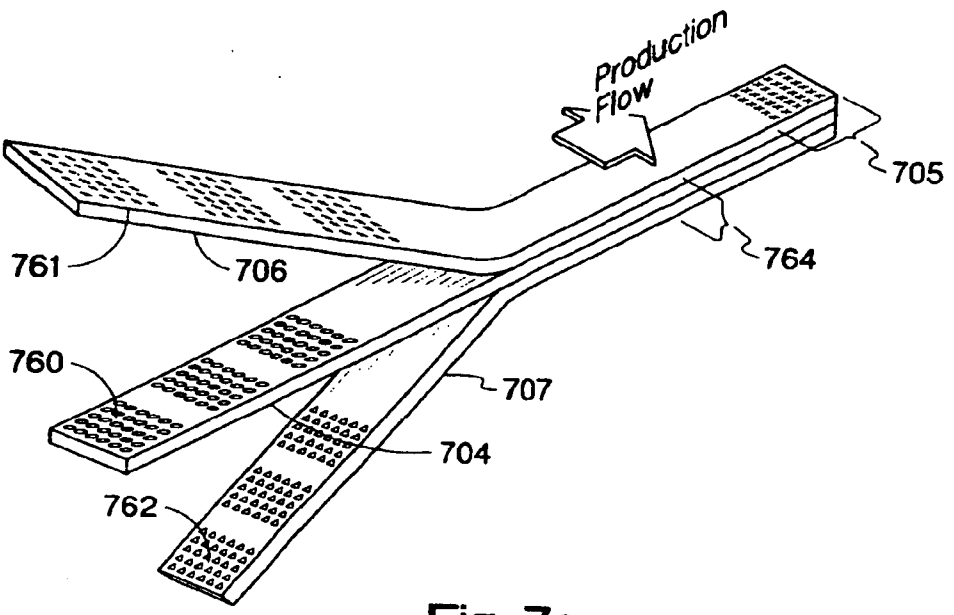

Fig. 7a

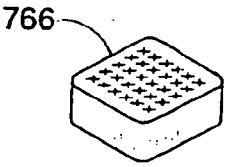

Fig. 7b

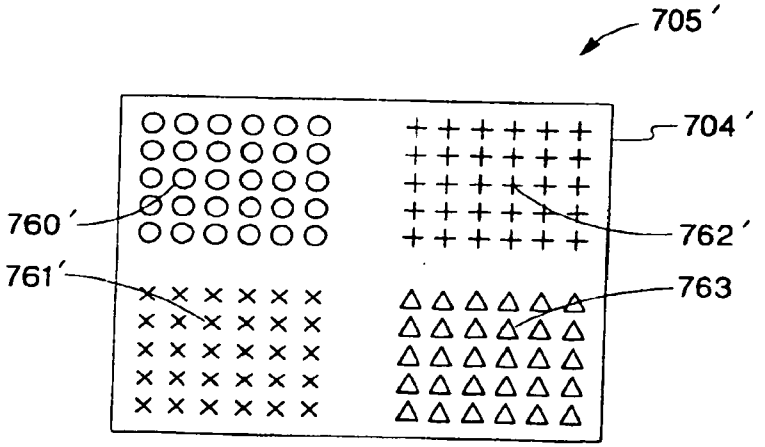

Fig. 7c

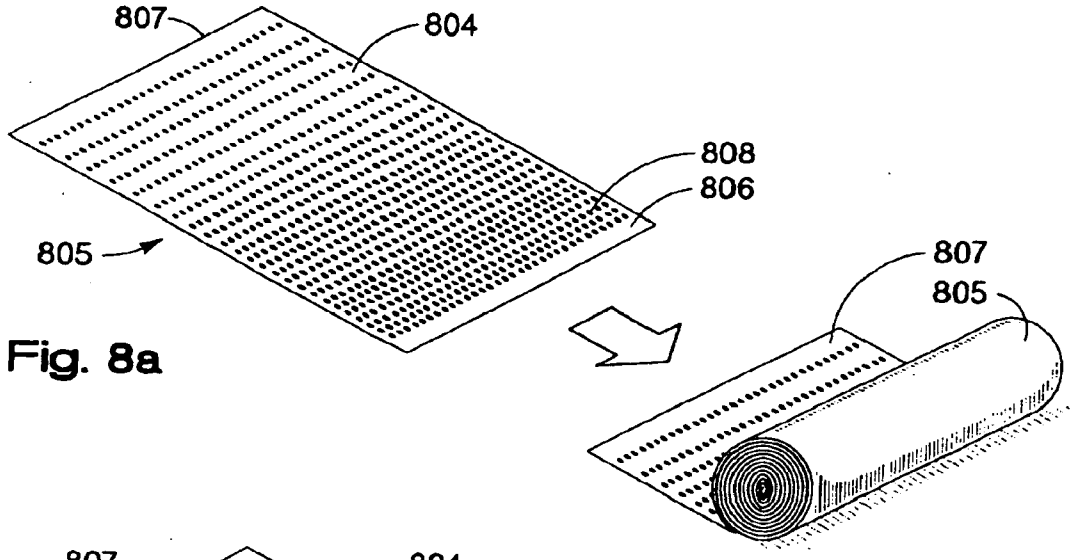

Fig. 8a

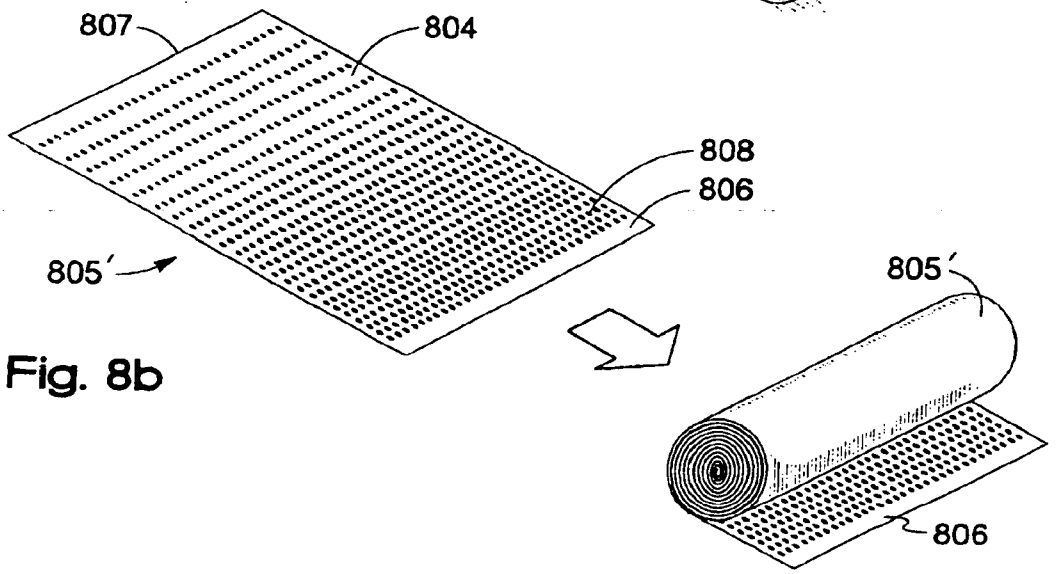

Fig. 8b

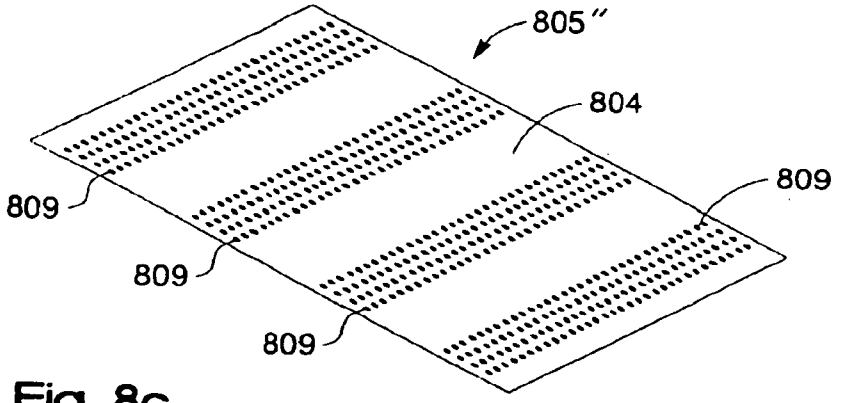

Fig. 8c

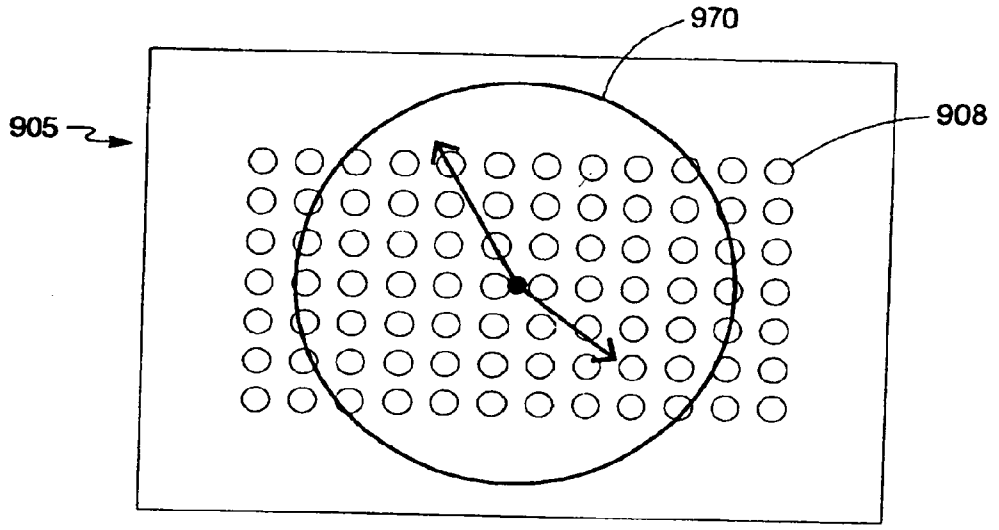

Fig. 9a

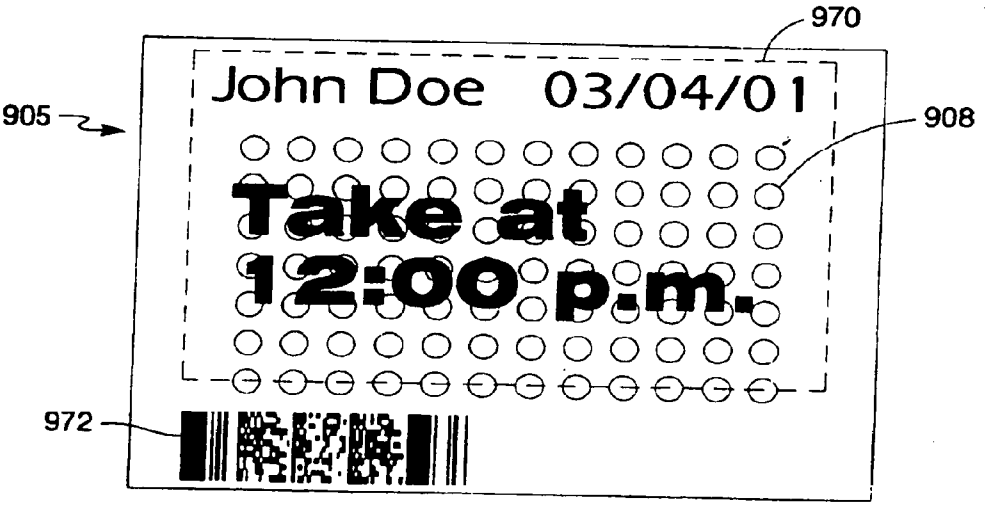

Fig. 9b

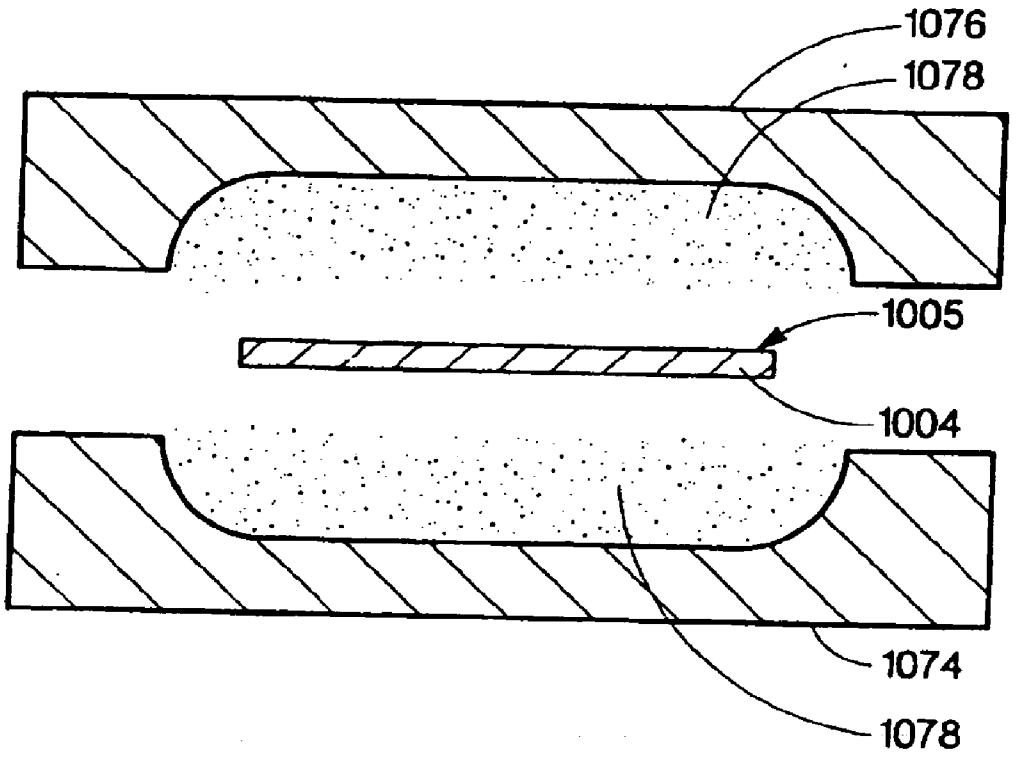

Fig. 10a

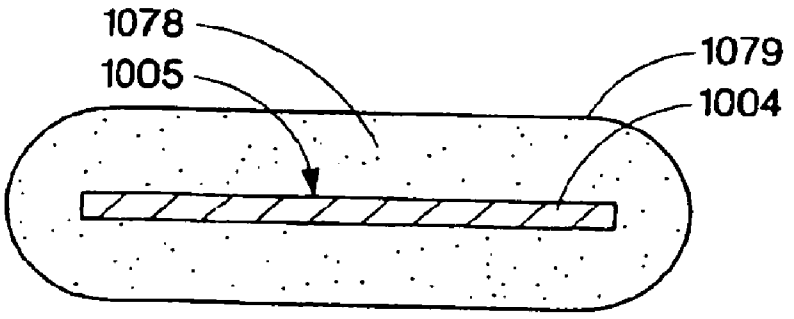

Fig. 10b

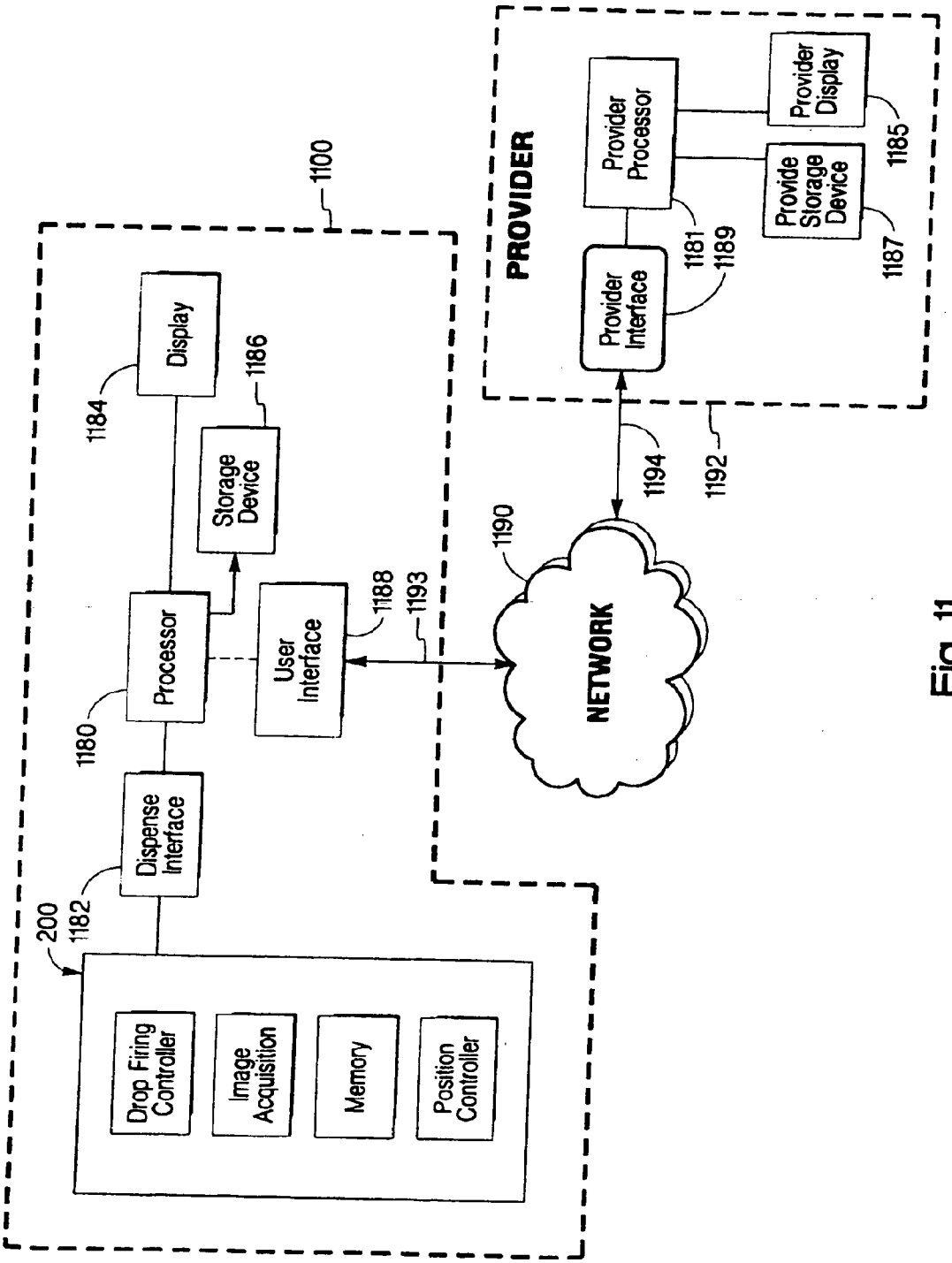
1100
Display
1184
1186
Storage Device
Processor
1180
User Interface
1188
1193
Dispense Interface
1182
200
Drop Firing Controller
Image Acquisition
Memory
Position Controller
NETWORK
1190
PROVIDER
Provider Processor
Provider Display
1185
Provide Storage Device
1187
Provider Interface
1181
1189
1194
1192

Fig. 11

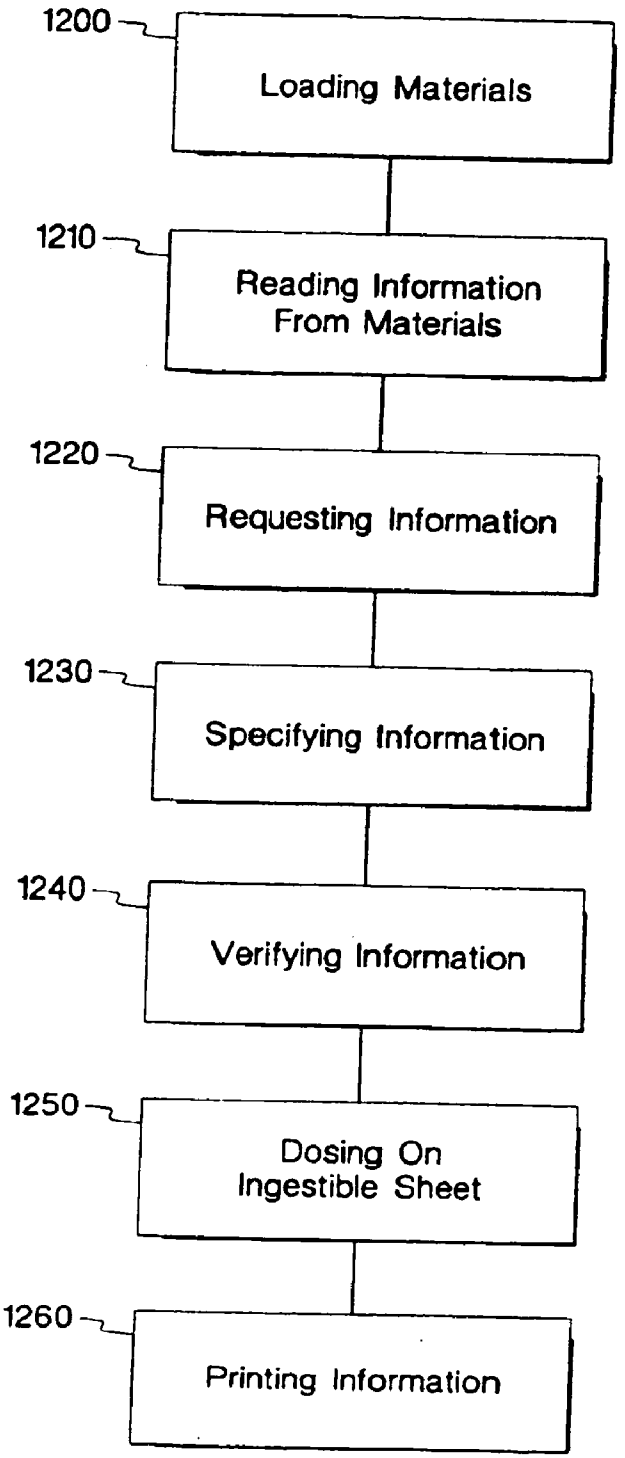
1200
Loading Materials
1210
Reading Information From Materials
1220
Requesting Information
1230
Specifying Information
1240
Verifying Information
1250
Dosing On Ingestible Sheet
1260
Printing Information

Fig. 12

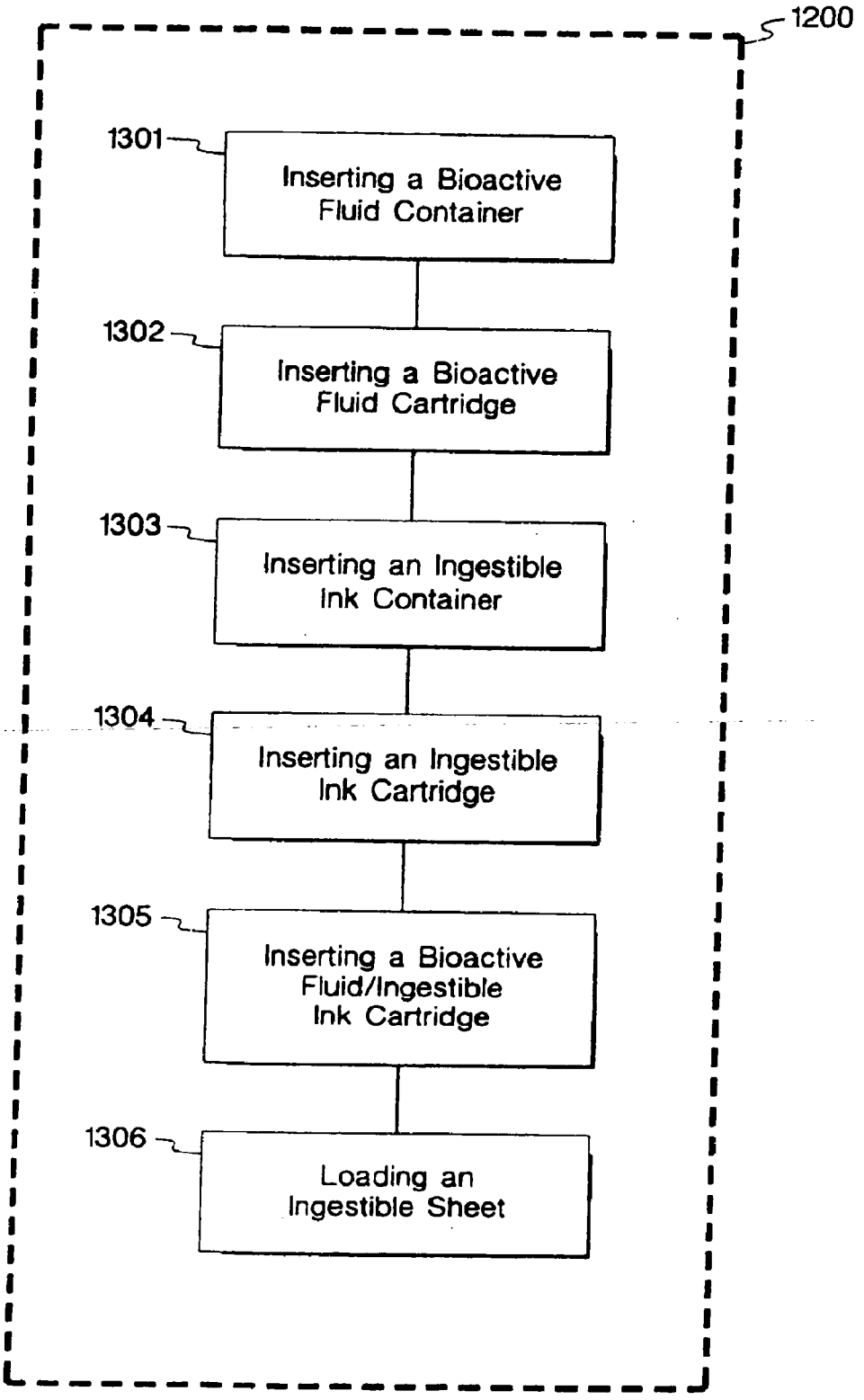
1200
1301
Inserting a Bioactive Fluid Container
1302
Inserting a Bioactive Fluid Cartridge
1303
Inserting an Ingestible Ink Container
1304
Inserting an Ingestible Ink Cartridge
1305
Inserting a Bioactive Fluid/Ingestible Ink Cartridge
1306
Loading an Ingestible Sheet

Fig. 13a

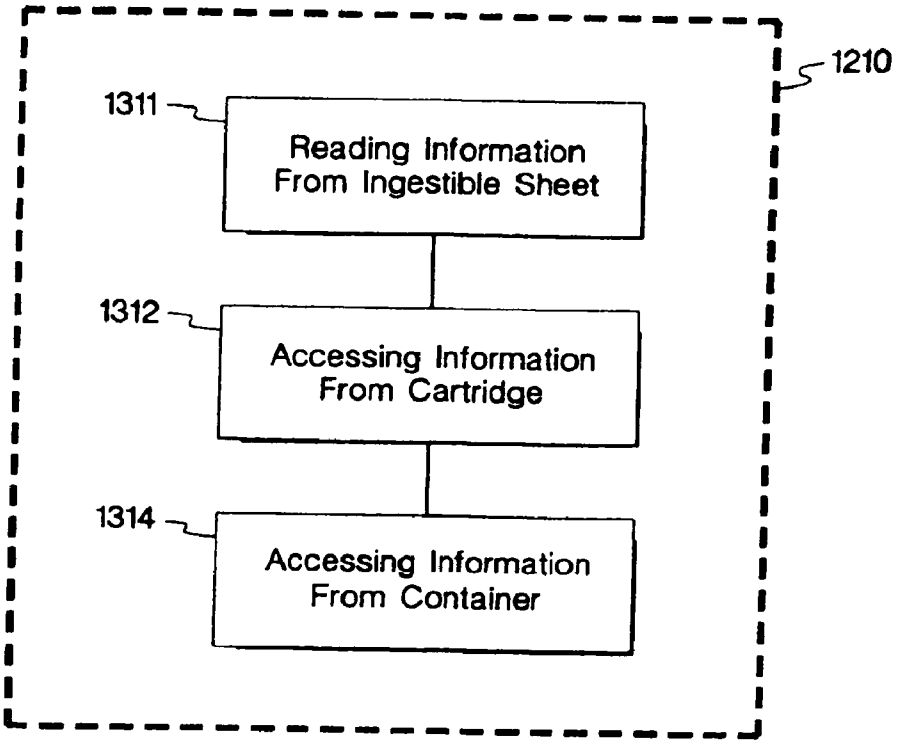

Fig. 13b

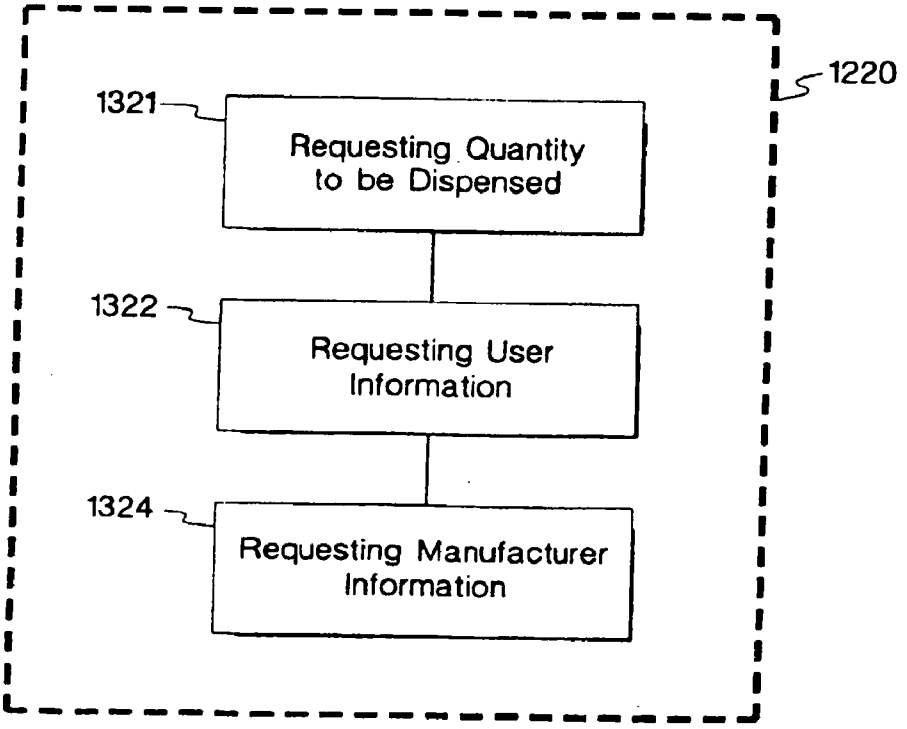

Fig. 13c

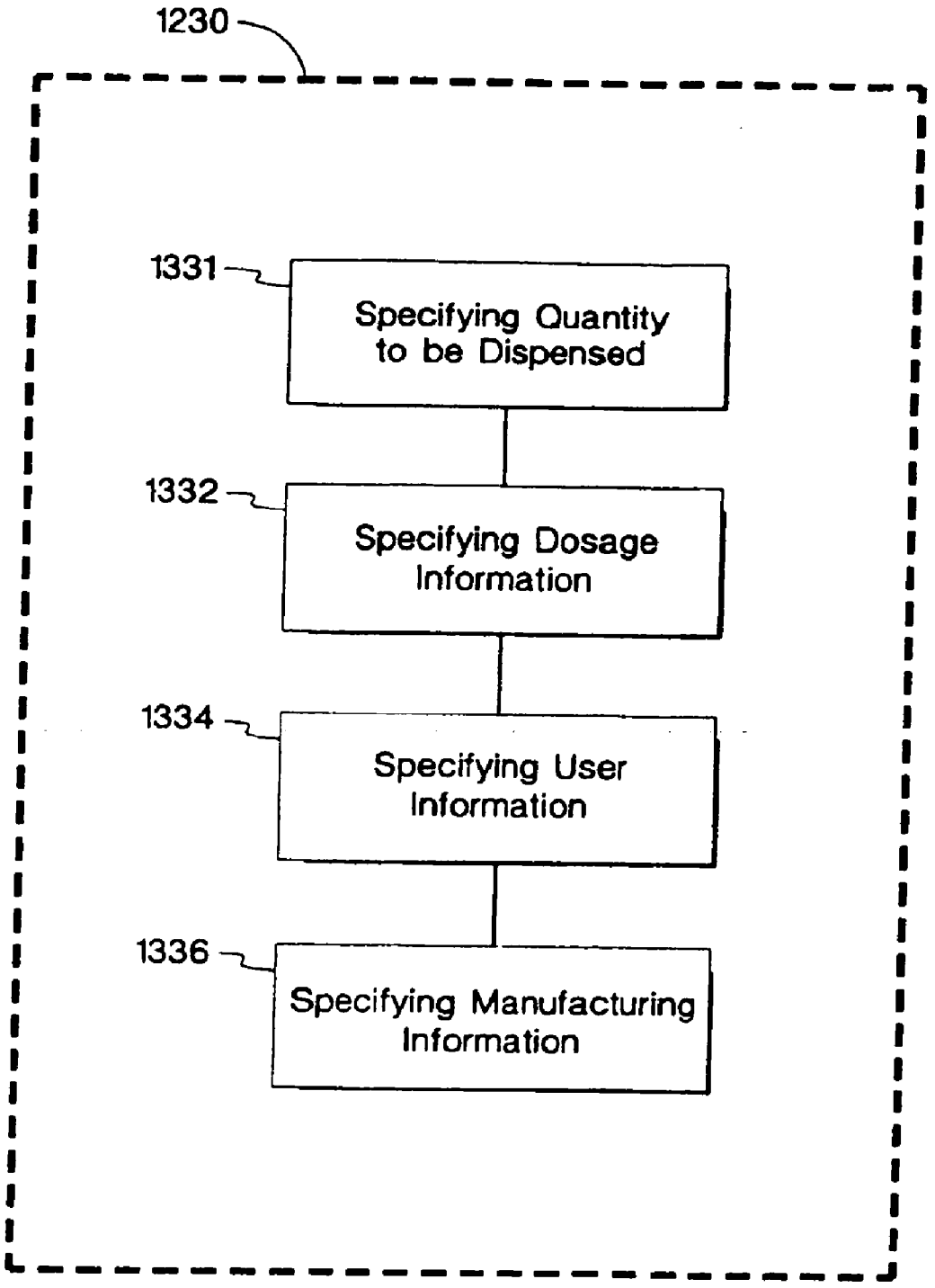
1230
1331
Specifying Quantity to be Dispensed
1332
Specifying Dosage Information
1334
Specifying User Information
1336
Specifying Manufacturing Information

Fig. 13d

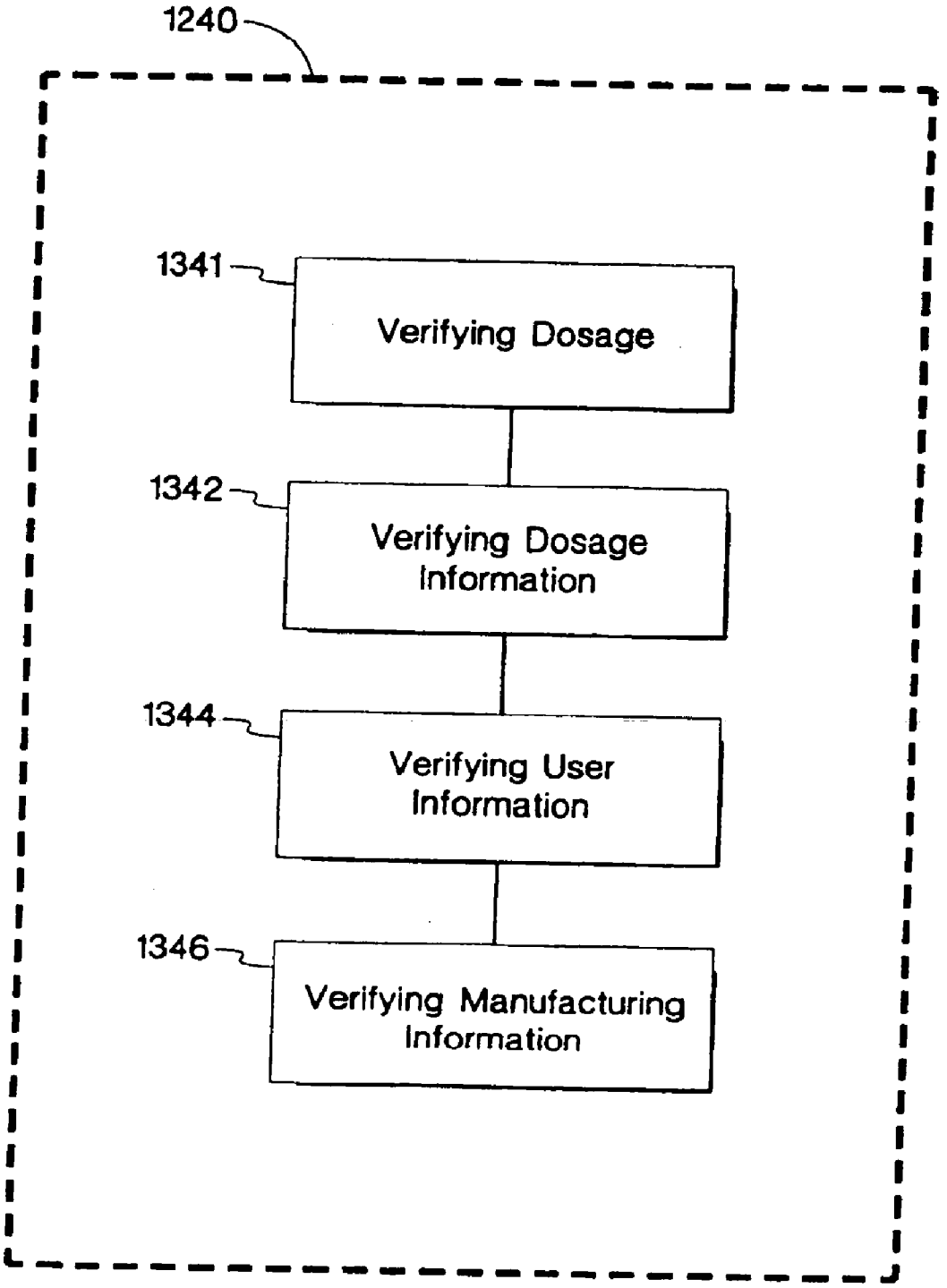
1240
1341
Verifying Dosage
1342
Verifying Dosage Information
1344
Verifying User Information
1346
Verifying Manufacturing Information

Fig. 13e

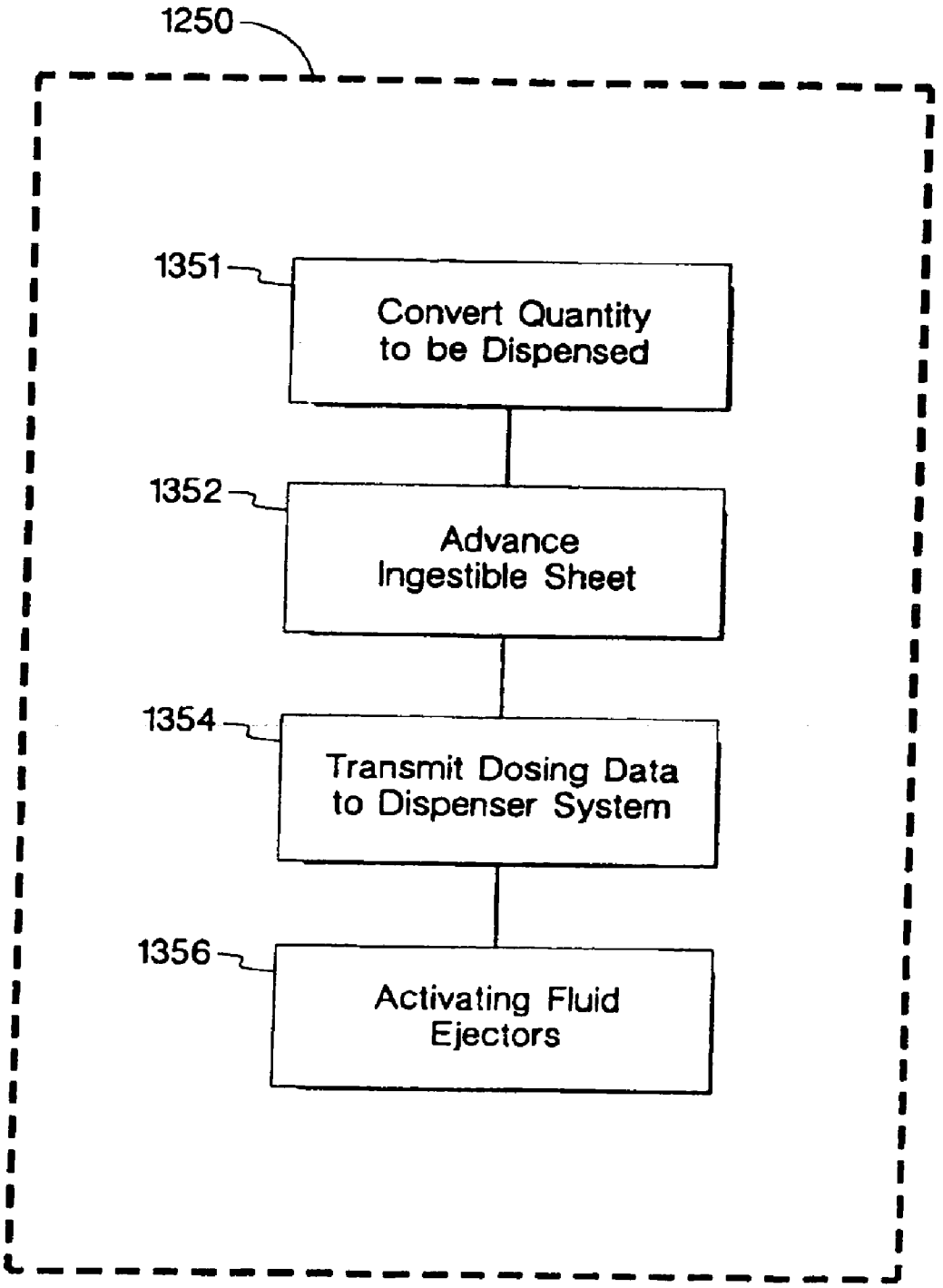
1250
1351
Convert Quantity to be Dispensed
1352
Advance Ingestible Sheet
1354
Transmit Dosing Data to Dispenser System
1356
Activating Fluid Ejectors

Fig. 13f

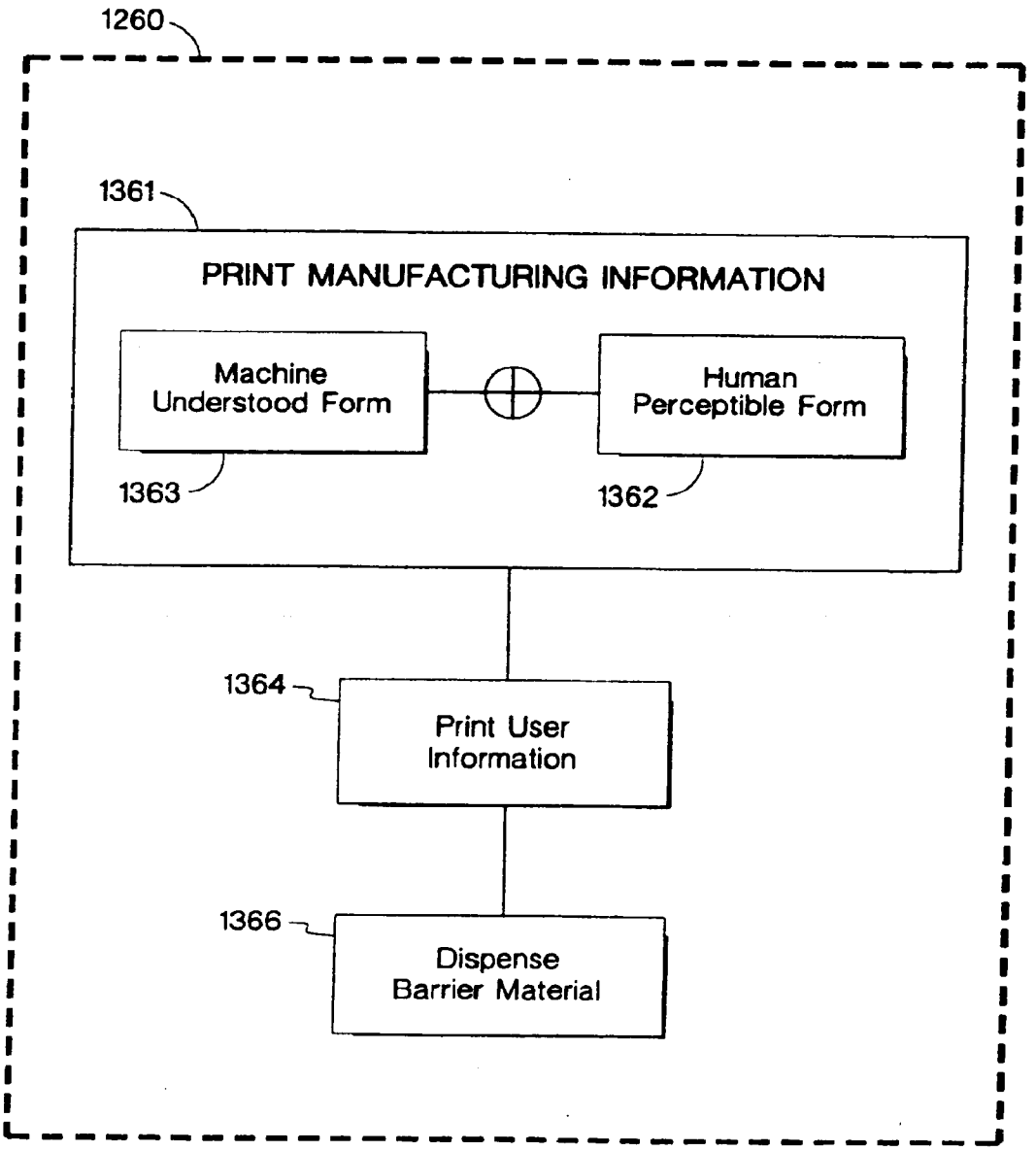
1260
1361
PRINT MANUFACTURING INFORMATION
Machine Understood Form
Human Perceptible Form
1363
1362
1364
Print User Information
1366
Dispense Barrier Material

Fig. 13g

FLUID-JET MEDICAMENT DELIVERY

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation under 35 U.S.C. §120 of U.S. patent application Ser. No. 11/048,368, filed Jan. 31, 2005, titled "Fluid-Jet Medicament Delivery," which is a continuation-in-part of U.S. patent application Ser. No. 10/028,450, filed Oct. 24, 2001, now U.S. Pat. No. 6,962,715. The disclosures of said applications are hereby incorporated herein by reference as if reproduced in full below.

BACKGROUND

[0002] 1. Field of the Invention

[0003] The present disclosure relates to fluid-jet medicament delivery. More particularly, the present disclosure relates to applying precise doses of medicament onto an edible sheet using fluid-jet technology.

[0004] 2. Description of the Art

[0005] Oral administration of pharmaceuticals is one of the most widely used methods to provide effective therapy for a variety of illnesses. Many powdered medications are typically administered orally to a person in a dosage form such as tablets or capsules, while still others are in liquid form. The release of orally administered medications falls into two broad categories, buccal or sublingual administration, and oral dissolution. For example, enteric coated tablets that release the medication in the intestinal tract of the patient. Further, many individuals suffer from chronic health problems that require the regular administration of medicaments. Diseases such as diabetes, allergies, epilepsy, heart problems, AIDS, and even cancer requires the regular delivery of precise doses of medicaments if patients are to survive over long periods of time. Such chronic treatment creates the need to regularly obtain additional medication. This can be extremely troublesome for those patients that lack the mobility to easily travel to a pharmacist to refill medications, such as the elderly and infirm. Thus, a method and a dosage form that provides the ability to make custom doses, outside of the large pharmaceutical manufacturing plants, is desirable.

[0006] Most pharmaceuticals involve dosage units in the microgram to milligram range of the purified active ingredient or ingredients. Thus, many pharmaceutical doses in tablet or liquid form are made in formulations of a predetermined quantity of pharmaceutical units in each dose. Such pharmaceutical doses are frequently available in fixed different strengths, such as 50 mg, 100 mg, etc.

[0007] Unfortunately, such conventional oral dosage forms suffer from a number of disadvantages. Typically, to effectively handle and dispense small doses a considerable amount of adjuvant material must be added in order that the final dosage form is of a manageable size. Thus, typical methods for manufacturing include the mixing of the pure drug with various other substances commonly referred to as excipients or diluents that are therapeutically inert and acceptable by regulatory bodies, such as the FDA. Excipients may also protect the drug from deterioration by oxidation, humidity, and light. Palatability can be improved through the addition of flavorants and identification by use of colorants. This mixing process often requires the use of sophisticated, complex expensive machinery. Certain excipients may be needed to improve the flowability of the drug and diluents through the mixing machinery. Therefore, a method and dosage form that reduces the mixing of the active drug with other substances, and utilizes less complex and expensive machinery would also be desirable.

[0008] These therapeutically inactive or inert materials also have the disadvantage that each such material must be evaluated before use in terms of potential incompatibilities with the medicaments present. For example, some of these materials, such as lubricants or disintegrants, may present problems concerning the bioavailability of the active ingredient. Further, the certification of new drugs is a lengthy and costly process involving animal studies followed by chemical trials to establish both the efficacy and safety of the new drug. Because a pharmaceutical's characteristics may be affected by changes in manufacturing and/or packaging, the approval process limits the approval to a particular manufacturing and packaging process. Thus, the ability to rapidly and easily change dosage units is extremely limited in conventional pharmaceutical manufacturing processes.

[0009] Drugs with a narrow therapeutic range must also be precisely dosed. If the patient falls below the range, the desired effect will not occur. However, if the patient is above the range then the risk of toxic effects increases. Clinicians assume the dose units manufactured are uniform and that generic equivalents have equal bioavailability. The many FDA generic formulation rejections and recalls for pharmaceuticals that have too high or low of a drug level, however, are evidence that accuracy and precision are still challenges for pharmaceutical manufacturing.

[0010] The ability to easily make a custom dose using tablets or capsules utilizing current technology is also difficult. It is virtually impossible to split or divide a capsule to decrease the dose administered requiring that the smallest dose be predetermined. Further, in the case of tablets a patient or pharmacist may often encounter difficulty in splitting or dividing even relatively large tablets that have a notch or groove at a predetermined breaking point to form a lower dosage unit. The splitting or breaking often results in fragments of unequal size. Thus, a method and dosage form that allows for variable doses to be formed outside the pharmaceutical manufacturing plant is desirable.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1***a* is a perspective view of a fluid cartridge containing an orally-ingestible medicament;

[0012] FIG. **1***b* is a perspective view of fluid ejection cartridges held within a carriage;

[0013] FIG. **1***c* is a perspective view of fluid ejection cartridges and an image acquisition system held within a carriage;

[0014] FIG. **2***a* is a perspective view of a orally-ingestible medicament dispensing system;

[0015] FIG. **2***b* is a perspective view of a orally-ingestible medicament dispensing system with an ingestible sheet tray;

[0016] FIG. **3** is a cross-sectional view of a fluid ejection cartridge;

[0017] FIG. **4** a perspective view of an ingestible sheet;

[0018] FIG. **5***a* is a plan view of an ingestible sheet;

[0019] FIG. **5***b* is a cross-sectional view of the ingestible sheet shown in FIG. **5***a*.

[0020] FIG. **6***a* is a cross-sectional view of a method for generating a dosage form;

[0021] FIG. **6***b* is a cross-sectional view of a method for generating a dosage form;

[0022] FIG. **6***c* is a cross-sectional view of a method for generating a dosage form;

[0023] FIG. **6***d* is a cross-sectional view of a method for generating a dosage form;

[0024] FIG. **7***a* is a perspective view of a process for manufacturing a dosage form;

[0025] FIG. **7***b* is a perspective view of an encapsulated and unitized single dose;

[0026] FIG. **7***c* is a plan view of a process for manufacturing a dosage form;

[0027] FIG. **8***a* is a perspective view of a dosage form to vary the amount of the medicament released over time;

[0028] FIG. **8***b* is a perspective view of a dosage form to vary the amount of the medicament released over time;

[0029] FIG. **8***c* is a perspective view of a dosage form to vary the amount of the medicament released over time;

[0030] FIG. **9***a* is a plan view of a dosage form containing user information;

[0031] FIG. **9***b* is a plan view of a dosage form containing user information and manufacturing information;

[0032] FIG. **10***a* is a cross-sectional view of a process for manufacturing a dosage form;

[0033] FIG. **10***b* is a cross-sectional view of a dosage form manufactured using the process shown in FIG. **10***a;*

[0034] FIG. **11** is a block diagram of a medicament dispensing system for the interactive dispensing of a medicament on an ingestible sheet;

[0035] FIG. **12** is a flow diagram of an interactive method for generating a dosage form;

[0036] FIG. **13***a* is a flow diagram showing a more detailed view of the steps for loading materials shown in FIG. **12**;

[0037] FIG. **13***b* is a flow diagram showing a more detailed view of the steps for reading information from materials shown in FIG. **12**;

[0038] FIG. **13***c* is a flow diagram showing a more detailed view of the steps for requesting information shown in FIG. **12**;

[0039] FIG. **13***d* is a flow diagram showing a more detailed view of the steps for specifying information shown in FIG. **12**;

[0040] FIG. **13***e* is a flow diagram showing a more detailed view of the steps for verifying information shown in FIG. **12**;

[0041] FIG. **13***f* is a flow diagram showing a more detailed view of the steps for applying the medicament on the ingestible sheet shown in FIG. **12**;

[0042] FIG. **13***g* is a flow diagram showing a more detailed view of the steps for printing information shown in FIG. **12**.

DETAILED DESCRIPTION

[0043] The present invention advantageously uses the multi-drop deposition capability of a fluid-jet ejection system to dispense medicaments on an ingestible carrier such as an ingestible sheet. Although one embodiment describes the use of a thermally activated fluid-jet ejection cartridge to dispense medications in the form of drops on an ingestible media, other methods of activating fluid-jet ejection, such as piezoelectric or acoustic activation, may also be used in the present invention. The fluid ejection system of the present disclosure includes a drop-on-demand type fluid dispenser. The present disclosure provides greater control of the drug dose than a typical diluting and mixing apparatus by producing precise and repeatable doses onto an ingestible carrier. Another feature of the present invention is the ability to dispense multiple different pharmaceuticals in varied quantities onto an ingestible carrier.

[0044] For purposes of this description, the term "medicament" shall mean a substance that treats or prevents or alleviates a disease or illness and/or the symptoms of the disease or illness. An example of a medicament is a pharmaceutical substance, such as a drug. The term "medicament" can be used to refer to such a substance in pure form, a mixture of the substance with other substances, and/or a solution including the substance. An "orally-ingestible medicament" is a medicament intended for intake into the digestive track via the mouth, as opposed to a medicament that is intended to be injected or surgically implanted. An orally-ingestible medicament may be configured to be digested and/or otherwise act in one or more of the mouth, throat, stomach, intestines, or any other portion of the alimentary canal.

[0045] Referring to FIG. **1***a,* an exemplary embodiment of a fluid ejection cartridge **102** is shown in a perspective view. In this embodiment, a fluid reservoir **128**, in the body portion of the fluid ejection cartridge **102**, typically contains a medicament used to generate the pharmaceutical dose and/or an ingestible ink used to generate an image or characters on an ingestible sheet or other carrier used to make a dosage form. The fluid reservoir **128** is fluidically coupled, preferably through internal passageways, to a substrate (not shown) that is attached to the back of a nozzle layer **126**. The substrate (not shown) normally contains an energy-generating element or fluid ejector (not shown) that generates the force necessary for ejecting the fluid held in the reservoir. Two widely used energy generating elements are thermal resistors and piezoelectric elements. The former rapidly heats a component in the fluid above its boiling point causing vaporization of the fluid component resulting in ejection of a drop of the fluid. While the latter utilizes a voltage pulse to generate a compressive force on the fluid resulting in ejection of a drop of the fluid. For more information on various transducers utilized in drop-on-demand fluid ejection cartridges see Stephen F. Pond, Ph. D. *Inkjet Technology and Product Development Strategies,* ch 4 (Torrey Pines Research, 2000); and more particularly for thermal inkjet technology see J. Stephen Aden et al., *The Third-Generation HP Thermal InkJet Printhead,* Hewlett-Packard Journal, vol. 45, no. 1, pg. 41-45, February 1994.

[0046] The substrate (not shown), the nozzle layer **126**, nozzles **124**, and a flexible circuit **125** form what is generally referred to as an ejector head **122**. In other embodiments the ejector head **122** includes the substrate (not shown), the nozzle layer **126** and the nozzles **124**. The nozzle layer **126** contains one or more nozzles **124** through which fluid, that is contained in a chamber around the fluid ejectors, is ejected by activation of the fluid ejectors (not shown) located in close proximity to the nozzles **124**. Each activation of a fluid ejector results in the ejection of a precise quantity of fluid in the form of a fluid drop; thus, the number of activations of the fluid ejector controls the number of drops ejected. For more information on drop formation see for example Jaime H. Bohorquez et al., *Laser-Comparable Inkjet Text Printing,* Hewlett-Packard Journal, vol. 45, no. 1, pg. 9-17, February 1994; or William A. Buskirk et al., *Development of a High Resolution Thermal Inkjet Printhead,* Hewlett-Packard Journal, vol. 39, no. 5, pg. 55-61, October 1988.

[0047] The fluid ejection cartridge **102** described in the present invention can reproducibly and reliably eject drops in

the range of from about ten femto-liters to about ten micro-liters depending on the parameters of the fluid ejection cartridge such as the size and geometry of the chamber around the fluid ejector, the size and geometry of the fluid ejector, and the size and geometry of the nozzle. Thus, the present invention has the ability to accurately dispense a medicament solution with a part per million to a part per billion accuracy. This is particularly advantageous when dispensing expensive medicaments, such as certain hormones, antibiotics, and medicaments derived from some natural products in scarce supply. The accuracy and precision is advantageous when dispensing concentrated substances with high potency. In addition, a further advantage of utilizing the fluid ejection cartridge **102** of the present invention is a reduction, to less than one percent by weight, in the amount of excess medicament that is dispensed to assure proper label dosage. In other words, medicament can be accurately applied to a carrier in the form of a plurality of closely sized drops, which include substantially equal amounts of medicament. By controlling the number of drops that are applied, the total amount of medicament can be controlled. As used herein, "target dose" shall mean the exact amount of medicament that is to be placed onto a carrier, and "therapeutic quantity" is a range of acceptable doses that includes the target dose. This embodiment is also advantageous for utilizing a mixture of the medicament and an ingestible ink contained in the fluid reservoir **128**.

[0048] Fluid ejection cartridge **102**, can utilize a method of creating discrete sized drops that are independently ejected from a particular nozzle utilizing a particular fluid ejector while maintaining a narrow drop volume distribution. In addition, the narrow drop volume distribution can be maintained over multiple nozzles each having a separate fluid ejector and fired independently or simultaneously. Such a cartridge can be characterized by a very narrow distribution of drop volumes and may have anywhere from a 2×, 3× or even more narrower drop volume distribution than conventional fluid ejector devices such as hydraulic, air assisted, or ultrasonic nozzles that form a spray of fluid having varying drop sizes. The range in drop volume is generally within 10 percent of the targeted or specified value and under steady state conditions can be within about 6 percent or less of the targeted value. Thus, a medicament can be accurately dispensed with a part per million to a part per billion accuracy.

[0049] The nozzle layer **126** may be formed of metal, polymer, glass, or other suitable material such as ceramic. Preferably, the nozzle layer **126** is formed from a polymer such as polyimide, polyester, polyethylene naphthalate (PEN), epoxy, or polycarbonate. In an alternate embodiment, the nozzle layer **126** is formed from a metal such as a nickel base enclosed by a thin gold, palladium, tantalum, or rhodium layer. Preferably, the components of the ejector head **122** and the fluid reservoir are formed of materials that are inert to the medicament and/or the ingestible ink which are to be dispensed therefrom. Thus, inert materials such as glass, ceramic, stainless steel, noble metals, and polymers inert to the medicament are preferred.

[0050] The fluid is selectively expelled from the one or more of the nozzles **124** by electrical signals communicated through electrical contacts **130** and associated conductive traces **132** disposed on the flexible circuit **125**. In the preferred embodiment, the flexible circuit **125** is typically bent around an edge of the fluid ejection cartridge **102** and secured. The electrical traces **132** are routed from the electrical contacts **130** to bond pads on the substrate (not shown) to provide electrical connection for the fluid ejection cartridge **102**. Thus, by communicating the proper electrical signal through the electrical contacts **130** a fluid ejector is activated the appropriate number of times to eject a predetermined number of drops.

[0051] An information storage element **133** is disposed on cartridge **102**. Preferably, the information storage element **133** is coupled to a flexible circuit such as the flexible circuit **125** as shown in FIG. **1***a*. The information storage element **133** is any type of memory device suitable for storing and outputting information that may be related to properties or parameters of the medicament contained within the fluid reservoir **128**. Preferably, the information storage element **133** is a memory chip mounted on the flexible circuit **125** and electrically coupled through the electrical traces **132** to the electrical contacts **130**. Alternatively, the information storage element **133** can be encapsulated in its own package with corresponding separate electrical traces and contacts.

[0052] When the fluid ejection cartridge **102** is either inserted into, or utilized in, a dispensing system the information storage element **133** is electrically coupled to a controller that communicates with the information storage element **133** to use the information or parameters stored therein. However, other forms of information storage can also be utilized for the information storage element **133**, such as a bar code or other device that allows storage of information. Further, the information storage element **133** can be mounted elsewhere on or within the body of the fluid ejection cartridge **102** with appropriate contacts and electrical connections to access the storage element depending on the particular application. In addition, the information storage element **133** can also be placed on an off-axis container utilized with semi-permanent ejector heads or cartridges.

[0053] The information storage element **133** may contain information such as the particular medicament or other material contained in the fluid reservoir **128**; the quantity of material remaining in the fluid reservoir **128** based on the number of drops dispensed or the number of times the fluid ejector has been activated. Other information can include the date of manufacture, inspection dates, quality control information, dispensing system parameters, and customer/patient information.

[0054] The fluid ejection cartridge **102**, or more preferably a set of individual fluid ejection cartridges **102** and **103**, capable of ejecting drops of medicament and/or ingestible ink or a combination thereof from ejector heads **122** and **123** are held within a carriage **111**, as illustrated in a perspective view in FIG. **1***b*. Alternative embodiments can include one or more semi-permanent ejector heads that are replenished from one or more fluidically-coupled off-axis fluid containers, or a single fluid ejection cartridge having one or more fluids available within the fluid ejection cartridge and fluid ejecting nozzles designated for each fluid integrally coupled with each fluid reservoir, or a single fluid ejection cartridge having a mixture of the medicament and ingestible ink. The present invention can be satisfactorily employed by at least these alternatives.

[0055] An alternate embodiment of the present invention where a carriage **111'** contains an image acquisition system **150** is shown in FIG. **1***c*. In this embodiment, the image acquisition system **150** contains a camera **151** and a light source **152**. As the cartridge **102** ejects drops of a medicament onto the ingestible sheet, the drops may exhibit spots on the

sheet having various visual or otherwise detectable geometric aspects, such as area extent, shape, and position. Preferably, the light source **152** is positioned relative to the camera **151** so that the camera **151** can image these detectable geometric aspects. Although as depicted in FIG. **1***c* the light source **152** comprises a single source, multiple sources can also be used. The light source **152** is preferably a light emitting diode (LED), although other light sources such as light bulbs or lasers can also be utilized.

[0056] The image acquisition system **150** also contains, a camera and light source, controller **153** that is preferably coupled to a drop-firing controller **214** as shown in FIG. **2***a*. When either fluid ejection cartridge **102** or **103** is activated by the drop-firing controller **214**, to dispense medicament or ingestible ink on an ingestible sheet, the camera controller **153** is correspondingly triggered by the drop-firing controller **214**; thus activating the camera **151** to gather image information pertaining to a portion of the surface of an ingestible sheet on which either a medicament or ingestible ink has been deposited. The camera **151** as shown in FIG. **1***c* can be any camera that can image the desired qualities on an ingestible sheet such as a camera that captures **2** dimensional images or line scan cameras that capture a narrow-stripped portion of the surface being imaged and these narrow-stripped portions are combined to for a complete two dimensional image.

[0057] In addition to capturing images of either the medicament or ingestible ink or other material dispensed on the ingestible sheet the image acquisition system **150** can also be utilized to capture images of information that has been placed on an ingestible sheet prior to deposition of the medicament or ingestible ink. Examples of such information are the composition of the ingestible sheet or results of quality control testing; data on compatibility with the medicaments, i.e. whether the ingestible sheet is compatible or incompatible with medicament being dispensed; patient information such as height, weight, name, age, prescribed dose etc.; expiration dates, temperature and/or humidity sensors, indicating that the ingestible sheet is no longer effective or it has been exposed to an extreme which could hinder its effectiveness. Although the image acquisition system **150**, as depicted in FIG. **1***c*, is mounted in carriage **111'**, other arrangements can also be utilized such as mounting the image acquisition system **150** on a separate carriage, or locating the image acquisition system in a different portion of a medicament dispensing system **200** shown in FIG. **2***a*.

[0058] The essential parts of a medicament dispensing system **200** according to an embodiment of the present invention is shown in a block diagram in FIG. **2***a*. In this embodiment, a platen to which an ingestible sheet **204**, such as a starch or glycerin based paper, is transported by mechanisms that are known in the art. The carriage **111** is typically supported by a slide bar **213** or similar mechanism within the system **200** and physically propelled along the slide bar **213** to allow the carriage **111** to be translationally reciprocated or scanned back and forth across the ingestible sheet **204**. The scan axis, X, is indicated by an arrow in FIG. **2***a*.

[0059] Under control of the drop firing controller **214** and a position controller **218**, the carriage **111** scans across the ingestible sheet **204**, and fluid drops are selectively ejected from fluid ejectors disposed within the fluid ejection heads of the set of fluid ejection cartridges **102** and **103** onto the ingestible sheet **204**. The power to activate the fluid ejectors is supplied by a power supply **215**. The drops are ejected to form predetermined dot matrix patterns, forming both the pharmaceutical dose from the cartridge containing the medicament, and images or alphanumeric characters from the cartridge containing the ingestible ink.

[0060] Rasterization of the data can occur in a host computer such as a personal computer or PC (not shown) prior to the rasterized data being sent, along with the system control commands, to the system, although other system configurations or system architectures for the rasterization of data are possible. This operation is under control of system driver software resident in the system's computer. The system interprets the commands and rasterized data to determine which drop ejectors to fire. An arrow in FIG. **2***a* indicates the fluid drop trajectory axis, Z, directed from the fluid ejection cartridges **102** and **103** toward the ingestible sheet **204**. When a swath of fluid ejection has been completed, the ingestible sheet **204** is moved an appropriate distance along the ingestible sheet axis, Y, indicated by the arrow, in preparation for the next swath. This invention is also applicable to medicament dispensing systems employing alternative means of imparting relative motion between the fluid ejection cartridges and the ingestible sheet, such as those that have fixed fluid ejection cartridges and move the ingestible sheet in one or more directions, and those that have fixed ingestible sheet and move the fluid ejection cartridges in one or more directions.

[0061] As can be appreciated from a preferred embodiment shown in FIG. **2***a*, the ingestible sheet **204** is advanced into a fluid ejection area beneath the ejector heads **122** and **123** (shown in FIG. **1***b*) by a sheet positioning mechanism commonly referred to as a sheet positioner or sheet advancer including rollers **217**, a platen motor **216**, and traction devices (not shown). In a preferred embodiment, the fluid ejection cartridges **102** and **103** are incrementally drawn across the ingestible sheet **204** on the platen by a carriage motor **212** in the ±X direction, perpendicular to the Y direction of entry of the medium. The platen motor **216** and the carriage motor **212** are typically under the control of the sheet and cartridge position controller **218**. An example of such a positioning and control apparatus may be found described in U.S. Pat. No. 5,070,410. Thus, the ingestible sheet **204** is positioned in a location so that the fluid ejection cartridges **102** and **103** may eject drops of fluid onto the ingestible sheet **104** as required for the particular dose being generated, and the particular data being written that is input to the drop-firing controller **214** of the medicament dispensing system **200**. These drops of fluid are expelled from selected orifices in the ejector heads **122**, **123** (as shown in FIG. **1***b*) in a band parallel to the scan direction as the fluid ejection cartridges **102** and **103** are translated across the ingestible sheet **204** by the carriage motor **212**. Once the fluid ejection cartridges **102** and **103** have reached the end of their traverse in the X direction on the slide bar, they are either returned back along the support mechanism while continuing to eject fluid or returned without fluid ejection.

[0062] When the fluid ejection cartridges **102**, **103** reach the end of their travel at an end of a fluid ejection swath on the ingestible sheet **204**, the ingestible sheet **204** is conventionally incrementally advanced by the position controller **218** and the platen motor **216**. Once the fluid ejection cartridges have reached the end of their traverse in the X direction on the slide bar **213** or similar support mechanism, they are either returned back along the slide bar **213** while continuing to eject fluid or returned without ejecting. The ingestible sheet **204** may be advanced by an incremental amount equivalent to the width of the fluid-ejecting portion of the fluid-ejecting head

or some fraction thereof related to the spacing between the nozzles. Control of the ingestible sheet **204**, positioning of the fluid ejection cartridge, and selection of the correct fluid ejectors for creation of both the medicament dose and the image or character written is determined by the position controller **218** and the drop-firing controller **214**. The controllers may be implemented in a conventional electronic hardware configuration and provided operating instructions from conventional memory **219**.

[0063] The medicament dispensing system **200** can also contain a heater **221** coupled to a heater controller **220** as shown in FIG. **2***a*. The heater **221** heats the ingestible sheet **204** to remove water and other solvents deposited on the ingestible sheet **204** after deposition of the medicament or ingestible ink. The heater also contains a temperature sensor (not shown) that is coupled to the heater controller **220** to maintain the ingestible sheet **204** at the appropriate temperature. The particular temperature that the temperature sensor maintains depends on the particular medicament or ingestible ink being dispensed, and on the particular ingestible sheet **204** being utilized. Although the heater **221** is located above the rollers **217** as depicted in FIG. **2***a* the heater can also be located in other portions of the medicament dispensing system **200** such as underneath the ingestible sheet **204** in front of the rollers **217**.

[0064] A perspective view of an alternate embodiment of the present invention where the medicament dispensing system **200** includes an ingestible sheet tray **299** is shown in FIG. **2***b*. In this embodiment, the tray **299** holds separate ingestible sheets **204'** that are advanced into the fluid ejection area beneath ejector heads (not shown) by rollers **217'** and other mechanisms as described above in FIG. **2***a*. Preferably the tray **299** holds from 1 to about 250 sheets, however, depending on the particular system, ingestible sheet, and medicament being utilized, the tray **299** may hold more than 250 sheets.

[0065] The apparatus described above makes unique use of an automated fluid ejecting device, having at least one medicament supply in a reservoir or chamber and at least one, and preferably, a plurality of fluid ejectors in an array, each ejector dispensing a precise volume of fluid in essentially individual droplets on each activation of the fluid ejector. This arrangement enables the quantity of the medicament dispensed to be varied in a specified area of the ingestible sheet thereby enabling either custom, or a wide range of doses to be more easily prepared. The apparatus or system as depicted in FIGS. **2***a* and **2***b* may be used in a manufacturing environment, a pharmacy, or even in other dispensing locations such as in a hospital, home etc. to automatically prepare pharmaceutical doses in response to patients needs.

[0066] A cross-sectional view of an alternate embodiment of the present invention where a fluid ejection cartridge **302** includes three fluid reservoirs **327**, **328**, and **329** contained within a cartridge body **334** is shown in FIG. **3**. In this embodiment, a substrate **336** is attached to the outer surface of the cartridge body **334**, and includes three groups of fluid ejectors **346**, **346'** and **346"**, in fluid communication with the three fluid reservoirs **327**, **328**, and **329** via three fluid routing channels **337**, **338**, and **339** respectively. Three fluid filters **340**, **341**, and **342**, are mounted within the fluid reservoirs **327**, **328**, and **329**, respectively. These filters are preferably constructed from stainless steel wire mesh of a desired porosity to provide good filtration of solid particles and air bubbles when fluid passes from the three fluid reservoirs **327**, **328**, and **329** into the three fluid routing channels **337**, **338**, and **339**.

[0067] Attached to the substrate **336** is a firing chamber layer **344** that defines the volume around each fluid ejector. Attached to the firing chamber layer **344** is a nozzle layer **326** that contains three groups of nozzles **324**, **324'** and **324"**. The fluid will flow from the three fluid reservoirs **327**, **328**, and **329** through the three fluid filters **340**, **341**, and **342** into the three fluid output ports **337**, **338**, and **339** through the substrate **336**. A firing chamber layer **344** includes fluid channels (not shown) and a firing chamber (not shown) formed into the layer that feeds fluid to the ejectors **346**, **346'** and **346"**. Upon appropriate activation, the ejectors **346**, **346'** and **346"** initiate the ejection of fluid out of the fluid ejection cartridge **302** through the three groups of nozzles **324**, **324'** and **324"**. Preferably, each group of nozzles is in a column and more preferably in staggered columns, however other patterns, such as circular patterns can also be utilized. This embodiment is particularly advantageous when the user desires a self-contained cartridge or integral replaceable unit containing the medicament, the ingestible ink, and a protective coating that is dispensed over the dispensed medicament. This embodiment is also advantageous when the user has three compatible medicaments that can be dispensed on the same sheet.

[0068] Although the properties of the ingestible sheets used in accordance with the present invention depend both on the particular medicament being dispensed and on the particular materials utilized in the sheet, it is generally preferable that the sheets are safely edible or ingestible, and do not have an objectionable "feel" in the mouth. In addition, the sheets preferably dissolve or degrade in body fluids and/or enzymes. However, the sheets can be made of non-degradable materials that are readily eliminated by the body. Preferably the sheets are hydrophilic and readily disintegrate in water and more preferably the dissolution or disintegration of the sheets is enhanced at the pH of the fluids in the stomach or upper intestine. Further, ingestible sheets that minimize unintended interactions with the medicament dispensed on the sheets and sheets that minimize the release of any sheet component that would cause unintended interactions with the medicament upon dissolution of the sheet, are also desirable.

[0069] Additional properties of the ingestible sheet that are desirable are the ability to remain stable over extended periods of time, at elevated temperatures, and at high or low levels of relative humidity. In addition, it is also preferable that the ingestible sheets are generally a poor medium for the growth of microorganisms to reduce spoilage. Further, ingestible sheets that possess reasonable mechanical properties such as tensile strength and tear strength are desirable to allow the sheets to be processed through the various steps of fabrication of the final dosage form using methods such as are recognized in the art.

[0070] Ingestible sheets that can be utilized in the present invention can be one or a mixture of organic film formers generally classified into two broad categories, i.e. polymeric and paper. Examples of such film formers are starch (i.e. both natural and chemically modified) and glycerin based sheets with or without a releasable backing. Other examples include, proteins such as gelatin, cellulose derivatives such as hydroxypropylmethylcellulose and the like; other polysaccharides such as pectin, xanthan gum, guar gum, algin and the like; synthetic polymers such as polyvinyl alcohol, polyvinylpyrrolidone and the like. Examples of ingestible sheets or edible films that can be utilized are those that are based on milk

proteins, rice paper, potato wafer sheets, and films made from restructured fruits and vegetables.

[0071] In particular, sheets or films made from restructured fruits and vegetables are advantageous were it is desirable to mask or modify the taste or smell of the medicament being delivered. Further, these restructured fruit and vegetable films also provide a convenient approach to encourage children to take various medications as well as providing a more pleasing and varied taste for various medications taken by adults. For more information on restructured fruit and vegetable films, see for example U.S. Pat. No. 5,543,164 and U.S. Pat. No. 6,027,758.

[0072] Dispensing the medicament on an ingestible sheet containing a water-expandable foam is preferable for those applications desiring rapid release of the medicament once ingested. Examples of such materials are an oxidized regenerated cellulose commercially available from Johnson and Johnson under the trademark SURGICEL®, and a porcine derived gelatin powder commercially available from Pharmacia Corporation under the trademark GELFOAM®.

[0073] The form of the ingestible sheet that can be utilized in the present invention can be any of the forms generally recognized in the art such as those used for paper, cardboard or polymeric films. The ingestible sheet or roll preferably is uniform in thickness and in width. Although the thickness of the ingestible sheet will depend on the particular medicament being dispensed, the particular ingestible sheet being utilized, and the particular method of manufacture used; the thickness of the ingestible sheet preferably ranges from about 10 to about 350 microns and more preferably from about 25 to about 100 microns thick.

[0074] The dosage forms produced in accordance with the present invention are eminently suited to span the range of production from individualized doses made in a home or hospital environment to the high speed high volume production in a pharmaceutical manufacturing environment. Thus, the particular width and length will not only depend on both the particular medicament being dispensed and the particular ingestible sheet being utilized, but more particularly on the particular method of manufacture used. Thus, the ingestible sheet can be in roll or individual sheet forms with widths varying from approximately one centimeter to several meters, and lengths from a few centimeters to several thousand meters, although other lengths and widths can also be utilized.

[0075] An embodiment of an ingestible sheet that is preferable for both high speed high volume manufacturing as well as for custom, individualized dispensing is illustrated in a perspective view in FIG. **4**. In this embodiment, an ingestible sheet **404** is in the form of a roll that contains perforations **447** that delineates each dosage form **405** and **405'**. In this embodiment, a medicament is dispensed preferably in a two-dimensional array, although other patterns can also be utilized, onto a first portion of the ingestible sheet **404**. A sheet advancer (not shown) then advances the ingestible sheet **404** and a second two dimensional array or alternate pattern is dispensed on a second portion of the ingestible sheet. The first and second portions form dosage forms **405** and **405'** respectively.

[0076] Preferably, after the medicament is dispensed on the dosage form **405** the user or system separates the dosage form **405** from the dosage form **405'** by tearing, by cutting along the perforations **447**, or by punching out the dispensed areas of the sheet. The user or system can also separate the dosage form **405** from the dosage form **405'** before dispensing of the medicament. This embodiment is particularly advantageous for systems such as those that have fixed fluid ejection cartridges; however, it can also be utilized in other systems as well. Preferably, the ejector head is approximately the width of the ingestible sheet **404** and the platen (not shown) moves the ingestible sheet in the direction of arrow **448** allowing both the dispensed dose of medicament as well as the appropriate characters or symbols utilizing the ingestible ink to be formed.

[0077] An alternate embodiment of an ingestible sheet that can also be used for custom, individualized pharmaceutical doses is shown in a plan view in FIG. **5***a* and in a cross-sectional view in FIG. **5***b*. In this embodiment, an ingestible sheet **504** is in the form of a sheet with a plurality of dosage forms **505** where each dosage form **505** contains dosage form separators **547** around its peripheral edge. Preferably, after the medicament is dispensed on the plurality of the dosage forms **505** contained in the ingestible sheet **504** the user or system separates the dosage form **505** from the dosage forms **505'** and **505"** by bending or, by pushing up in the center of the dosage form **505**, or some other convenient method and peeling the dosage form **505** from a releasable backing **549** shown in FIG. **5***b*. This embodiment is particularly advantageous for systems used to dispense custom pharmaceutical doses at home, in a hospital or a pharmacy; however, it can also be utilized in other systems as well. Although FIG. **5***a* shows the ingestible sheet **504** utilizing dosage form separators **547**, the ingestible sheet **504** can utilize any convenient means of separation such as perforations shown in FIG. **4**.

[0078] An embodiment of a method for generating a dosage form where the medicament is dispensed onto the ingestible sheet is shown in a cross-sectional view in FIG. **6***a*. In this embodiment, a drop-firing controller in a fluid dispensing system (not shown) activates one and, typically, a plurality of fluid ejectors, of a fluid ejection cartridge (not shown), to eject fluid drops **650**, **650'**, and **650"** of the medicament onto an ingestible sheet **604** forming deposits **651**, **651'**, and **651"**, respectively. For clarity in understanding the invention, the fluid drops **650**, **650'**, and **650"** are shown as being deposited on the surface of the ingestible sheet **604**. Although this will occur for non-porous, non-absorbing ingestible sheets, typically, the ingestible sheet **604** will be a porous and absorbing material which will allow the medicament to be absorbed into the interior of the ingestible sheet **604**. A dosage form **605** is generated when the required number of fluid drops of the medicament, to create the desired pharmaceutical dose, have been dispensed on a portion of the ingestible sheet **604**. Preferably, the dosage form **605** contains a two-dimensional array of the deposits **651**, **651'** and **651"** of the medicament on the ingestible sheet **604**. However, other arrangements can also be utilized, such as overlapping deposits forming a layer, or a different geometrical arrangement of the deposits **651**, **651'**, and **651"**.

[0079] An alternate embodiment of the present invention where the process used for generating a dosage form includes a barrier material deposited over the medicament is shown in a cross-sectional view in FIG. **6***b*. In this embodiment, the drop-firing controller activates one and, typically, a plurality of fluid or barrier ejectors, to eject fluid drops of a barrier material over the deposits **651**, **651'**, and **651"** of the medicament to form barrier deposits **652**, **652"**, and **652"**. The barrier deposits **652**, **652'**, and **652"** and deposits **651**, **651'**, and **651"** of the medicament on the ingestible sheet **604** form dosage

form **606**. The barrier material acts to seal the medicament from the environment. Depending on the particular medicament dispensed, and the particular ingestible sheet used, the barrier material provides various protective properties, such as humidity protection, protection from oxidation, inactivation, or contamination. The barrier material is an edible coating made from a suitable polymeric material such as a water-soluble polyoxyethylene or cellulose ether derivative. In addition, preferably the barrier material is an inert material, which will not interact with the deposited medicament. Further, the barrier material may also act as an adhesive as will be discussed later. In this embodiment, the fluid ejectors activated by the drop-firing controller are either, a different subgroup of fluid ejectors on the fluid ejection cartridge used to dispense the medicament, or a different fluid ejection cartridge.

[0080] An alternate embodiment of the present invention where the process used for generating a dosage form includes ingestible ink deposited over the medicament is shown in a cross-sectional view in FIG. **6***c*. In this embodiment, after the medicament and the barrier material has been deposited onto the surface of the ingestible sheet **604**, as described above, the drop-firing controller activates one and, typically, a plurality of ink ejectors, to eject fluid drops of an ingestible ink at various locations on the ingestible sheet **604** to form dots **654**, **654'** and **654"**. The dots **654**, **654'** and **654"** are deposited in patterns using dot matrix manipulation or other means to generate an image, alphanumeric characters, or a machine understood code such as a one or two dimensional bar code, on the ingestible sheet **604**. The dots **654**, **654'** and **654"**, the barrier deposits **652**, **652"**, and **652"** and deposits **651**, **651'**, and **651"** of the medicament on the ingestible sheet **604** form dosage form **607**.

[0081] An alternate embodiment of the present invention where the process used for generating a dosage form includes deposition of more than one medicament onto the ingestible sheet **604'** is shown in a cross-sectional view in FIG. **6***d*. In this embodiment, the deposits **651**, **651'**, and **651"** of the medicament and the deposits **652**, **652'** and **652"** of the barrier material have been formed on the ingestible sheet **604'** as described above. Next, the drop-firing controller activates one and, typically, a plurality of fluid ejectors, to eject fluid drops of a second medicament on the ingestible sheet **604'** to form deposits **656**, **656'** and **656"**. In this embodiment, the fluid ejectors activated by the drop-firing controller to eject the second medicament are either, a different subgroup of fluid ejectors on the fluid ejection cartridge used to dispense the first medicament, or a different fluid ejection cartridge.

[0082] After the second medicament has been dispensed, a second barrier is then formed over the deposits **656**, **656'** and **656"** forming barrier deposits **658**, **658'** and **658"** forming dosage form **608**. Preferably the second barrier material is the same as the first, however, depending on the properties and compatibilities of the first and second medicaments as well as the first barrier material the second barrier material may be different from the first barrier material. Although FIG. **6***d* depicts two different medicaments deposited on the ingestible sheet, more than two medicaments can be deposited on an ingestible sheet.

[0083] FIGS. **6***a*-**6***d* depict isolated deposits of the medicament and barrier material being deposited onto the ingestible sheet; however, by depositing overlapping deposits of, either or both, the medicament and barrier material layers of each material can be formed. In addition, the order of deposition can also be varied depending on the particular application. For example, the ingestible ink can be deposited before the medicament and the barrier material. Further, the ingestible sheet **604** or **604'** shown in FIGS. **6***a*-**6***d* can have, either or both, a releasable backing (not shown) or barrier material (not shown) coated on the surface opposite to the surface on which the medicament is dispensed.

[0084] An alternate embodiment of the present invention of a process for manufacturing a dosage form containing more than one medicament is shown in a perspective view in FIG. **7***a*. In this embodiment, multiple ingestible sheets **704**, **706**, and **707** each having multiple portions **760**, **761**, **762** respectively that have a medicament deposited thereon. The center ingestible sheet **704** is then sandwiched between the outer sheets **706** and **707** to form a laminated structure **764** where each of the multiple portions **760**, **761**, **762** are positioned where the portion **761** is above the portion **760** which is above the portion **762**. This arrangement forms a dosage form **705** that contains multiple medicaments.

[0085] Although FIG. **7***a* depicts three layers of ingestible sheet being laminated, laminated structures containing two or more layers can be utilized. The ingestible sheets **704**, **706**, and **707** can be formed from the same or different materials. In addition, the various processes and resultant structures depicted in FIGS. **6***a*-**6***b* can also be utilized. Further, other films such as a barrier film or ingestible adhesive film can also be laminated or coated on the different ingestible sheets **704**, **706**, and **707** to improve various properties such as water vapor transmission rate or adhesion depending on the particular medicaments and the particular ingestible sheets being utilized. Subsequent to the lamination process the laminated structure **764** can further be encapsulated and unitized to form single dose **766** as shown in perspective view in FIG. **7***b*.

[0086] An alternate embodiment of the present invention of a process for manufacturing a dosage form containing more than one medicament is shown in a plan view in FIG. **7***c*. In this embodiment, an ingestible sheet **704'** contains multiple portions **760'**, **761'**, **762'**, and **763** each containing a different medicament deposited thereon. The four multiple portions form a dosage form **705'** that contains multiple medicaments. Although FIG. **7***c* depicts four multiple portions, the ingestible sheet **704'** containing two or more multiple portions can be utilized. The various processes and resultant structures depicted in FIGS. **6***a*-**6***b* can also be utilized in this embodiment. In addition, other films such as a barrier film or ingestible adhesive film can also be laminated or coated on the ingestible sheet **704'** to improve various properties such as water vapor transmission rate, acid resistance, or drug release rate depending on the particular medicaments and the particular ingestible sheet being utilized. Further the multiple portions **760'**, **761'**, **762'** and **763** can also be utilized in the laminated structure **764** shown in FIG. **7***a* by either making a larger dosage form or by folding.

[0087] As noted above an expandable foam may be desirable for the rapid release of a medicament once ingested, however, some applications may want to vary the amount of the medicament released over time. An advantage of the present invention is the ability to make dosage forms that can vary the amount of medicament or drug released over time as shown in FIGS. **8***a*-**8***c*. In an alternate embodiment, shown in FIG. **8***a*, a fluid ejection cartridge (not shown) containing at least a medicament ejects the medicament onto an ingestible sheet **804** to form deposits **808** of the medicament dispensed in a two dimensional array over the surface of the ingestible

sheet **804**. In this embodiment, a dosage form **805** contains a first edge **806** having a greater density of the deposits **808** than a second edge **807** where the density of the deposits **808** between the first edge **806** and second edge **807** varies, forming a gradient of the medicament dispensed on the ingestible sheet. Although as shown in FIG. **8***a* the medicament is dispensed in the form of deposits **808** over the entire surface of dosage form **805** other forms can also be utilized such as centering the two dimensional array of deposits **808** in a narrower strip in the center of the dosage form **805** running from the edge **806** to the edge **807**. The dosage form **805** is wound into a coil, where the edge **806** having the higher dot density forms the edge contained in the center of the coil and the edge **807** having the lower dot density forms the outer edge of the coil.

[0088] As the ingestible sheet **804** dissolves the radius of the coiled dosage form **805** decreases, resulting in a smaller surface area, thus the amount of medicament released can be varied or maintained constant. For example as shown in FIG. **8***a* a gradient that increases as the surface area decreases can be used to maintain a constant or increasing release rate depending on the particular gradient used. Thus, in this example the medicament is deposited in a gradient adapted to provide a dosage form that, after being ingested, the amount of the medicament released increases over time. Further, the medicament can also be deposited in a gradient adapted to provide a dosage form that, after being ingested, the amount of the medicament released remains constant over time However, as shown in FIG. **8***b*, a dosage form **805'** that is coiled in the opposite direction where the edge **807**, having the lower dot density, forms the center of the coil and the edge **806**, having the higher dot density, forms the exterior surface of the coil; generates a gradient that decreases as the surface area decreases. Such a dosage form can be used to decrease the release rate as a function of time creating a loading dose. Thus, in this example the medicament is deposited in a gradient adapted to provide a dosage form that, after being ingested, the amount of the medicament released decreases over time.

[0089] A perspective view of an alternate embodiment of the present invention where repeat dosages are formed is shown in FIG. **8***c*. In this embodiment a fluid ejection cartridge (not shown) containing at least one medicament ejects the medicament onto the ingestible sheet **804** to form the deposits **808** of the medicament dispensed in a two dimensional array over discrete portions **809** on the surface of the ingestible sheet **804**. The dosage form **805"** is wound into a coil where each of the discrete portions **809** will release the deposited medicament at different times depending on the thickness of the ingestible sheet **804**, the rate of dissolution of the ingestible sheet **804** and the particular placement of each discrete portion **809** among other variables. This embodiment provides a dosage form where a discrete amount of the medicament is released at either repeatable times or discrete amounts of the medicament is released at different times. Although each of the alternative embodiments shown in FIGS. **8***a*-**8***c* are described in terms of fixed dot size and varying the dot density, other methods can also be utilized such as varying the drop size and keeping the dot density constant. This ability to vary the dosage release rate over time is an advantage over a conventionally formed tablet, which would release less medicament as the diameter of the tablet decreases. Thus, the present disclosure allows for a dosage form where the amount of medicament released over time, increases, decreases, remains constant, is repeatable, or a discrete dose is released at different times.

[0090] Referring to FIGS. **9***a*-**9***b*, an alternate embodiment of the present invention is shown where the dosage form **905** contains user information **970** to be conveyed to the user or patient. For example, FIG. **9***a* depicts the user information **970** as a clock showing the time the dose is to be taken or administered. In this particular example the user information **970** is deposited over the two dimensional array of the deposits **908** of the medicament. However, depending on the particular medicament and the particular ingestible sheet being utilized the medicament can also be deposited over the user information. Another example is shown in FIG. **9***b* where the information is a message indicating the name, date, and time to take the medicament. However, the user information **970** can be any symbol, icon, image, or text or combinations thereof, such as a company logo or cartoon character. Other examples of the type of information that can be conveyed to the user are the name of the medicament, the expiration date, the flavor of the ingestible sheet, or information having some marketing value. In addition, the dosage form **905** can also contain manufacturing information **972** to be used by the manufacturer and/or distributor. For example, FIG. **9***b* depicts the manufacturing information **972** as a two-dimensional bar code. The manufacturing information **972**, however, can be any symbol, icon, image, or text or combinations thereof. Examples of various forms are a one-dimensional bar code, a text message, a code, or hologram. Examples of the various types of information that can be utilized in the manufacturing information **972** would be the composition of the ingestible sheet or results of quality control testing, data on compatibility with medicaments, expiration dates, or part tracking information.

[0091] A cross-sectional view of an alternate embodiment of the present invention where a dosage form **1005** is encapsulated in a tablet **1079** is shown in FIG. **10***b*. In this embodiment, a lower die chamber **1074** and an upper die chamber **1076** are substantially filled with an excipient powder **1078** as shown in FIG. **10***a*. Dosage form **1005**, which contains the medicament deposited on an ingestible sheet **1004**, is positioned between the two die chambers such that the excipient powder formulation encases or encloses the dosage form **1005**. Compressing the lower die chamber **1074** against the upper die chamber **1076** forms the tablet **1079**. Preferably, the tablet is cylindrical with convex outer surfaces typically about 5 to 15 mm. in diameter and about 5 mm. in thickness. However, a variety of regular and irregular shapes and sizes can be utilized, such as elliptoids, cuboids, indentations, polygonoids and other convex and concave surfaces. Optional subsequent processes including dedusting, drying, and coating may be performed.

[0092] Depending on the desired pharmacokinetic characteristics of the medicament dispensed on the ingestible sheet **1004**, the excipient formulation may be similar to the ingestible sheet **1004** or one may select excipients that are dissimilar to the ingestible sheet to obtain tabletting or pharmacokinetic characteristics unlike the ingestible sheet **1004**. For example microcrystalline sugar (97% sucrose and 3% maltodextrin) or cellulose, calcium phosphate, and sodium carboxymethylcellulose can be used with a cellulosic-based ingestible sheet. Sugars and corn, wheat, or rice starches can be used with starch-based ingestible sheets. Whereas silica

added to improve flowability, stearates for lubrication, and guar gum or gelatin as binders are examples of dissimilar materials.

[0093] A preferable excipient formulation for direct compression tabletting of a dosage form made from an ingestible sheet which does not include the weight of the ingestible sheet nor the weight of the medicament dispensed is: about 70 weight percent lactose, about 25 weight percent microcrystalline cellulose, about 2 weight percent di-calcium phosphate dihydrate, 2 weight percent sodium carboxymethylcellulose, about 0.3 weight percent fumed silica and about 0.5 weight percent magnesium stearate. However, excipient ranges in formulations for direct compression tabletting of a dosage form made from an ingestible sheet which does not include the weight of the ingestible sheet nor the weight of the medicament dispensed are 0 to about 80 weight percent sugar, 0 to about 25 weight percent microcyrstalline cellulose, 0 to about 90 weight percent calcium phosphate, about 5 to about 25 weight percent starch, about 1 to about 2 weight percent sodium carboxymethylcellulose, about 0.2 to about 0.3 weight percent silica and about 0.5 to about 1 weight percent magnesium stearate can also be utilized.

[0094] In addition to improve adhesion between the excipient powder formulation and the ingestible sheet the excipient formulation can be modified by adding natural or synthetic polymers such as proteins, carboxymethylcellulose, polyvinylacetate, gelatins, or dextrins can be utilized to improve the adhesive properties of the excipient powder. It is also contemplated that an ingestible adhesive can be dispensed between the two die chambers prior to applying pressure to form the tablet. For example, a monomeric methyl or ethylcyanoacrylate type adhesive can be utilized. Alternatively, the ingestible sheet **1004** of the dosage form **1005** can be perforated to allow greater contact area between excipient powder **1078** contained in the upper die chamber **1076** and the lower die chamber **1074** or the dosage form **1005** can be formed in the shape of a ring containing an area in the center of the dosage form **1005** that allows the excipient powder in the two chambers to bond.

[0095] The process described above for compression tabletting of an ingestible sheet containing a medicament is advantageous over conventional tabletting in that the number of mixing steps can be reduced as well as the need to assure thorough mixing of the excipient with the pharmaceutical material to ensure proper dilution. In addition, flowability and drying criteria of the excipient formulation can also be relaxed.

[0096] An exemplary system **1100** for the interactive dispensing of a medicament on an ingestible sheet is shown as a schematic diagram in FIG. **11**. In this embodiment a processor **1180** is coupled to a drop-firing controller via dispense interface **1182**. The processor **1180** converts a specified quantity of the medicament to be dispensed into a number of drops or ejections to be activated by the drop-firing controller. This number is transmitted via the dispense interface **1182** to the drop-firing controller of the medicament dispensing system **200**. The specified quantity of the medicament is then ejected onto the ingestible sheet forming a dosage form. The system **1100** also includes a storage device **1186** and a display device **1184** coupled to the processor **1180** to store and display information. For example user input information, system parameters, information and parameters associated the ingestible sheet can all be stored on storage device **1186** and/or displayed on display device **1184**.

[0097] The system **1100** having the processor **1180**, display device **1184**, and storage device **1186** is advantageous over current methods of forming pharmaceutical doses in that it allows a user such as a doctor or pharmacist to generate variable doses as well as custom doses in the convenience of a hospital, pharmacy, or home environment. Further, such a system can also be utilized as a point of sale machine, in such locations as a pharmacy or a supermarket, to allow customers to create variable or custom doses of vitamins, nutritional supplements, or other over-the-counter medications.

[0098] In addition, the system **1100** also includes a user interface **1188** or signal receiver that is coupled to the processor **1180** and is also coupled via communication channel **1193** to an external communication network **1190** as shown in FIG. **11**. Preferably, the external communication **1190** is a digital network such as what is commonly referred to as the Internet. Other communication channels such as wireless communication, wireline telephone, digital cable television, as well as other point-to-point, point-to-multipoint, and broadcast communications methods can also be used. The user interface or signal receiver **1188** receives a signal from a remote signal source specifying information to be utilized by system **1100**. For example, the remote signal source can specify the quantity of medicament to be dispensed or an authorization code verifying the authority of the user to dispense the medicament. As shown in FIG. **11**, the system **1100** can also be coupled to a provider system **1192** via network **1190**.

[0099] The provider system **1192** includes a provider processor **1181**, coupled to a provider display **1185**, a provider storage device **1187**, and a provider interface **1189**. The provider interface **1189** is coupled via provider channel **1194** to the external communication network **1190**. The provider system **1192** is utilized, for example, by a health care provider such as a doctor, a pharmacist, a nurse, appropriate insurance personnel, or other appropriate health care professional. Although FIG. **11** shows a single provider coupled to the system **1100** it also preferable to have multiple providers, such as doctors, pharmacists, nurses, insurance providers, and pharmaceutical manufacturers all coupled to the system **1100** over the external network **1190**. This is particularly advantageous where system **1100** is located in a home where the patient can request information on the medicament and appropriate dosage information from a pharmacist, request information on the ingestible sheet from the manufacturer, and current health information from a doctor or nurse over the network; to form the appropriate pharmaceutical dose for that time or multiple doses to cover a period of the next day to several days or weeks. Such a system also allows potentially adverse drug interactions and individual allergies or intolerances and sensitivities to be flagged.

[0100] An exemplary embodiment of an interactive method for generating a dosage form where the medicament is dispensed onto the ingestible sheet is shown as flow diagrams in FIGS. **12-13**. An overview of the method is shown in FIG. **12**. In step **1200**, the various materials such as the medicament and the ingestible sheet are loaded or inserted into a medicament dispensing system. In Step **1210**, information indicative of the materials is read either by the system or by a user who then manually enters the information into the system, such as the composition of the ingestible sheet and the active ingredients of the medicament. In step **1220**, various forms of information are requested by the system such as requesting from the doctor or pharmacist the quantity or dose of the

medicament to be dispensed. In step **1230**, various forms of information are specified and then transmitted and received by the system, such as the doctor or pharmacist specifying the quantity or dose of the medicament to be dispensed. Various forms of information are verified in step **1240** such as verifying that the dose is within the correct range. The medicaments as well as other materials such as the barrier material are dispensed on the ingestible sheet in step **1250** providing all of verification steps were successfully completed. In optional step **1260**, appropriate user and manufacturing information is printed on the ingestible sheet.

[0101] A more detailed view of the various steps associated with the loading step **1200** is shown in FIG. **13***a*. In step **1301**, an off-axis medicament container is inserted into the dispensing system where the container, after insertion is fluidically coupled to a medicament reservoir of a semi-permanent cartridge. Either a replaceable or semi-permanent medicament ejection cartridge is inserted in the dispensing system in step **1302**. An off-axis ingestible ink container, and either a replaceable or semi-permanent ingestible ink ejection cartridge, are inserted into the dispensing system in steps **1303** and **1304** respectively, where the off-axis ink container is fluidically coupled to an ink reservoir in a semi-permanent ink cartridge. Depending on the particular ingestible sheet, and medicament utilized, a cartridge containing a mixture of the medicament and the ingestible ink can be inserted into the system in step **1305**. In step **1306**, an ingestible sheet is loaded into the dispensing system.

[0102] A more detailed view of the various steps associated with the reading step **1210** is shown as a flow diagram in FIG. **13***b*. In step **1311**, information is read from the ingestible sheet. For example, the composition or the expiration date of the ingestible sheet can be read by the system utilizing an image acquisition system scanning a bar code. Preferably this information is stored in a machine readable form, however, a human perceptible form can also be utilized. In steps **1312** and **1314** information from the medicament cartridge and from the medicament container is accessed or read respectively. Preferably this information is stored in a memory chip that this accessed, however, other means can also be utilized such as printing the information on the cartridge in a machine readable or human perceptible form.

[0103] A more detailed view of the various steps associated with the requesting step **1220** is shown as a flow diagram in FIG. **13***c*. In step **1321** the quantity of the medicament to be dispensed is requested by the medicament dispensing system. For example, this could be displayed on a display device located in the vicinity of the dispensing system or it can be displayed on a remote display device such a doctor's or pharmacist's office. User information is requested by the system in step **1322**. This information is any information about the user, i.e. typically the patient, that can be utilized for example in determining the appropriate dose, such as the patient's height, weight, age, etc. or information that is used by the user in administering the dosage form. In step **1324**, manufacturer's information is requested by the system. This information is any information from the manufacturer of the medicament and/or the ingestible sheet. For example, this information can be the same or similar to that obtained in steps **1311**, **1312**, **1314** and can be used in conjunction with that information to act as a verification.

[0104] A more detailed view of the various steps associated with the specifying step **1230** is shown as a flow diagram in FIG. **13***d*. In step **1331**, the quantity of the medicament to be dispensed is specified, for example by a doctor or pharmacist, transmitted to and received by the medicament dispensing system. In step **1332**, dosage information, such as dosage forms that vary the amount of medicament released over time as shown in FIG. **8**, is specified, transmitted to and received by the system. User information is specified transmitted to and received by the system in step **1334**. This information is any information about the user, i.e. typically the patient, that can be utilized for example in determining the appropriate dose, such as the patient's height, weight, age, etc. or information that is used by the user in administering the dosage form. In step **1336**, manufacturer's information is specified. This information is any information from the manufacturer of the medicament and/or the ingestible sheet. For example, this information can be the same or similar to that obtained in steps **1311**, **1312**, **1314** and can be used in conjunction with that information to act as a verification.

[0105] A more detailed view of the various steps associated with the verifying step **1240** is shown as a flow diagram in FIG. **13***e*. In step **1341**, the dosage quantity is verified. Step **1341** verifies information obtained in a previous step such as step **1331** or multiple steps is used to verify the dosage specified, is either correct or within an acceptable range. For example, the information accessed from the medicament cartridge in step **1312** is compared to the specified quantity to be dispensed in step **1331**. Another example would be the use of a third party authorization key where the dosage quantity is verified utilizing the key that is located on the user's system or is accessed via a network such as the Internet. The dosage information specified in step **1332** is verified in step **1342**. For example, if the information has been previously entered then the information specified in step **1332** can be verified from stored information stored on a storage device. However, if step **1332** is being performed for the first time with a given user then either the information can be retransmitted back to the person specifying or the information can be verified by a third party such as a doctor or an insurance agent via a network such as the Internet. In step **1344**, user information is verified. This step can also be carried out using either previously stored information or a third party as described above in step **1342**. The manufacturer's information is verified in step **1346**. This step can also be carried out using either previously stored information or a third party as described above in step **1342**. The manufacturer's information is any information from the manufacturer of the medicament or the ingestible sheet obtained in steps **1336** or step **1210**.

[0106] A more detailed view of the various steps associated with dosing of the medicament on the ingestible sheet in step **1250** is shown as a flow diagram in FIG. **13***f* provided the verification steps described above have been successfully completed. In step **1351**, the quantity of medicament to be dispensed is converted on a processor into a number of activations of a fluid ejector. The ingestible sheet is advanced into a fluid ejection area beneath the ejector head or heads in step **1352**. The dosing data preferably in the form of the number of activations of a fluid ejector is transmitted from the processor to the dispense system in step **1354**. In step **1356**, the fluid ejectors are activated to produce the pharmaceutical dose. Preferably, the drops are ejected in a predetermined fluid swath pattern using dot matrix manipulation, forming the pharmaceutical dose from the cartridge containing the medicament, however other processes of firing the fluid ejectors can also be utilized. In addition, a custom medicament dose can also be generated by inputting the user information, the

manufacturing information, dosage information, as well as appropriate information from the medicament cartridge into a dose algorithm. The dose algorithm then combines this information in a predetermined manner to generate a custom medicament dose.

[0107] A more detailed view of the various steps associated with printing information on the ingestible sheet, in step **1260**, is shown as a flow diagram in FIG. **13***g*. In step **1361**, appropriate manufacturing information, such as the composition of the ingestible sheet and the name or the medicament, is printed on the ingestible sheet. The manufacturing information printed in step **1361** can be printed either in a machine understood form in step **1363** or it can be printed in a human perceptible form in step **1362** or in some combination thereof. The user information, such as the name of the user or patient and the date and time for administering the dosage form, is printed on the ingestible sheet in step **1364**. In step **1366**, preferably the barrier material is dispensed over the medicament previously dispensed in step **1356**. However, depending on the particular ingestible sheet, medicament, and dosage structure (e.g. capsule or laminated structure) being utilized, the barrier material may be dispensed before the medicament is dispensed.

[0108] The present invention can advantageously reduce the number of therapeutically inactive materials, the number of dilutions, and the number of mixings in the manufacture of unit dosage forms. In addition, the medicament cartridge and the medicament dispensing system of the present invention provides for the custom dispensing of pharmaceutical unit dosage forms where the type of pharmaceutical and the quantity of the selected drug can be easily varied to meet a specific prescription. The medicament cartridge and the medicament dispensing system of the present invention provides the ability of dispensing multiple, different pharmaceuticals in varied, selected quantities to a single receiving medium thus simplifying the taking of drugs, especially combinations of different drugs by providing multiple drugs in one dose.

What is claimed is:

1. An interactive system comprising:

a medicament dispensing assembly including a drop firing controller, fluid drop ejectors and an ingestible sheet transporter;

a network interface; and

a processor coupled to said network interface and to said dispensing assembly, wherein said processor determines a customized medicament dose for a specific individual based on information received across the network from a remote provider, and

wherein said medicament dispensing assembly dispenses medicament fluid drops onto the ingestible sheet based on the customized dose.

2. The interactive system of claim **1**, further comprising a provider interface coupled to the network.

3. The interactive system of claim **1**, further comprising multiple provider interfaces coupled to the network.

4. The interactive system of claim **1**, wherein the information comprises information about the individual, a provider sending the signal, or a medicament dosage, or a combination of any of those.

5. The interactive system of claim **4**, wherein the information about the individual comprises current health information.

6. The interactive system of claim **4**, wherein the information about a medicament dosage comprises a quantity or dose of the medicament to be dispensed.

7. The interactive system of claim **4**, wherein the information about the provider comprises an authorization code verifying the authority of the provider to dispense the medicament.

8. The interactive system of claim **4**, wherein the provider is a health care provider.

9. A system comprising:

means for determining a medicament dosage customized for a specific individual;

means for dispensing a medicament onto an ingestible sheet based on the customized medicament dosage; and

means for forming a customized dosage form from said ingestible sheet containing said medicament.

10. An interactive method of generating a dosage form that is customized for a specific individual, comprising:

(a) loading a medicament and an ingestible sheet into the medicament dispensing system of claim **1**;

(b) receiving from a remote provider a signal comprising information to be utilized by the medicament dispensing system;

(c) determining, by the processor, a customized dosage for the individual based on the received signal;

(d) dispensing, by the medicament dispensing system, medicament fluid drops onto the ingestible sheet based on the customized dose; and

(e) forming the ingestible sheet containing the customized dosage into a dosage form.

11. The interactive method of claim **10**, wherein (d) and (e) are performed in a home, pharmacy, hospital or supermarket.

12. The interactive method of claim **10**, wherein in (b), receiving said signal from a remote provider comprises transmitting the signal over the network.

13. The interactive method of claim **10**, wherein (c) comprises verifying the information received from a remote provider.

14. The interactive method of claim **13**, wherein said verifying comprises verifying that the quantity or dose of the medicament received in (b) is in a correct range.

15. The interactive method of claim **13**, wherein said verifying comprises comparing information written on said ingestible sheet to information received in (b).

16. The interactive method of claim **10**, comprising dispensing the medicament onto the ingestible sheet, and dispensing an edible barrier material over the medicament.

17. The interactive method of claim **10**, comprising dispensing two different medicaments onto the ingestible sheet.

18. The interactive method of claim **10**, comprising printing user information on the ingestible sheet using an ingestible ink.

19. The interactive method of claim **10**, wherein said ingestible sheet is adhered to a releasable backing.

20. The interactive method of claim **10**, wherein said ingestible sheet comprises a dosage region comprising a first edge and a second edge, and in (d), dispensing the customized dosage onto the ingestible sheet includes ejecting a two-

dimensional droplet array of the medicament onto the dosage region to form a density gradient of medicament dots between said first and second edges, wherein either the first or second edge has a greater density of medicament dots than the other edge, and

wherein, in (e), forming the ingestible sheet containing the customized dosage into a dosage form includes winding the sheet into a coil.

* * * * *