



US 20090148523A1

(19) **United States**

(12) **Patent Application Publication**
Sowden

(10) **Pub. No.: US 2009/0148523 A1**

(43) **Pub. Date: Jun. 11, 2009**

(54) **SYSTEM AND PROCESS FOR PROVIDING AT LEAST ONE OPENING IN DOSAGE FORMS**

Publication Classification

(76) Inventor: **Harry S. Sowden**, Glenside, PA (US)

(51) **Int. Cl.**
A61K 9/22 (2006.01)
A61P 43/00 (2006.01)

Correspondence Address:
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003 (US)

(52) **U.S. Cl. 424/468**

(57) **ABSTRACT**

(21) Appl. No.: **12/366,854**

(22) Filed: **Feb. 6, 2009**

Related U.S. Application Data

(62) Division of application No. 11/006,038, filed on Dec. 7, 2004.

The present invention relates to apparatus, methods, and processes for making solid dosage forms comprising at least one active ingredient, a core and shell configuration, wherein the shell comprises a hardenable material, such as a thermal-gelling polymer, for example gelatin; and the shell is provided with at least one opening. The opening(s) are formed while the shell is still in a softened state.

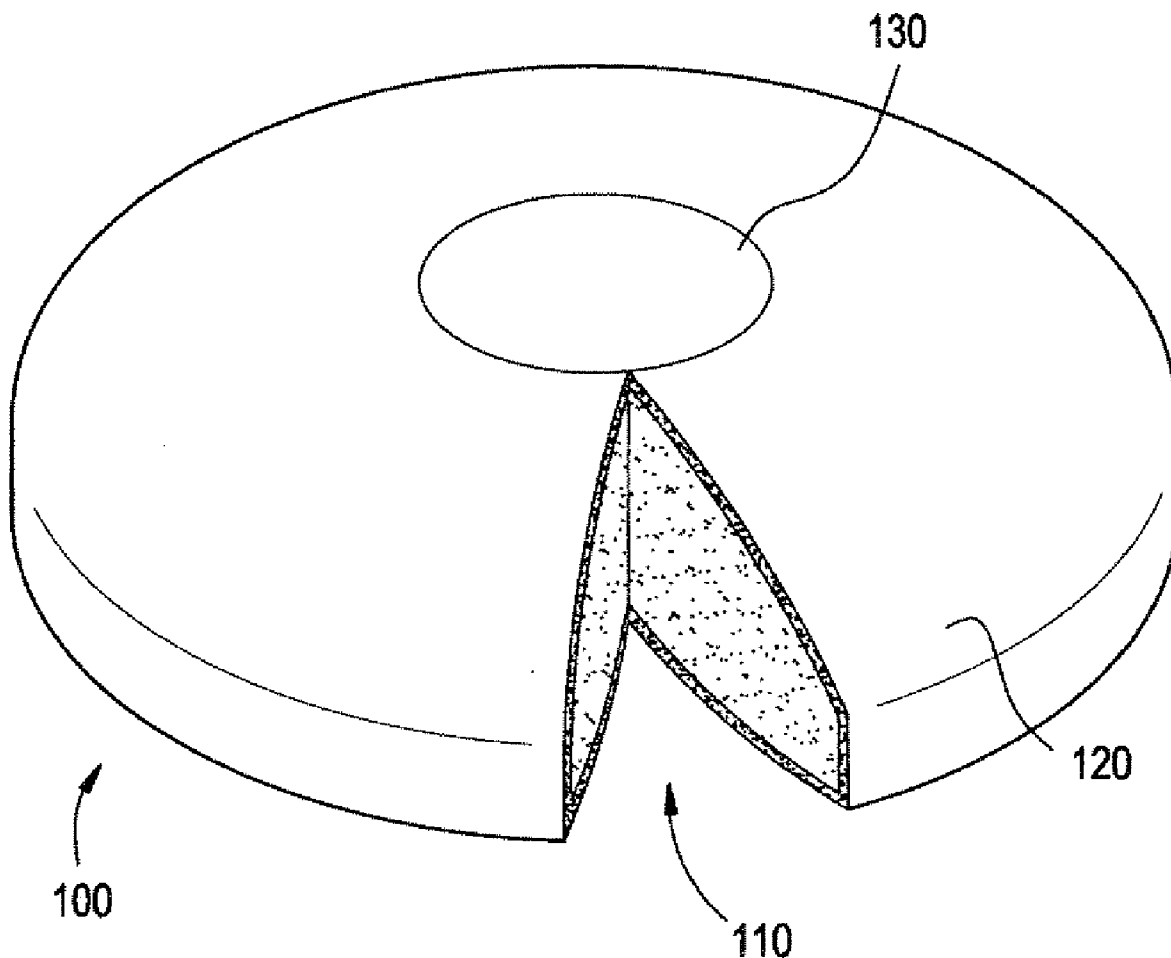
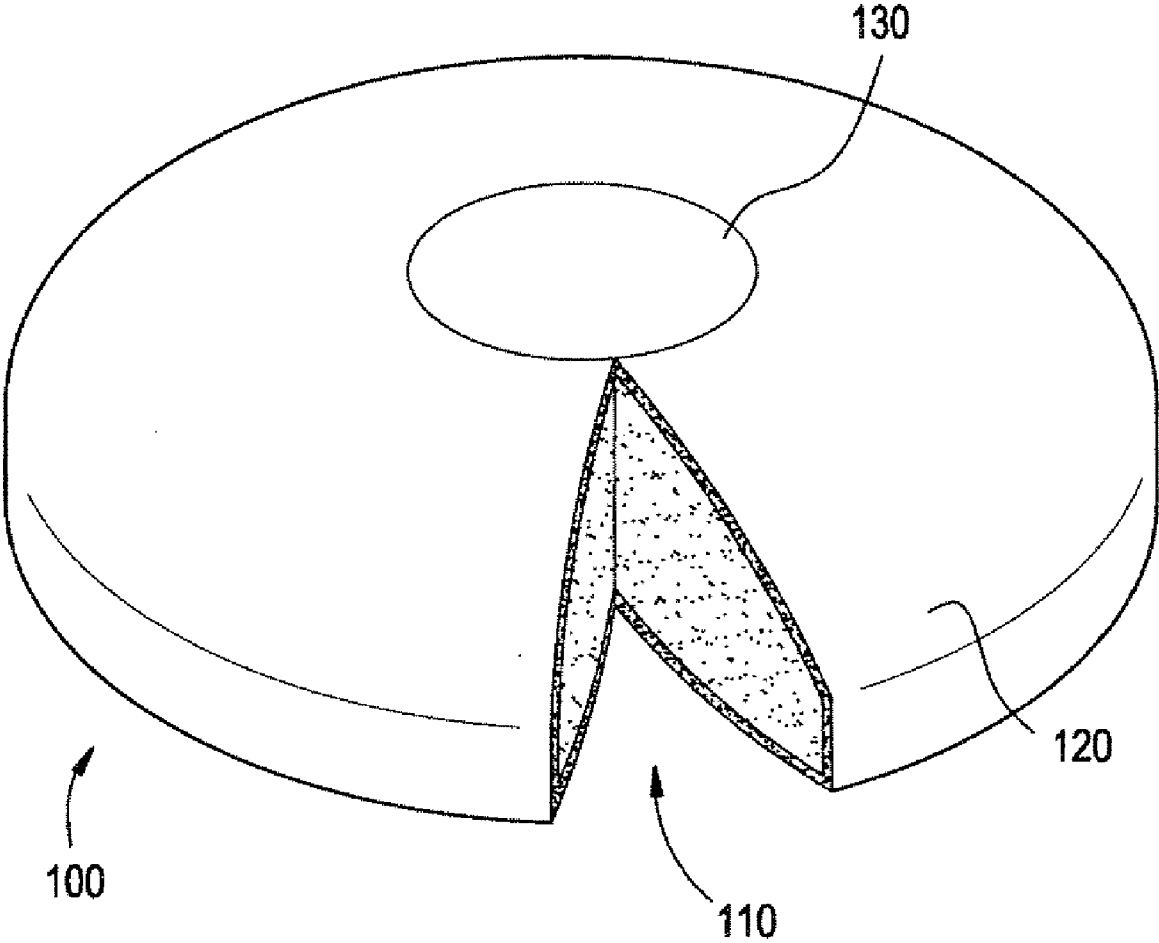


FIG. 1



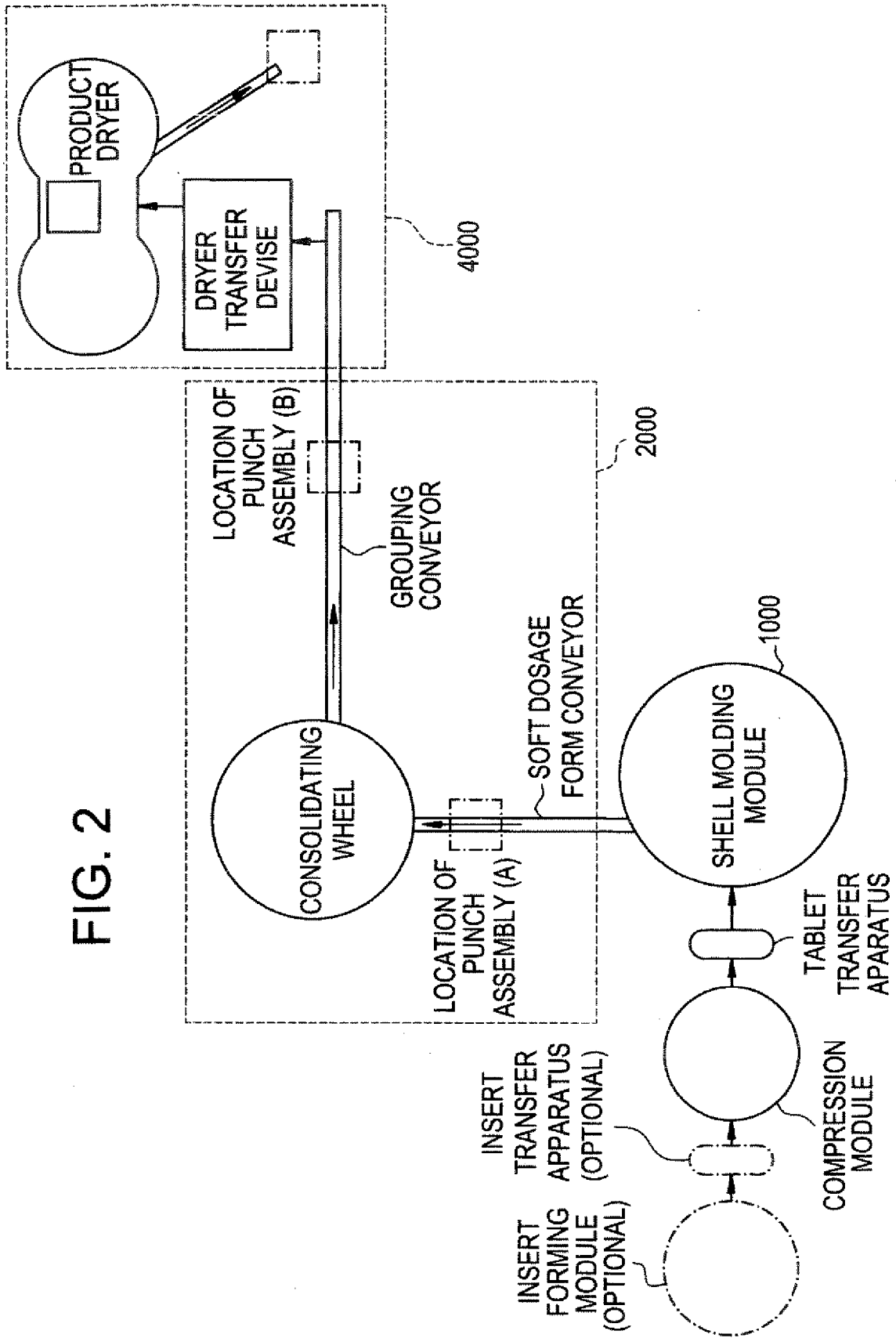


FIG. 2

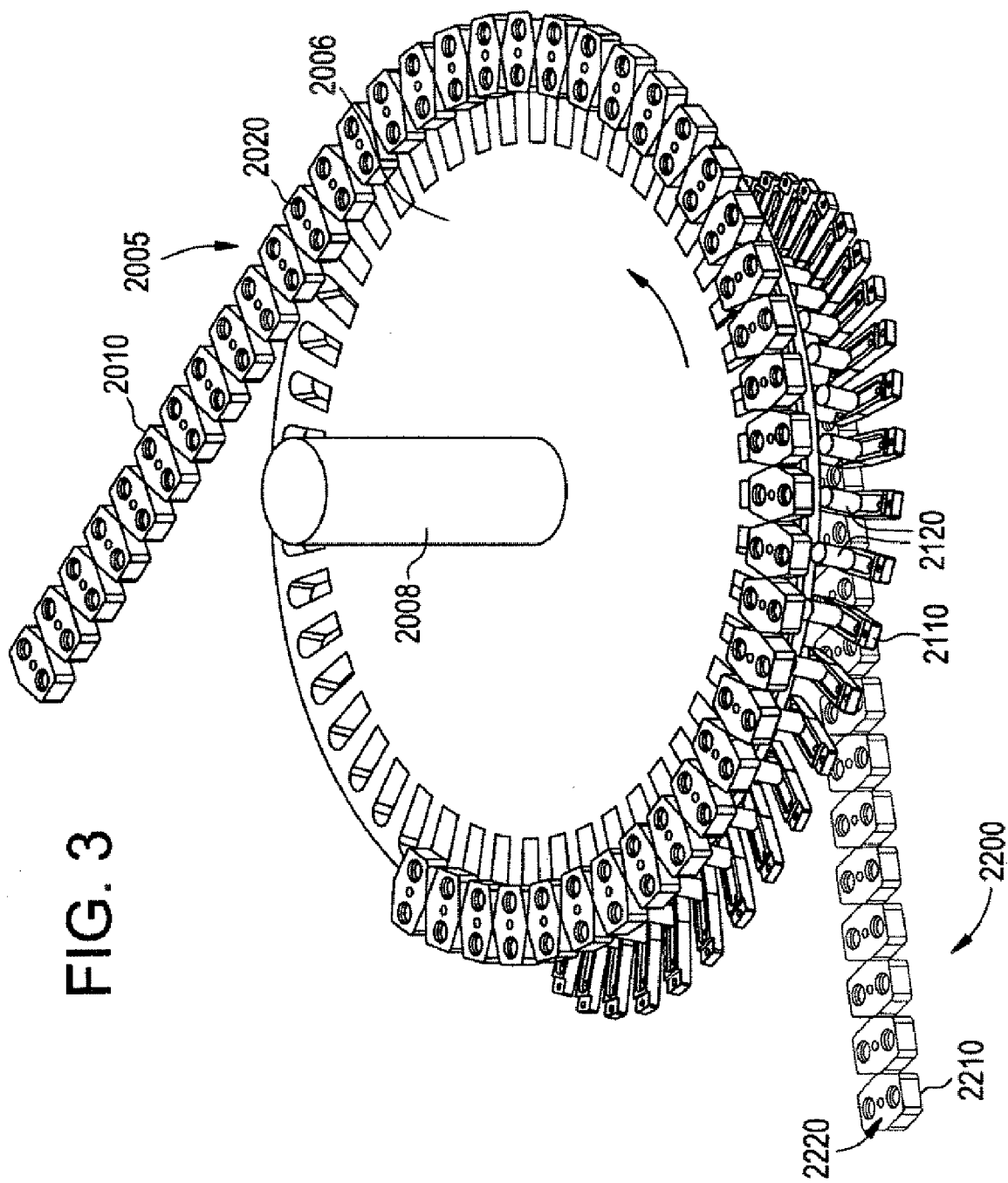


FIG. 4

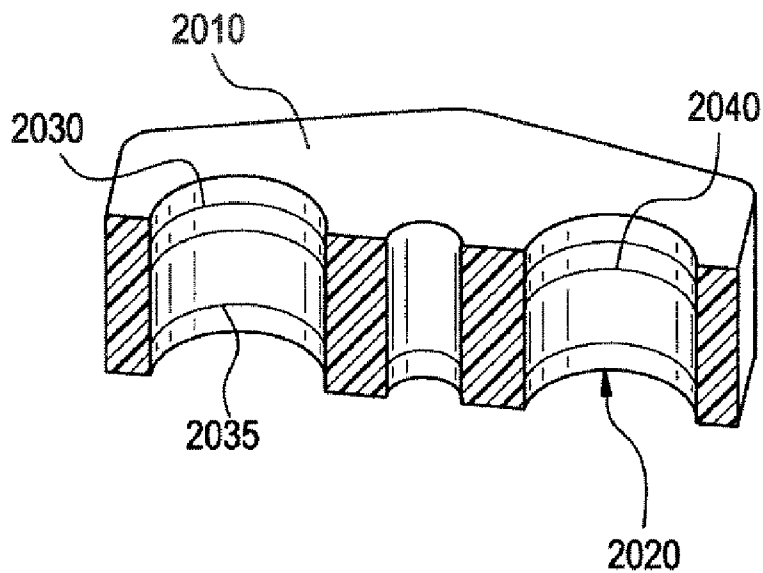


FIG. 4A

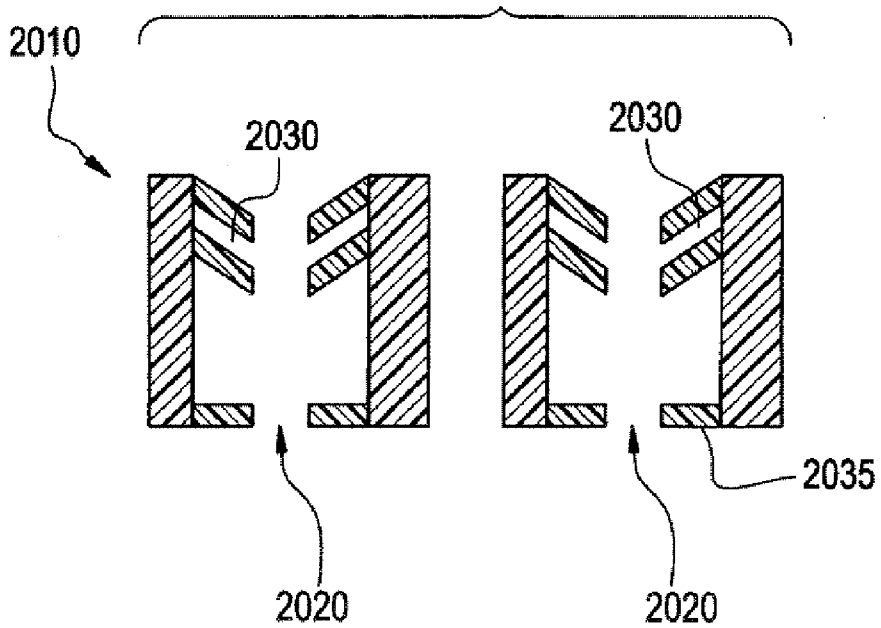
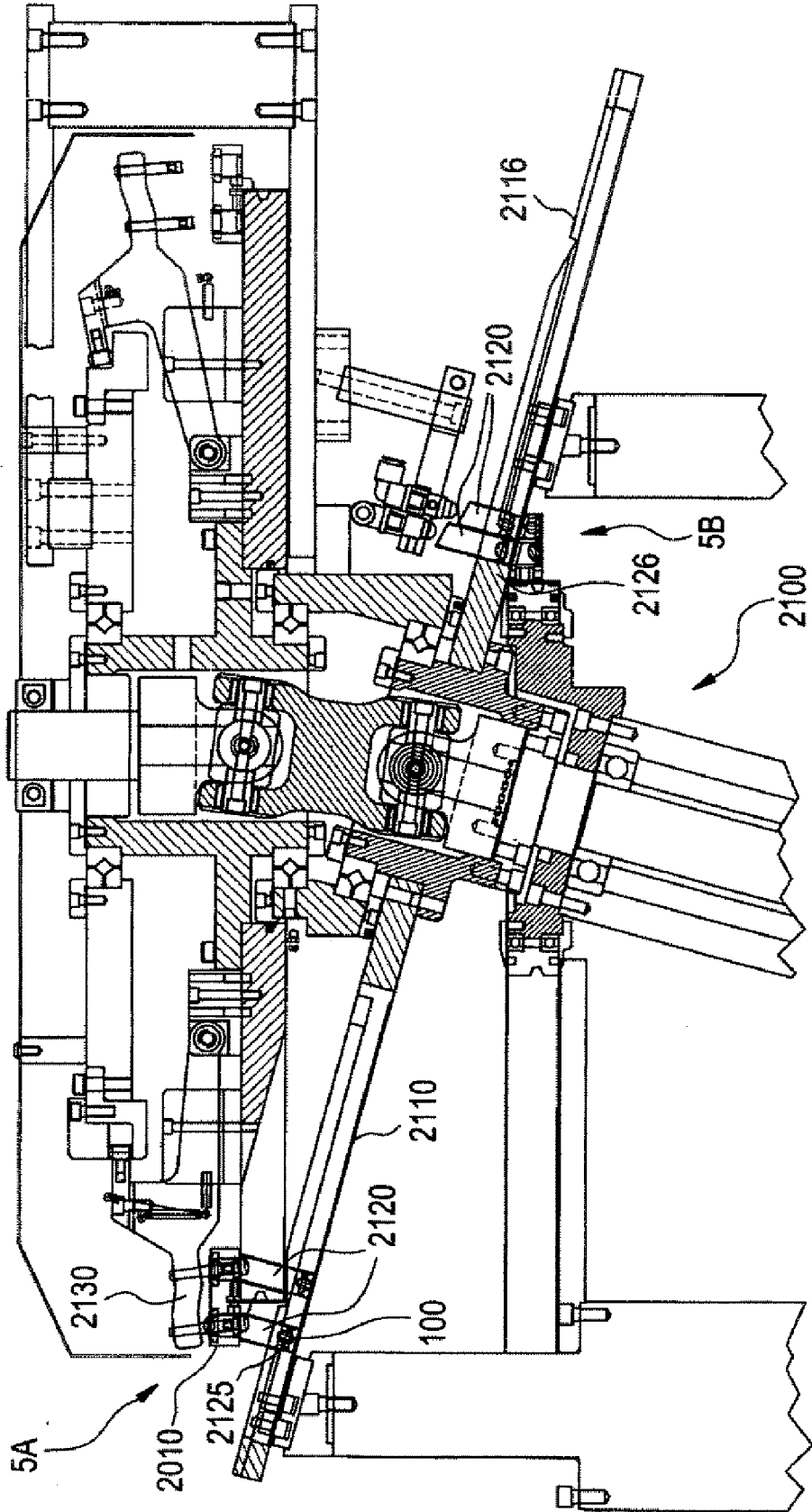


FIG. 5



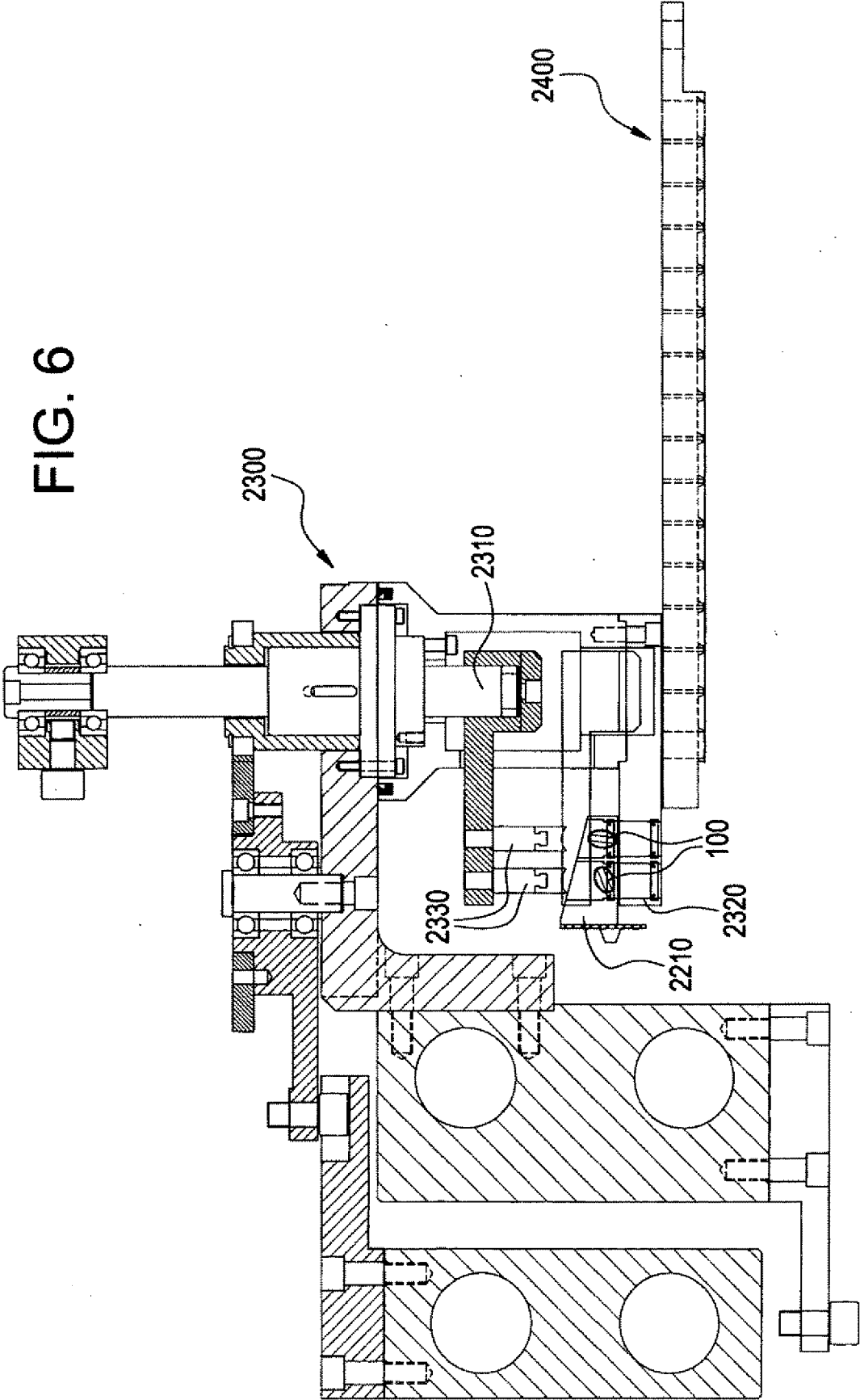


FIG. 7

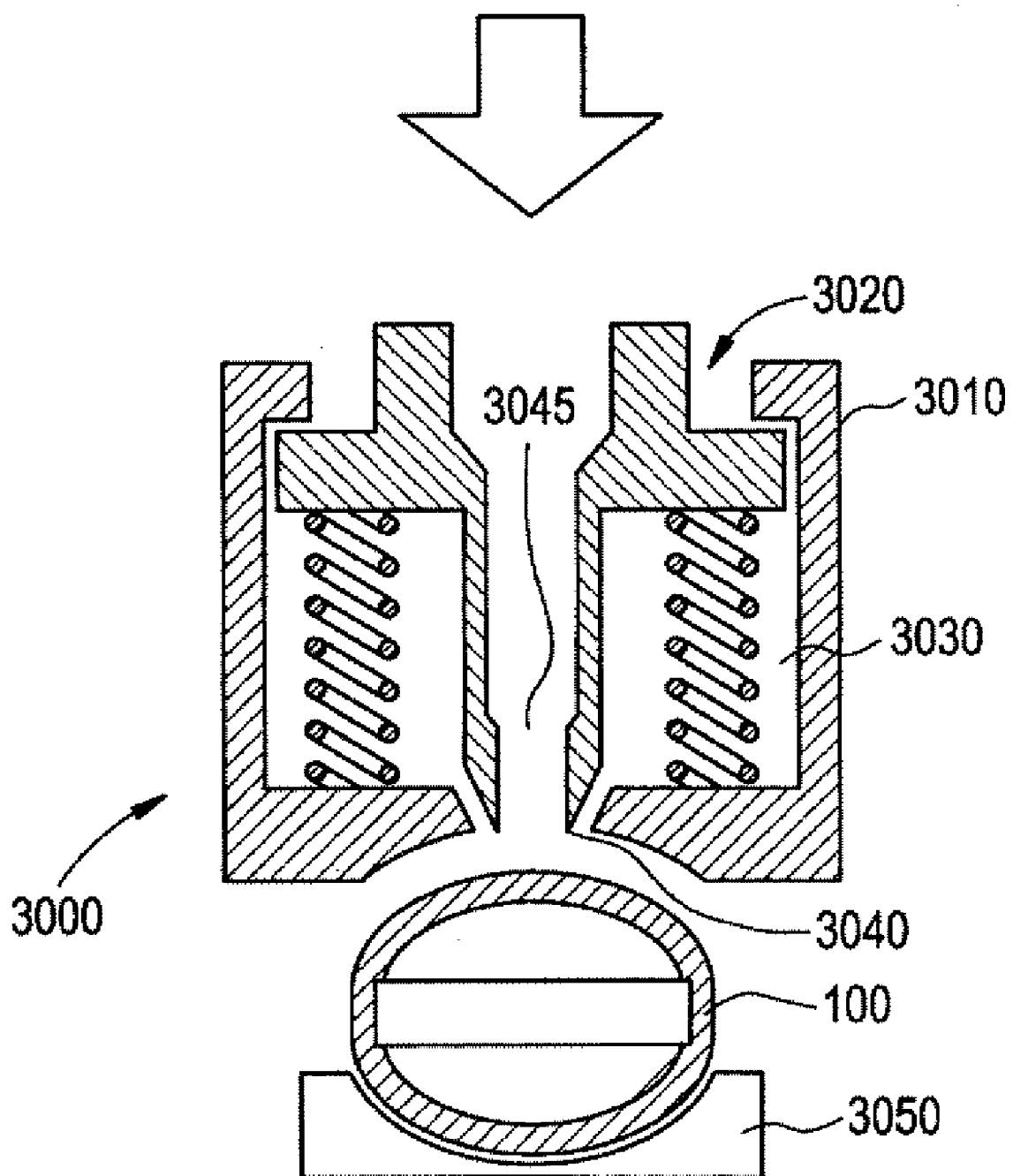


FIG. 8

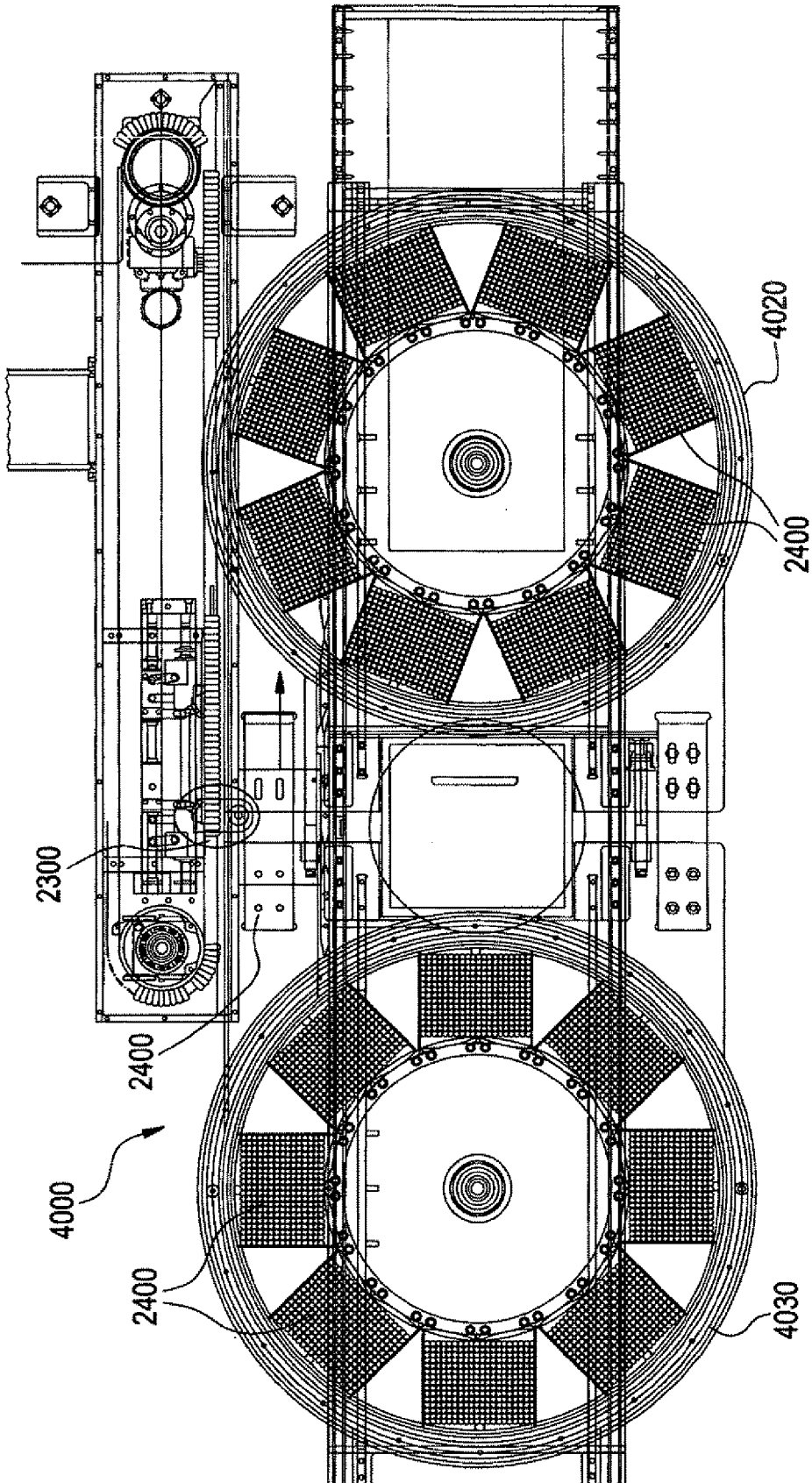
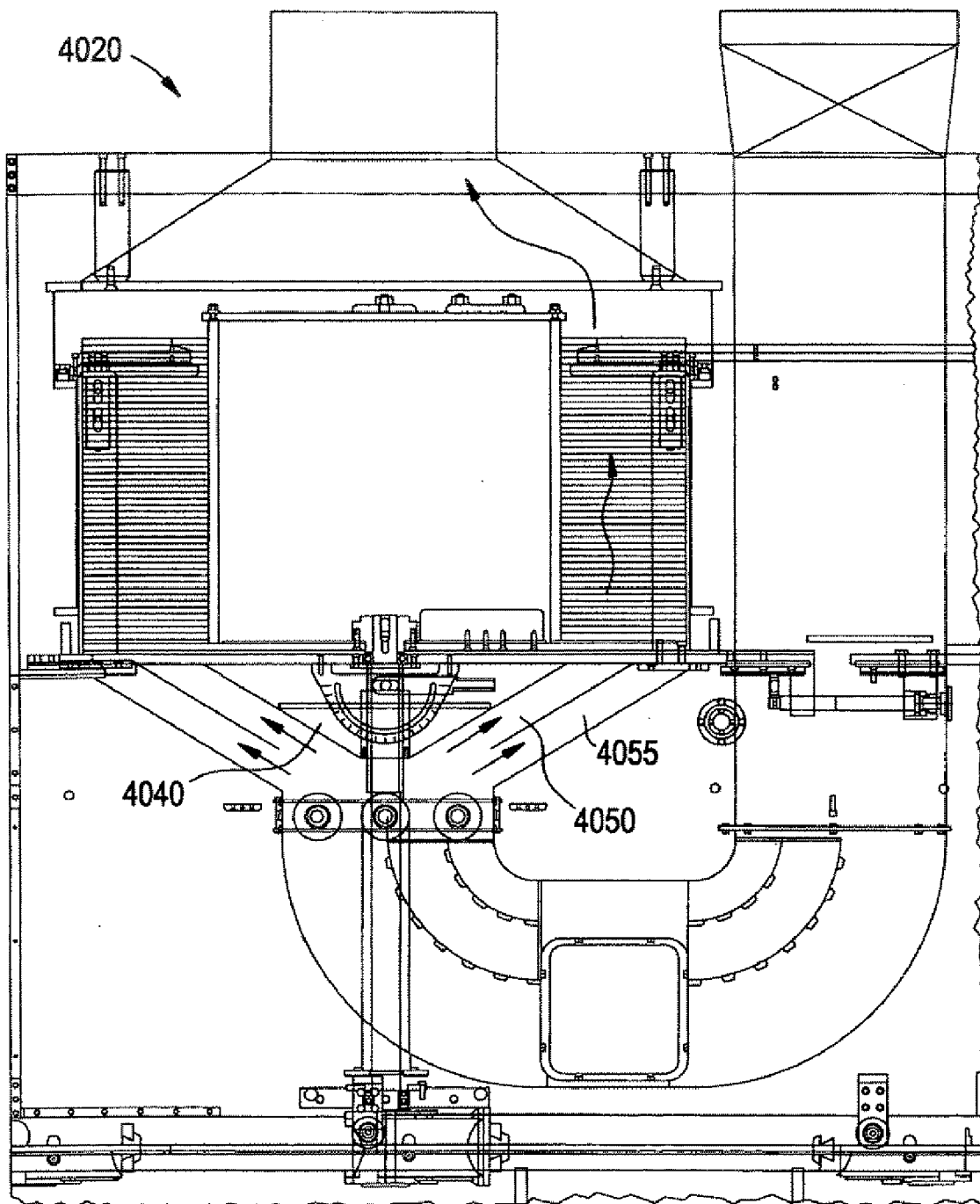


FIG. 9



SYSTEM AND PROCESS FOR PROVIDING AT LEAST ONE OPENING IN DOSAGE FORMS

SUMMARY OF THE INVENTION

[0001] The present invention relates to apparatus, methods, and processes for making solid dosage forms comprising at least one active ingredient, a core and shell configuration, wherein the shell comprises a hardenable material, such as a thermal-gelling polymer, for example gelatin; and the shell is provided with at least one opening. The opening(s) are formed while the shell is still in a softened state.

BACKGROUND

[0002] A variety of dosage forms, such as tablets, capsules and gelpcaps are known in the pharmaceutical arts. Tablets generally refer to relatively compressed powders in various shapes. One type of elongated, capsule-shaped tablet is commonly referred to as a "caplet." Capsules are typically manufactured using a two piece gelatin shell formed by dipping a steel rod into gelatin so that the gelatin coats the end of the rod. The gelatin is hardened into two half-shells and the rod extracted. The hardened half-shells are then filled with a powder and the two halves joined together to form the capsule.

[0003] Dosage forms having core and shell portions are well-known. Outer shell portions are provided over active cores for many reasons. The shell can, for example, provide taste-masking of bitter actives, modify the dissolution profile, delay the delivery thereof, or provide means for identifying the sources of goods.

[0004] Gelatin-coated tablets, commonly known as geltabs and gelpcaps, are an improvement on gelatin capsules and typically comprise a tablet coated with a gelatin shell. Several well known examples of gelpcaps are McNeil Consumer Healthcare's acetaminophen based products sold under the trade name Tylenol®. U.S. Pat. Nos. 4,820,524; 5,538,125; 5,228,916; 5,436,026; 5,679,406; 5,415,868; 5,824,338; 5,089,270; 5,213,738; 5,464,631; 5,795,588; 5,511,361; 5,609,010; 5,200,191; 5,459,983; 5,146,730; 5,942,034 describe geltabs and gelpcaps and methods and apparatuses for making them. Conventional methods for forming gelpcaps are generally performed in a batchwise manner using a number of stand alone machines operating independently. Such batch processes typically include the unit operations of granulating, drying, blending, compacting (e.g., in a tablet press), gelatin dipping or enrobing, drying, and printing.

[0005] Another method of producing gelatin coated dosage forms is via an enrobing process wherein two separate films made of gelatinous material are applied to opposite sides of a tablet by a pair of rotary dies, as disclosed for example, in U.S. Pat. Nos. 5,146,730 and 5,459,983. Film formulations for producing gelpcaps and geltabs prepared via enrobing methods such as those disclosed in U.S. Pat. Nos. 5,146,730 and 5,459,983 typically comprise a water-based gelatin preparation having about 45% gelatin and about 9% plasticizer (glycerin and/or sorbitol) by weight. Glycerin and sorbitol can be used as single plasticizers or in combination with each other. In addition, other sugars and poly-hydroxy compounds can be used as additives and plasticizers. If a tamper-evident gelatin-coated medicine tablet is the desired end product, then the ratio of plasticizer to gelatin in the gelatin formulation should be in the range of about 1:5.

[0006] Certain dosage forms containing apertures or embossments are known. For instance, "osmotic pump" dosage forms for the administration of pharmaceutically active ingredients are known in the art. They typically comprise a semipermeable wall that surrounds a reservoir containing drug. The wall is permeable to the passage of an external fluid, impermeable to the passage of drug, and has a passageway through the semipermeable wall for delivering drug from the osmotic system. For example, U.S. Pat. No. 4,576,604 discloses an osmotic device comprising a drug compartment surrounded by a wall (coating) having a passageway therein. The wall may comprise an immediate release dose of drug, and the inner drug compartment may comprise a sustained release dose of drug.

[0007] U.S. Pat. No. 4,449,983 discloses another osmotic device comprising two separately housed drugs that are separately dispensed from the device. The device comprises two compartments, one for each drug, separated by a partition. Each compartment has an orifice for communicating with the exterior of the device.

[0008] U.S. Pat. No. 3,823,816 discloses a water-soluble package provided in the form of a hard shell capsule filled with powder, granules, or the like. The capsule is apertured, and a water-soluble barrier film covers the apertures. The film is more water soluble than the capsule so that when the package contacts water, the film rather than the capsule dissolves first, exposing the contents for dissolution and/or release by way of the apertures while the capsule is intact.

[0009] U.S. Pat. No. 5,256,440 relates to an intagliated dosage form comprising one or more circumscribed regions on its surface. The dosage form is spray coated with a latex polymer. When placed in an environment of use, the latex coating within the circumscribed region is reproducibly expelled, leaving a coated core tablet with a predefined aperture, which exposes a discrete portion of the core surface to the environment of use.

SUMMARY OF THE INVENTION

[0010] The present invention is directed to a system for manufacturing one or more dosage forms having a core and a shell that surrounds at least a portion of the core and having one or more openings. The system comprises a shell-forming module that overcoats at least a portion of the core with a soft shell, a post-coating transfer module for conveying a soft dosage form from the shell-forming module, and a punch assembly for producing at least one opening in the soft shell. The system can further comprise a hardening module for substantially solidifying the shell.

[0011] The hardening module can employ a drying module for substantially eliminating moisture from the shell. The post-coating transfer module can include a substrate velocity modifying means that enables a controlled transfer of individual substrates between two unit operations that convey individual substrates at different velocities. The post-coating transfer module can be characterized by having a first dosage form conveyor from the shell-forming module, a substrate velocity modifying means for modifying the velocity of dosage forms received from the first dosage form conveyor and a second dosage form conveyor from the substrate velocity modifying means. A transfer arm can move dosage forms from the second conveyor to a third conveyor into a dryer unit.

[0012] The substrate velocity modifying means can be characterized as having a rotating turret with a plurality of slats for holding individual dosage form carriers. Each slat

preferably comprises two carrier tubes. The carrier tubes can move from the outer periphery of the rotating turret towards the center of the rotating turret. Alternatively, the carrier tubes move closer to one another in a radial direction.

[0013] The soft shell dosage form preferably has a water-content at least 20% greater than its moisture content at equilibrium at 25° C. and 60% relative humidity. The shell can contain one or more gelatin or gelling materials. The average thickness of the shell, excluding uncoated or exposed areas of the core, is preferably in the range from about 100 to about 400 microns. The core comprises at least one active ingredient that can be provided for immediate release. The core can be in the form of a compressed tablet, preferably having a hardness from about 1 to about 30 kp/cm². One or more openings can be provided into or through the shell, each opening can be from about 200 to about 2000 microns in diameter (if circular) or provide similar a similar opening area regardless of the shape of the opening.

[0014] The post-coating transfer module can convey a soft dosage form from the shell-forming module to the punch assembly for producing at least one opening in the soft shell. The punch assembly can be located along the path of the first dosage form conveyor, adjacent to the means for modifying dosage form velocity, along the path of the second conveyor or along the path of the third conveyor.

[0015] The present invention is also directed to a process for making a dosage form having a core and a shell that surrounds at least a portion of the core and having one or more openings. The process comprises providing a shell over at least a portion of the compressed core and providing at least one opening in said shell, wherein the shell is soft at the time the opening is provided in said shell. One or more openings through the shell can contact the core. The soft shell preferably has, at a point in time immediately before one or more openings are provided therein, a water-content at least 20% greater than its moisture content at equilibrium at 25° C. and 60% relative humidity.

[0016] The present invention is particularly advantageous for providing openings through outer coatings comprising gelatin. Dry gelatin, such as that in hard gelatin capsule shells or finished gelcap coatings cannot be ablated using lasers due to scorching. Forming openings by punching while the gelatin is still in a hydrated (soft and deformable) state allows for both an easier punch through and some smoothing of the edges of the punched opening due to cold flow.

BRIEF DESCRIPTION OF DRAWINGS

[0017] FIG. 1 is an exemplary dosage form resulting from the present invention.

[0018] FIG. 2 is a schematic diagram of the processes and systems associated with the present invention.

[0019] FIG. 3 illustrate a soft dosage form conveyor line and a carrier therefore useful for the practice of the present invention.

[0020] FIGS. 4 and 4a illustrate a carrier useful for the practice of the present invention.

[0021] FIG. 5 illustrate a consolidating wheel useful for the practice of the present invention.

[0022] FIG. 6 illustrates a dryer transfer device and a tray capable of containing a plurality of dosage forms useful for the practice of the present invention.

[0023] FIG. 7 illustrates a punch assembly useful for the practice of the present invention.

[0024] FIG. 8 illustrates a drying conveyor mechanism and drying columns for dosage forms.

[0025] FIG. 9 illustrates a distributor for airflow in drying columns useful for the practice of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The present invention is directed to apparatus, methods, and processes for making solid dosage forms comprising at least one active ingredient, a core and shell configuration, wherein the shell comprises a hardenable material, such as a thermal-gelling polymer, for example gelatin; and the shell is provided with at least one opening. The opening(s) are formed using the method of the invention described herein. Certain materials and equipment useful in the practice of the present invention are disclosed and described more fully in U.S. Pat. No. 6,767,200, published U.S. Patent Application 2003-008367 A1, published U.S. Patent Application 2003-0086973 A1, and copending application Ser. No. 10/677,984, all of which are incorporated herein by reference.

[0027] An exemplary dosage form is shown in FIG. 1. Dosage form 100 comprises a core 110, a shell 120 and at least one opening 130. As used herein, the term “dosage form” applies to any solid object or semi-solid composition designed to contain a specific predetermined amount (dose) of a certain ingredient, for example an active ingredient as defined below. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, mucosal delivery, or subcutaneous implants, or other implanted drug delivery systems; or compositions for delivering minerals, vitamins and other nutraceuticals, oral care agents, flavorants, and the like. Preferably the dosage forms of the present invention are considered to be solid, however they may contain liquid or semi-solid components. In a particularly preferred embodiment, the dosage form is an orally administered system for delivering a pharmaceutical active ingredient to the gastro-intestinal tract of a human.

[0028] Suitable active ingredients for use in this invention include for example pharmaceuticals, minerals, vitamins and other nutraceuticals, oral care agents, flavorants and mixtures thereof. Suitable pharmaceuticals include analgesics, anti-inflammatory agents, antiarthritics, anesthetics, antihistamines, antitussives, antibiotics, anti-infective agents, antivirals, anticoagulants, antidepressants, antidiabetic agents, antiemetics, antiflatulents, antifungals, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, oral contraceptives, diuretics, expectorants, gastrointestinal agents, migraine preparations, motion sickness products, mucolytics, muscle relaxants, osteoporosis preparations, polydimethylsiloxanes, respiratory agents, sleep-aids, urinary tract agents and mixtures thereof.

[0029] In one embodiment of the invention, the active ingredient may be selected from bisacodyl, famotadine, ranitidine, cimetidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, antacids, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0030] In another embodiment, the active ingredient is selected from analgesics, anti-inflammatories, and antipyretics, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), including propionic acid derivatives, e.g. ibuprofen, naproxen, ketoprofen and the like; acetic acid derivatives, e.g. indomethacin, diclofenac, sulindac, tolmetin, and the like;

fenamic acid derivatives, e.g. mefenamic acid, meclofenamic acid, flufenamic acid, and the like; biphenylcarbodylic acid derivatives, e.g. diflunisal, flufenisal, and the like; and oxicams, e.g. piroxicam, sudoxicam, isoxicam, meloxicam, and the like.

[0031] In one particular embodiment, the active ingredient is selected from propionic acid derivative NSAID, e.g. ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, indoprofen, ketoprofen, fluprofen, piroprofen, carprofen, oxaprozin, pranoprofen, suprofen, and pharmaceutically acceptable salts, derivatives, and combinations thereof. In another particular embodiment of the invention, the active ingredient may be selected from acetaminophen, acetyl salicylic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, diclofenac, cyclobenzaprine, meloxicam, rofecoxib, celecoxib, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0032] In another embodiment of the invention, the active ingredient may be selected from pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan, diphenhydramine, astemizole, terfenadine, fexofenadine, loratadine, desloratadine, cetirizine, mixtures thereof and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0033] The active ingredient or ingredients are present in the dosage form in a therapeutically effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular active ingredient being administered, the bioavailability characteristics of the active ingredient, the dosing regimen, the age and weight of the patient, and other factors must be considered, as known in the art.

[0034] Typically, the dosage form comprises at least about 1 weight percent, preferably, the dosage form comprises at least about 5 weight percent, e.g. at least about 25 weight percent of a combination of one or more active ingredients. In one preferred embodiment, a core comprises a total of at least about 50 weight percent, e.g. at least about 70 weight percent, say at least about 80 weight percent (based on the weight of the core) of one or more active ingredients.

[0035] The active ingredient or ingredients may be present in the dosage form in any form. For example, the active ingredient may be dispersed at the molecular level, e.g. melted or dissolved, within the dosage form, or may be in the form of particles, which in turn may be coated or uncoated. If the active ingredient is in form of particles, the particles (whether coated or uncoated) typically have an average particle size of about 1-2000 microns. In one preferred embodiment, such particles are crystals having an average particle size of about 1-300 microns. In another preferred embodiment, the particles are granules or pellets having an average particle size of about 50-2000 microns, preferably about 50-1000 microns, most preferably about 100-800 microns.

[0036] The core can be any solid form. The core may be prepared by any suitable method, including for example compression or molding. As used herein, "core" refers to a material that is at least partially enveloped or surrounded by another material. Preferably, the core is a self-contained unitary object, such as a tablet or capsule. Typically, the core comprises a solid, for example, the core may be a compressed or molded tablet, hard or soft capsule, suppository, or a confectionery form such as a lozenge, nougat, caramel, fondant, or fat based composition.

[0037] In one embodiment the core is a compressed tablet having a hardness from about 2 to about 30 kp/cm², e.g. from about 6 to about 25 kp/cm². "Hardness" is a term used in the art to describe the diametral breaking strength of either the core or the coated solid dosage form as measured by conventional pharmaceutical hardness testing equipment, such as a Schleuniger Hardness Tester. In order to compare values across different size tablets, the breaking strength must be normalized for the area of the break. This normalized value, expressed in kp/cm², is sometimes referred in the art as tablet tensile strength. Preferably, the cores have a density of at least about 0.9 g/cc, e.g. at least about 1.0 g/cc.

[0038] The core may have one of a variety of different shapes. For example, the core may be shaped as a polyhedron, such as a cube, pyramid, prism, or the like; or may have the geometry of a space figure with some non-flat faces such as a cone, truncated cone, cylinder, sphere, torus, or the like. In certain embodiments, a core has one or more major faces. For example, in embodiments wherein a core is a compressed tablet, the core surface typically has two opposing major faces formed by contact with the upper and lower punch faces in the compression machine. In such embodiments the core surface typically further comprises a "belly-band" located between the two major faces, and formed by contact with the die walls in the compression machine. A core may also comprise a multilayer tablet.

[0039] The core typically comprises active ingredient and a variety of excipients, depending on the method by which it is made.

[0040] In embodiments in which the core is made by compression, suitable excipients include fillers, binders, disintegrants, lubricants, glidants, and the like, as known in the art. In embodiments in which the core is made by compression and additionally confers modified release of an active ingredient contained therein, such core preferably further comprises a release-modifying compressible excipient.

[0041] Suitable fillers for use in making the core by compression include water-soluble compressible carbohydrates such as sugars, which include dextrose, sucrose, maltose, and lactose, sugar-alcohols, which include mannitol, sorbitol, maltitol, xylitol, starch hydrolysates, which include dextrans, and maltodextrins, and the like, water insoluble plastically deforming materials such as microcrystalline cellulose or other cellulosic derivatives, water-insoluble brittle fracture materials such as dicalcium phosphate, tricalcium phosphate and the like and mixtures thereof.

[0042] Suitable binders for making the core by compression include dry binders such as polyvinyl pyrrolidone, hydroxypropylmethylcellulose, and the like; wet binders such as water-soluble polymers, including hydrocolloids such as acacia, alginates, agar, guar gum, locust bean, carrageenan, carboxymethylcellulose, tara, gum arabic, tragacanth, pectin, xanthan, gellan, gelatin, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, inulin, whelan, rhamnan, zooglan, methylan, chitin, cyclodextrin, chitosan, polyvinyl pyrrolidone, celluloses, sucrose, starches, and the like; and derivatives and mixtures thereof.

[0043] Suitable disintegrants for making the core by compression, include sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and the like.

[0044] Suitable lubricants for making the core by compression include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, glycerides and waxes.

[0045] Suitable glidants for making the core by compression, include colloidal silicon dioxide, and the like.

[0046] In certain embodiments, the core or a portion thereof may optionally comprise release modifying excipients as known in the art. Suitable release-modifying compressible excipients for making the core by compression include swellable erodible hydrophilic materials, insoluble edible materials, pH-dependent polymers, and the like.

[0047] Suitable pharmaceutically acceptable adjuvants for making the cores by compression include, preservatives; high intensity sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharin; flavorants; colorants; antioxidants; surfactants; wetting agents; and the like and mixtures thereof.

[0048] In embodiments wherein one or more cores are prepared by compression, a dry blending (i.e. direct compression), or wet granulation process may be employed, as known in the art. In a dry blending (direct compression) method, the active ingredient or ingredients, together with the excipients, are blended in a suitable blender, than transferred directly to a compression machine for pressing into tablets. In a wet granulation method, the active ingredient or ingredients, appropriate excipients, and a solution or dispersion of a wet binder (e.g. an aqueous cooked starch paste, or solution of polyvinyl pyrrolidone) are mixed and granulated. Alternatively a dry binder may be included among the excipients, and the mixture may be granulated with water or other suitable solvent. Suitable apparatuses for wet granulation are known in the art, including low shear, e.g. planetary mixers; high shear mixers; and fluid beds, including rotary fluid beds. The resulting granulated material is dried, and optionally dry-blended with further ingredients, e.g. adjuvants and/or excipients such as for example lubricants, colorants, and the like. The final dry blend is then suitable for compression.

[0049] The dry-blended, or wet granulated, powder mixture is typically compacted into tablets using a rotary compression machine as known in the art, such as for example those commercially available from Fette America Inc., Rockaway, N.J., or Manesty Machines LTD, Liverpool, UK. In a rotary compression machine, a metered volume of powder is filled into a die cavity, which rotates as part of a "die table" from the filling position to a compaction position where the powder is compacted between an upper and a lower punch to an ejection position where the resulting tablet is pushed from the die cavity by the lower punch and guided to an ejection chute by a stationary "take-off" bar.

[0050] In one optional embodiment, the core may be prepared by the compression methods and apparatus described in U.S. Pat. No. 6,767,200, the disclosure of which is incorporated herein by reference. Specifically, the core is made using a rotary compression module comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus having a double row die construction. The dies of the compression module are preferably filled using the assistance of a vacuum, with filters located in or near each die.

[0051] A transfer device can be used to transfer the compressed cores from the compression module to the shell-forming module. Such a transfer device can have the structure shown in published application U.S. 2003-0068367 A1. The transfer device comprises a plurality of transfer units attached

in cantilever fashion to a belt. The transfer device rotates and operates in sync with the compression module and the shell-forming module to which it is coupled.

[0052] A shell surrounds the cores. The shell comprises one or more openings therein. The opening or openings can provide or facilitate formation of a passageway for communication between the core and the exterior of the dosage form. The openings may extend completely through the thickness of the shell to contact or extend into the core, or only partially through the shell. The opening(s), in other words, constitute regions in which the shell material is missing or has been mechanically displaced.

[0053] The shell can be substantially unitary and continuous with the exception of the openings therein, or the shell may comprise multiple portions, e.g. a first shell portion and a second shell portion. In certain embodiments the shell or shell portions are in direct contact with the core. In certain other embodiments, the shell or shell portions are in direct contact with a subcoating that substantially surrounds the core. In embodiments in which the shell comprises a first and second shell portion, at least a first shell portion comprises openings therein.

[0054] In certain embodiments the first shell portion and second shell portion are compositionally different. As used herein, the term "compositionally different" means having features that are readily distinguishable by qualitative or quantitative chemical analysis, physical testing, or visual observation. For example, the first and second shell portions may contain different ingredients, or different levels of the same ingredients, or the first and second shell portions may have different physical or chemical properties, different functional properties, or be visually distinct. Examples of physical or chemical properties that may be different include hydrophilicity, hydrophobicity, hygroscopicity, elasticity, plasticity, tensile strength, crystallinity, and density. Examples of functional properties which may be different include rate and/or extent of dissolution of the material itself or of an active ingredient therefrom, rate of disintegration of the material, permeability to active ingredients, permeability to water or aqueous media, and the like. Examples of visual distinctions include size, shape, topography, or other geometric features, color, hue, opacity, and gloss.

[0055] In one embodiment, the dosage form of the invention comprises: a) a core containing an active ingredient; b) an optional subcoating that substantially covers the core; and c) a shell comprising first and second shell portions residing on the surface of the subcoating, the first shell portion comprising one or more openings, and the first shell portion being readily soluble in gastrointestinal fluids. As used herein, "substantially covers" shall mean at least about 95 percent of the surface area of the core is covered by the subcoating.

[0056] The use of subcoatings is well known in the art and disclosed in, for example, U.S. Pat. No. 3,185,626, which is incorporated by reference herein. Any composition suitable for film-coating a tablet may be used as a subcoating according to the present invention. Examples of suitable subcoatings are disclosed in U.S. Pat. Nos. 4,683,256, 4,543,370, 4,643,894, 4,828,841, 4,725,441, 4,802,924, 5,630,871, and 6,274,162, which are all incorporated by reference herein. Additional suitable subcoatings include one or more of the following ingredients: cellulose ethers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose; polycarbohydrates such as xanthan gum, starch, and maltodextrin; plasticizers including for example,

glycerin, polyethylene glycol, propylene glycol, dibutyl sebacate, triethyl citrate, vegetable oils such as castor oil, surfactants such as Polysorbate-80, sodium lauryl sulfate and dioctyl-sodium sulfosuccinate; polycarbohydrates, pigments, and opacifiers.

[0057] The dried subcoating typically is present in an amount, based upon the dry weight of the core, from about 0 percent to about 5 percent.

[0058] The shell can be formed from a flowable material comprising solid particles suspended in a molten matrix, for example a polymer matrix. The flowable material may be completely molten or in the form of a paste. The flowable material may comprise an active ingredient dissolved in a molten material. The flowable material may comprise solid particles dispersed in a fluid carrier. Alternatively, the flowable material may be made by dissolving a solid in a solvent, which solvent is then evaporated after the molding step.

[0059] In one embodiment, solvent-based or solvent-free molding is performed by thermal cycle molding using the method and apparatus described in published application US 2003-0086973 A1, the disclosure of which is incorporated herein by reference. Thermal cycle molding is performed by injecting a flowable material into a heated molding chamber. The flowable material may comprise active ingredient and a thermoplastic material at a temperature above the set temperature of the thermoplastic material but below the decomposition temperature of active ingredient. The flowable material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[0060] In the thermal cycle molding method and apparatus of published application US 2003-0086973 A1 a thermal cycle shell-forming module having the general configuration shown in FIG. 3 therein is employed. The thermal cycle shell-forming module comprises a rotor around which a plurality of mold units is disposed. The thermal cycle shell-forming module includes a reservoir for holding flowable material. In addition, the thermal cycle shell-forming module is provided with a temperature control system for rapidly heating and cooling the mold units.

[0061] One form of the shell-forming module useful for the practice of this invention comprises center mold assemblies, upper mold assemblies, and lower mold assemblies. Upper mold assemblies and lower mold assemblies mate to form mold cavities having a desired shape, for instance of a core or a shell surrounding one or more cores. As rotor rotates, opposing center and upper mold assemblies or opposing center and lower mold assemblies close. Flowable material, which is heated to a flowable state in reservoir, is injected into the resulting mold cavities. The temperature of the flowable material is then decreased, hardening the flowable material. The mold assemblies open and eject the shell-coated substrate. Preferably the shell is in a somewhat soft or non-brittle state, and will be hardened upon further processing, e.g. drying, etc.

[0062] In another optional embodiment of the invention, the shell is applied to the dosage form using a zero cycle molding apparatus of the general type shown in copending U.S. application Ser. No. 10/677,984 comprising rotatable center mold assemblies, lower mold assemblies and upper mold assemblies. Cores are continuously fed to the mold assemblies. Shell flowable material, which is heated to a flowable state in reservoir, is injected into the mold cavities created by the closed mold assemblies holding the cores. The

mold assemblies open and eject the coated substrates. Shell coating is preferably performed in two steps, each half of the cores being coated separately.

[0063] The primary steps of the present invention are shown in FIG. 2 having a shell-forming module **1000**, a post-coating transfer module **2000**, and a drying module **4000**. As previously described, the coated, hydrated and/or impressionable unfinished dosage form (soft dosage form) **100** is ejected from shell-forming module **1000** using a pin or plunger as an ejection means.

[0064] After ejection, one or more openings **130** are provided in shell **120** prior to subjecting the shell to a hardening step, such as a drying step, or otherwise allowing the shell to cure, set-up or harden. In other words, one or more openings **130** are provided in shell **120** while it is still in its hydrated and/or impressionable state. Hydrated means, for purposes of this application, having a water content at least 20% greater than its moisture content at equilibrium under ambient conditions, e.g. 25° C., 60% relative humidity.

[0065] Gelatin-based films such as those used in certain preferred coatings in the present invention or those used in hard gelatin capsules, for example, typically have a preferred moisture content at equilibrium in the range of 13-16% by weight. Additionally, gelatin capsules are considered soft and likely to distort when the moisture content is equal to or greater than 18% by weight. Hard Capsule Development, pp. 77-78, K. Ridgway (1987).

[0066] Gelation, as used herein, is initiation of formation of a polymeric or interconnecting network in an aqueous or solvent based system in which the polymer(s) are dispersed. Full cure is the highest possible degree of cure for the particular polymeric or hardenable material. Cure, as used herein is as a process for changing the properties, e.g. hardness, deformability, brittleness, elasticity, tensile strength, and the like of a resin or polymer or polymeric mixture or dispersion via chemical reaction, drying, or other physical change. Typically, a resin or polymer will exhibit an increase in viscosity or hardness during the curing process. Consequently, "full cure" would be the point at which the polymer or resin exhibits its greatest viscosity and/or hardness. In embodiments employing thermal gelling materials, impressionable means, for purposes of this application, that the shell coating has passed the point of gelation so that in the absence of external force, the shell retains its shape, but has not achieved full cure. In embodiments employing non-gelling materials, such as non-solvent based melts, impressionable, as used herein means the applied shell or coating or portion thereof has cooled below its melting temperature, so that in the absence of external force, the shell retains its shape, but has not achieved its maximum hardness, i.e. resistance to indentation.

[0067] The term "soft dosage form" shall be used herein to mean a dosage form having a shell coating that is hydrated, impressionable or both.

[0068] In one embodiment, transfer module **2000** comprises a series of conveyors and associated transfer units that move soft dosage form **100** from shell-forming module **1000** to a "punching position" and then onwards to drying module **4000**.

[0069] Post-coating transfer module **2000** receives soft dosage form **100** from shell-forming module **1000**. Transfer module **2000** comprises, in one embodiment, a moving soft dosage form conveyor line **2005** having carriers **2010** shown in FIG. 3. The carriers on soft dosage form conveyor line **2005**

follow a path, that includes one or more portions running along pulley wheels **2006**, and that conforms to a portion of the perimeter of mold units for shell-forming module **1000** and runs at a speed synchronous with shell-forming module **1000**. Pulley wheel **2006** engages each carrier **2010** and is caused to rotate by forces acting on axle **2008**.

[**0070**] Each carrier **2010** has one or more channels **2020** that are larger in diameter than a soft dosage form, and provide an opening through both ends, e.g. top and bottom, of carrier **2010**. See FIGS. **4** and **4a**. Each channel **2020** has an upper liner **2030** and a lower ring **2035**. Upper liner **2030** can be one or more downward-sloped elastomeric rings or alternatively fingers that grip soft dosage form **100**. Upper liner **2030** allows soft dosage form **100** to be ejected from shell-forming module **1000** and pressed into a dosage form compartment **2040** formed by channel **2020** and upper liner **2030**. In a preferred embodiment, each carrier **2010** comprises multiple, for example 2, channels **2020**. Each carrier, excluding upper line **2030** and lower ring **2035**, is preferably made in conventional fashion by machining a selected metallic material. Other materials, such as polymers, could be utilized in machining or molding processes.

[**0071**] In one embodiment, carrier **2010** moves soft dosage forms **100** from shell-forming module **1000** to a consolidating wheel **2100** shown in FIGS. **2** and **5**. Consolidating wheel **2100** slows the speed of and reduces the distance between soft dosage forms **100**. Consolidating wheel **2100** comprises radially oriented slats **2110**, and a plurality of carrier tubes **2120**. Slats **2110** enable carrier tubes **2120** to move in a circular and preferably sloped direction from the receipt of soft dosage forms **100** to ejection thereof. The sloped configuration of consolidating wheel **2100** is a space efficient means for changing the elevation of soft dosage forms **100** but is by no means the only configuration available for this purpose.

[**0072**] Each slat **2110** conveys one or more carrier tube **2120** and more preferably at least two carrier tubes **2120** that are moveable from periphery **2125** to center region **2126** of consolidating wheel **2100** and back again. Carrier tubes **2120**, which are provided on each slat **2110**, move relative to one another and relative to the center of consolidating wheel **2100**. Consolidating wheel **2100** has a radius that is calculated based on the velocity differential between soft dosage forms **100** coming from shell forming module **1000**, and the velocity of soft dosage forms **100** in the subsequent unit operation, or (in embodiments where multiple conveyors are employed to move the dosage forms to the next unit operation) on the subsequent conveyor.

[**0073**] Once carriers **2010** reach a designated point over consolidating wheel **2100**, soft dosage forms **100** are pushed by ejector pin and/or pressurized air through the bottom of dosage form compartment **2040**, into carrier tubes **2120**. One dosage form is positioned in each carrier tube **2120**. Consolidating wheel **2100** rotates as carrier tubes **2120** move from an outer ring or periphery of consolidating wheel **2100** toward the center of consolidating wheel **2100**, thereby effectively reducing the linear velocity and reducing the (circumferential) distance between soft dosage forms **100**. In preferred embodiments employing 2 or more independently movable carrier tubes **2120** per slat **2110**, the radial distance between soft dosage forms **100** is reduced by reducing the distance between the 2 carrier tubes **2120**. Carrier tubes **2120** each have a portion positioned in a groove in slat **2110**, and an attached cam follower portion, positioned in a cam track beneath consolidating wheel **2100**. Carrier tubes **2120** are

caused to move along a groove in slat **2110** toward the center of consolidating wheel **2100** by the path of the cam track as the consolidating wheel rotates.

[**0074**] Consolidating wheel **2100** is capable of modifying the velocity of dosage forms **100** and, as exemplified, comprises an apparatus having a rotating turret and a plurality of slats for holding individual dosage form carriers. Each slat preferably comprises two carrier tubes, wherein the carrier tubes move from the outer periphery of the rotating turret towards the center of the rotating turret. The turret is driven by an engine at a specified speed relative to the associated conveyor systems. The diameter of each carrier tube **2120** is preferably larger than the diameter of the dosage form, e.g. at least about 2 times the thickness or width of the dosage form, yet smaller than one-half the distance between the outer edges of soft dosage form compartments **2040**.

[**0075**] Dosage forms **100** are released from consolidating wheel **2100** and carrier tube **2120** from the end opposite from which dosage forms **100** entered carrier tubes **2120**, into a grouping conveyor line **2200** having grouping carriers **2210**. A section of grouping conveyor line **2200** and a series of carriers **2210** are shown in FIG. **3** and illustrated schematically in FIG. **2**. In a preferred embodiment, each group carrier **2210** comprises multiple, for example 2, dosage form compartments **2220**.

[**0076**] Grouping conveyor line **2200** moves carriers **2210** along a path more slowly than carriers **2010** of soft dosage form conveyor line **2005**. In a preferred embodiment, grouping conveyor line **2200** moves the pairs of soft dosage forms **100** into position for further transfer by a dryer transfer device **2300** into a tray **2400** capable of containing a plurality of dosage forms, shown in FIG. **6**, for example 20 rows of 15 dosage forms, and to further slow their velocity. Tray **2400** is commercially available.

[**0077**] A dryer transfer device **2300**, such as a walking beam, follows along grouping conveyor line **2200** for a period of time at the same speed as dosage form carriers **2210**, receives a specified number (for example 15) of dosage forms **100** from carriers **2210**, stops moving forward, and pivots to place dosage forms **100** into one or more rows of tray **2400**. Dryer transfer device **2300** receives dosage forms **100** from each carrier **2210** preferably by action of a mechanical punch **2310** and/or forced air. Mechanical punch **2310** forces dosage form **100** from carrier **2210** into transfer carrier **2320**. A plurality of filled transfer carriers **2320** pivot over tray **2400** along with individual punches **2330**. Once in position over a desired location in tray **2400**, individual punches **2330** force dosage forms **100** into the underlying tray **2400**.

[**0078**] Dryer transfer device **2300** functions to further decrease the velocity of the dosage forms as it places a plurality, e.g. 15 at a time, into drying trays **2400**. Tray **2400** is conveyed along a dryer conveyor line **4010** from that point into a drying system **4000**. Dryer transfer device **2300**, then returns to its original position, resumes moving along with carriers **2210**, and repeats the process. The process is repeated for each tray **2400** such that optimally each position within every row contains a single dosage form **100**.

[**0079**] In review, one embodiment of the post-coating transfer module **2000** has been described above as having soft dosage form conveyor line **2005**, consolidating wheel **2100**, grouping conveyor line **2200** and dryer transfer device **2300**. Each of the foregoing conveyor lines can be broken up into multiple parallel or series segments. Similarly, multiple consolidating wheels **2100** could be used in series or parallel for

its intended purposes. One advantage of the post-coating transfer module described above is the individual handling of soft dosage form **100** from beginning to end. Such handling is important when working with soft dosage forms. Without departing from individual handling, it would be possible to utilize a series of conveyor lines having sequentially slower speeds.

[0080] A punch assembly **3000** is preferably provided before the soft dosage forms **100** enter drying module **4000**. However, punch assembly could be provided along dryer conveyor line **4010**. Punch assembly **3000** punches the desired opening(s) **130** in soft shell **120**. Dosage form **100** is positioned under punch assembly **3000** shown in FIG. 7. Punch assembly **3000** can be positioned substantially anywhere along the path of the post-coating transfer module **2000**.

[0081] Two exemplary non-limiting locations are shown in FIG. 2. In one embodiment, punch assembly **3000** is positioned along soft dosage form conveyor line **2005** as embodiment A. Alternatively, punch assembly **3000** is positioned along grouping conveyor line **2200** as embodiment B. In yet another embodiment, punch assembly **3000** is positioned along a further rotary conveying module between grouping conveyor line **2200** and dryer transfer device **2300**. In yet another embodiment, one or a plurality of punch assemblies **3000** are positioned on dryer transfer device **2300**, e.g. on a "walking beam". Those skilled in the art will recognize that ablative methods, such as laser, could be employed to create openings in the soft dosage form at similar points along the path of the post-coating transfer module **2000**.

[0082] Punch assembly **3000** comprises a spring-loaded stripper plate **3010**, a punch **3020**, and a spring **3030**. Stripper plate **3010** prevents soft dosage form **100** from being removed from its carrier and helps prevent the shell from peeling back from the core during punching. For embodiments A and B noted above, either carrier plate **2010** or grouping carrier **2210** conveys dosage form **100** into the punching position. Dosage form **100** is carried along in a dosage compartment and retained in position due to frictional engagement with an inner elastomeric ring or set of rings. Elastomeric rings provide sufficient frictional force to overcome the force of gravity and retain dosage forms in position during movement.

[0083] Punch **3020** includes a punch tip **3040** that can have the exterior shape of the desired opening and an interior bore **3045** that is shaped to allow for the cut-out shell pieces to be pushed up through the center of the punch. A vacuum can be provided to assist in the removal of material from interior bore **3045** during and/or after the cutting operation. It is not desirable for dosage forms **100** to be released from the carriers during the punching operation. Stripper plate **3010** prevents any movement up and out from the carrier.

[0084] As punch **3020** moves into a striking position, a dosage form support plate **3050** moves into the channel containing dosage form **100**. Dosage form support plate **3050** prevents dosage form **100** from being ejected from the carrier due to the force of punch **3020** and optionally reposition dosage form **100** to expose a portion to be struck. Spring **3030** provides tension to hold the stripper plate in place against the portion of the shell that is not being removed, as the punch pulls back and removes a portion of the shell covering to create opening **130**.

[0085] Punch **3020** and dosage form support plate **3050** may be activated and caused to move by a variety of known mechanical means. In one embodiment, punch **3020** and sup-

port plate **3050** are squeezed together between compression rollers similarly to the upper and lower punches on a rotary tablet press. The same mechanical punch activating means moves punch **3020** back to its original position after the opening(s) is formed. In one optional embodiment, dosage form support plate **3050**, may be replaced by a second punch assembly **3000** comprising second punch **3020**, stripper plate **3010**, and spring **3030**, in order to simultaneously create openings on both faces of the soft dosage form. In this embodiment, simultaneous punch assemblies provide opposing forces that prevent any movement of soft dosage form **100** in the carrier. In a still further embodiment, sequential and opposing combinations of punch assemblies and dosage form support plates are utilized to provide openings on the same and/or opposite faces of soft dosage form **100**.

[0086] In embodiments resulting in openings having substantially rounded portions, punch **3030** can be rotated for a portion of a circle during punching to utilize horizontal shear force to supplement the downward forces acting to cut the shell. Each opening may have dimensions, e.g., length, width, or diameter, in the range of about 0.1% to about 100%, of the diameter of the dosage form, or of any dimension (e.g. diameter, length, or width) of a major face of the dosage form. The diameter or width of each opening is preferably from about 0.5% to about 5% of the diameter of the dosage form, or of any dimension (e.g. diameter, length, or width) of a major face of the dosage form. In certain embodiments the diameter or width of the openings may range from about 200 to about 2000 microns. The length of the openings may range from about 1% to about 100% of the diameter of the dosage form, or of the diameter of a major face of the dosage form. In certain particular embodiments, the length or diameter of a major face of the dosage form is from about 10,000 to about 20,000 microns. In one particular embodiment, the length of the openings is from about 100 to about 20,000 microns.

[0087] The depth of the openings is typically from about 75% to about 125% of the thickness of the shell at the location of the openings. Greater than 100% thickness means that the opening is provided entirely through the shell and any optional intermediate layers, and into the core. Less than 100% means that the "opening" does not extend entirely through the shell but forms an indentation or pressed indentation. In certain embodiments, the thickness of the shell at the location of the openings typically ranges from about 20 to about 800 microns, e.g. from about 100 to about 400 microns. In one particular embodiment, the depth of the openings is from about 75 to about 400 microns. If a plurality of openings is present, they are typically spaced from one another by at least about one half, e.g. at least about one, times the smallest dimension of the smallest opening. The openings may have a variety of shapes, or be arranged in a variety of different patterns, and may have similar or different sizes.

[0088] In one embodiment, the size of the openings is small enough to prevent the core from being tasted, yet the number of openings is large enough to provide communication between a certain percentage of surface area of the core and the exterior of the dosage form.

[0089] Drying system **4000** comprises a drying conveyor mechanism **4010** for trays **2400**, each carrying a plurality (e.g. 15x20) of soft dosage forms **100**. Drying conveyor mechanism conveys trays **2400** containing a plurality of dosage forms **100** through first (ascending) and second (descending) dryer columns **4020** and **4030** shown in FIG. 8. Drying conveyor mechanism follows a path that spirals upward

through an ascending dryer column **4020**, moves horizontally to descending dryer column **4030** then spirals downward through descending dryer column **4030**. Trays **2400** discharge dried dosage forms and ultimately return to receive soft dosage forms **100** from dryer transfer device **2300**.

[0090] Air flows from the bottom to the top of drying system **4000**, advantageously providing the driest air to the wettest dosage forms entering the bottom of ascending dryer column **4020**, and to the driest dosage forms as they exit from the bottom of descending dryer column **4030**. Air entering ascending dryer column **4020** and descending dryer column **4030** is distributed via a distributor **4040** comprising concentric cones **4050** and **4055**. Distributor **4040** is moveable in the vertical direction to modulate the flow of air through concentric cones **4050** and **4055** by restricting or increasing the flow of air through inner cone **4050** and consequently causing outer cone **4055** to receive more or less air, respectively. Concentric cones **4050** and **4055** direct a portion of the airflow toward the periphery of the columns in order to promote more even drying across the entire tray area.

1-24. (canceled)

25. A process for making a dosage form that comprises a core and a shell surrounding at least a portion of the core and having one or more openings comprising:

- a) providing a shell over at least a portion of the compressed core; and
- b) providing at least one opening in said shell, wherein the shell is soft at the time the opening is provided in said shell.

26. The process according to claim **25**, wherein one or more openings contact the core.

27. The process according to claim **25**, wherein the soft shell has a water content at least 20% greater than its moisture content at equilibrium at 25° C. and 60% relative humidity.

28. The process according to claim **25**, wherein the core comprises at least one active ingredient.

29. The process according to claim **28**, wherein the dosage form provides for immediate release of at least one active ingredient contained in the core.

30. The process according to claim **25**, wherein the core comprises a compressed tablet.

31. The process according to claim **25**, wherein the compressed tablet has a hardness from about 1 to about 30 kp/cm².

32. The process according to claim **25**, wherein the shell comprises gelatin.

33. The process according to claim **25**, wherein the average thickness of the shell, excluding uncoated or exposed areas, is in the range from about 100 to about 400 microns.

34. The process according to claim **25**, wherein the diameter or width of the one or more openings is from about 200 to about 2000 microns.

35. The process according to claim **26**, wherein the soft shell has a water content at least 20% greater than its moisture content at equilibrium at 25° C. and 60% relative humidity.

36. The process according to claim **26**, wherein the core comprises at least one active ingredient.

37. The process according to claim **36**, wherein the dosage form provides for immediate release of at least one active ingredient contained in the core.

38. The process according to claim **26**, wherein the core comprises a compressed tablet.

39. The process according to claim **26**, wherein the compressed tablet has a hardness from about 1 to about 30 kp/cm².

40. The process according to claim **26**, wherein the shell comprises gelatin.

41. The process according to claim **26**, wherein the average thickness of the shell, excluding uncoated or exposed areas, is in the range from about 100 to about 400 microns.

42. The process according to claim **26**, wherein the diameter or width of the one or more openings is from about 200 to about 2000 microns.

43. The process according to claim **29**, wherein the average thickness of the shell, excluding uncoated or exposed areas, is in the range from about 100 to about 400 microns.

44. The process according to claim **37**, wherein the diameter or width of the one or more openings is from about 200 to about 2000 microns.

* * * * *