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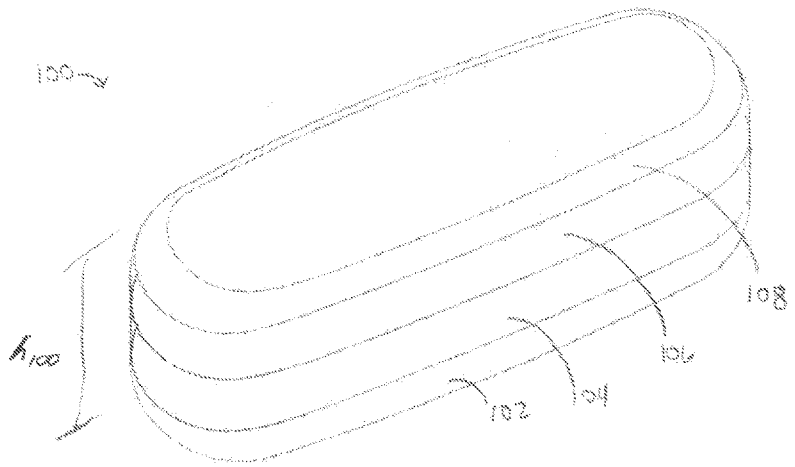
FIG. 3



(57) Abstract: 3D printed functional dosage forms, and methods for making thereof are disclosed. In one aspect of the disclosure, a dosage form is presented that includes an outer shell printed from a first material and at least one inner core containing an active pharmaceutical ingredient (API) disposed within the outer shell. The dosage form includes an opening structure extending from an outer surface of the outer shell to the at least one inner core. The dosage form may include a plurality of pH sensitive mucoadhesive projections printed from a third material and extending from the outer shell. The dosage form may include a plug printed from the second or third material within the opening structure and can include an outer cap printed over the plug from a fourth material. The dosage form also may include an internal hollow cavity such that the dosage form is buoyant in an aqueous solution.

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[Continued on next page]

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ADDITIVELY MANUFACTURED FUNCTIONAL DOSAGE FORMS

This application is being filed on 30 July 2018, as a PCT International patent application, and claims priority to U.S. Provisional Patent Application No. 62/539,303, filed July 31, 2017, the disclosure of which is hereby incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0001] This application relates to three-dimensionally printed functional dosage forms having at least one active pharmaceutical ingredient, and associated methods.

BACKGROUND

[0002] Traditionally formed and three-dimensionally ("3D") printed drug dosage forms are known. However, administration of traditional solid dosage forms can result in poor bioavailability, especially for APIs having limited solubility. Additionally, the provision of customized dosage forms is difficult and impractical using traditional manufacturing methods. Improved solid dosage forms for controlled and sustained release of APIs are desired.

SUMMARY

[0003] An aspect is a filament for feeding a 3D printer. The filament comprises a substrate material, wherein the substrate material comprises greater than 40 wt% of a water soluble linear polymer; and an active pharmaceutical ingredient (API) integrated into the substrate material.

[0004] Another aspect is a filament for feeding a 3D printer, alone or in combination with the previous filament for feeding a 3D printer, wherein the substrate material is selected from the group consisting of: polyvinyl alcohol (PVA), poly-lactic acid (PLA), PVA copolymer, acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), methoxypolyethylene glycol (MPEG), and combinations thereof.

[0005] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the API comprises an amorphous solid dispersion or a crystalline solid dispersion within the substrate material.

[0006] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the API comprises nano-crystals and the nano-crystals are embedded into the substrate material.

[0007] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the API is covalently linked to the polymer matrix via a biodegradable link.

[0008] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material consists of polyvinyl alcohol and a setting system, and the setting system consists of hydrocolloids or mixture and cations.

[0009] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material contains polyvinyl alcohol in an amount of about 90% to about 97% by weight, water in an amount of about 2% to about 7% by weight, hydrocolloids in an amount of at least about 0.01% by weight, and cations in an amount of about 0.001% to about 5% by weight.

[0010] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material comprises at least one of a copolymer and a plasticizer.

[0011] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material comprises a hydrocolloid and/or a release agent.

[0012] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material is configured for free-radical polymerization.

[0013] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material comprises a monomer, a plasticizer, and a release agent.

[0014] Another aspect is a filament for feeding a 3D printer, alone or in any combination with the previous filaments for feeding a 3D printer, wherein the substrate material comprises the release agent in an amount from about 0.1 wt% to about 3 wt%.

[0015] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous filaments for feeding a 3D printer. The pharmaceutical dosage form comprising: a drug substance dosage containing capsule defining a first container compartment; wherein the capsule is formed out of or comprises layers comprising gelatinized gelatin, HPMC, PVA, PLA, acid labile polymer, anionic copolymers based on methacrylic acid and methyl methacrylate, or Copolymers thereof.

[0016] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or

filaments for feeding a 3D printer, further comprising a drug substance dosage within the first container compartment.

[0017] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the capsule has a wall thickness of between approximately 0.3 mm and approximately 0.5 mm.

[0018] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the capsule comprises: side walls defining the first container compartment, the side walls tapering in a conical shape; an end portion, the end portion being open to the first container compartment; and an opposite end portion, the opposite end portion being closed and comprising a generally hemispherical end wall, the generally hemispherical end wall comprising a central part, the central being generally flat.

[0019] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the generally hemispherical end wall defining an opening for receiving a plug.

[0020] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the drug dosage substance is a formulation comprising an active pharmaceutical ingredient (API), a diluent, a dispersing agent, and a surfactant.

[0021] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the API is CEP-701, the diluent is water, the dispersing agent is PEG-1000, and the surfactant is MYRJ-52.

[0022] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the API is present in the drug dosage substance at about 5 wt%, the diluent or co-solvent is present in the drug dosage substance at about 8 wt%, the dispersing agent is present in the drug dosage substance at about 43.5 wt%, and the surfactant is present in the drug dosage substance at about 43.5 wt%.

[0023] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, further comprising a second container compartment separated from the first container compartment.

[0024] Another aspect is a pharmaceutical dosage form, alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein a portion of the side walls defining the first container compartment has a thickness different than a portion of the side walls defining the second container compartment.

[0025] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous pharmaceutical dosage forms and/or filaments for feeding a 3D printer, the process comprising preheating at least one first component filament material to a temperature above a gelation temperature of the first component filament material; localized and layered dispensing of said gelatinized material through a nozzle to form at least a first part of a capsule, the first part defining a first container compartment; filling the first container compartment with a dosage of at least one pharmaceutically active ingredient, pharmaceutically acceptable excipients, or combinations thereof; and forming at least a second part of the capsule to enclose the first container compartment.

[0026] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer. The process comprises: forming at least a third part of the capsule from the first component filament material, the third part defining a second container compartment.

[0027] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein filling the first container compartment includes dispensing through a nozzle the at least one pharmaceutically active ingredient, pharmaceutically acceptable excipients, or combinations thereof.

[0028] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the first component filament material comprises gelatinized gelatin, HPMC, PVA, PLA, or Copolymers thereof.

[0029] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein localized and layered dispensing of said gelatinized material through a nozzle comprises forming a capsule wall thickness between approximately 0.3 mm to approximately 0.5 mm.

[0030] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein dispensing the first filament material to form a generally conical wall defining the first container compartment, the generally conical wall comprising an end portion, the end portion being open to the first container compartment; and forming a second part of the capsule comprises dispensing the first filament material to form an opposite end portion of the generally conical wall, the second end portion comprising a generally hemispherical wall, the generally hemispherical wall comprising a generally flat central portion.

[0031] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, the process further comprising forming an opening in the generally hemispherical end wall, the opening configured and arranged to receive a plug.

[0032] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the at least one pharmaceutically active ingredient and/or pharmaceutically acceptable excipients is a formulation comprising an active pharmaceutical ingredient (API), a diluent, a dispersing agent, and a surfactant.

[0033] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or

filaments for feeding a 3D printer, wherein the API is CEP-701, the diluent or co-solvent is water, the dispersing agent is PEG-1000, and the surfactant is MYRJ-52.

[0034] Another aspect is a process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process being used alone or in combination with any of the previous processes for forming a capsule and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer, wherein the API is present in the formulation at about 5 wt%, the diluent is present in the formulation at about 8 wt%, the dispersing agent is present in the formulation at about 43.5 wt%, and the surfactant is present in the formulation at about 43.5 wt%.

[0035] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes, the 3D printed functional dosage form comprising a body printed from a first material including a first API, the first material having a density higher than that of water; the body defining at least one internal hollow cavity; and wherein the body is buoyant in aqueous solution.

[0036] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, wherein the at least one internal hollow cavity is a single internal hollow cavity.

[0037] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, wherein the at least one internal hollow cavity includes a plurality of internal hollow cavities.

[0038] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, wherein at least some of the plurality of internal hollow cavities have a generally spherical shape.

[0039] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, wherein the first material comprises: a substrate material, wherein the substrate material comprises greater than about 40 wt% of a water soluble linear polymer; and the active pharmaceutical ingredient (API) is integrated into the substrate material, wherein the API is a BCS Class II compound.

[0040] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, wherein the substrate material is selected from the group consisting of: polyvinyl alcohol (PVA), poly-lactic acid (PLA), PVA copolymer, acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), methoxypolyethylene glycol (MPEG), and combinations thereof.

[0041] Another aspect is a 3D printed functional dosage form being used alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, the 3D printed functional dosage form comprising: a plurality of tablets printed from a first material including an API, each tablet having a diameter of approximately 3 mm or less.

[0042] Another aspect is a 3D printed dispensing device, alone or in combination with any of the previous foregoing 3D printed functional dosage forms and/or pharmaceutical dosage forms and/or filaments for feeding a 3D printer and/or processes for forming a capsule, the 3D printed dispensing device comprising: a handle portion; a body portion connected to the handle portion, the body portion including a plurality of recesses for holding a plurality of dosage forms; and a cover connected to the body portion, the cover being movable with respect to the body to expose a predetermined number of the recesses in the body portion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] Figure 1 is a schematic view of a first example of a 3D printing apparatus suitable for making the functional dosage forms disclosed herein.

[0044] Figure 1A is a schematic view of a variation of the 3D printing apparatus shown in Figure 1.

[0045] Figure 2 is a schematic view of a second example of a 3D printing apparatus suitable for making the functional dosage forms disclosed herein.

[0046] Figure 3 is a schematic perspective view of a first example of a 3D printed functional dosage form including at least one active pharmaceutical ingredient.

[0047] Figure 4 is a top view of the functional dosage form shown in Figure 3.

[0048] Figure 5 is a schematic perspective view of a second example of a 3D printed functional dosage form including at least one active pharmaceutical ingredient.

[0049] Figure 6 is a top view of the functional dosage form shown in Figure 5.

[0050] Figure 7 is a schematic perspective view of a third example of a 3D printed functional dosage form including at least one active pharmaceutical ingredient.

[0051] Figure 8 is a top view of the functional dosage form shown in Figure 7.

[0052] Figure 9 is a schematic perspective view of a fourth example of a 3D printed functional dosage form including at least one active pharmaceutical ingredient.

[0053] Figure 10 is a top view of the functional dosage form shown in Figure 9.

[0054] Figure 11 is a schematic perspective view of a fifth example of a 3D printed functional dosage form including at least one active pharmaceutical ingredient.

[0055] Figure 12 is a top view of the functional dosage form shown in Figure 11.

[0056] Figure 13 is a schematic perspective view of a sixth example of a plurality of 3D printed functional dosage forms including at least one active pharmaceutical ingredient.

[0057] Figure 14 is a schematic top view of the functional dosage form shown in Figure 13 arranged in an array.

[0058] Figure 15 is a schematic perspective view of an array of functional dosage forms including at least one active pharmaceutical ingredient.

[0059] Figure 16 is a schematic perspective exploded view of a dispenser for dispensing the dosage forms shown in Figure 15.

[0060] Figure 17 is a schematic perspective view of the assembled dispenser shown in Figure 16 with the functional dosage forms of Figure 15 inserted therein.

[0061] Figure 17A is a schematic perspective view of an alternative dispenser upon which is printed an array of functional dosage forms including at least one active pharmaceutical ingredient.

[0062] Figure 18 is a schematic top view of multiple examples of functional dosage forms configured as implants for controlled release purposes.

[0063] Figure 19A shows mean area under the curve (AUC) of the blood concentration of CEP-701 post oral dosing in dogs. A is drug powder fill in traditional HPMC capsules, B is micronized drug powder fill in traditional HPMC capsules, and C is CEP-701 formulated solution in traditional HPMC capsules.

[0064] Figure 19B shows dissolution profiles of 3D printed caplets comprising CEP-701 SEDDS core and PVA or PLA shell compared to historical data for HPMC capsules.

[0065] Figure 20A shows dissolution profiles of CEP-701 in SEDDS formulation fill in 3D printed PLA caplets with or without a PVA plug.

[0066] Figure 20B shows one 3D printed PLA caplet configuration having a pH sensitive thin film seal over orifice.

[0067] Figure 20C shows another 3D printed PLA caplet configuration having a thin film seal over orifice with carbonate plug.

[0068] Figure 21A shows dissolution profiles of 3D printed PLA caplet with CEP-701 SEDDS core formulation with and without Eudragit L100-55 seal over 2 mm orifice in SGF.

[0069] Figure 21B shows dissolution profiles of 3D printed PLA caplet with CEP-701 SEDDS core formulation with and without Eudragit L100-55 seal over 2 mm orifice in SIF.

[0070] Figure 22 shows dissolution profile of 3D printed PLA caplets with CEP-701 SEDDS core in 0.5% SLS having either 1 mm or 2 mm diameter orifice.

[0071] Figure 23 shows dissolution release profiles of TEV-50939 (solid line) and carbidopa(dashed line) from dual compartment 3D printed PLA caplets.

[0072] Figure 24 shows dissolution profile of TEV-50939 from gastric retentive 3D printed capsule in SGF.

[0073] Figure 25A shows dissolution profiles of 3D printed PLA caplets with Sumatriptan Succinate core formulation with Eudragit L100-seal over 2 mm orifice in SGF and SIF.

[0074] Figure 25B shows dissolution profiles of 3D printed PLA caplets with Sumatriptan Succinate core formulation with Eudragit EPO/$MgCO_3$ seal over 2 mm orifice in SGF and SIF.

DETAILED DESCRIPTION

[0075] Various embodiments will be described in detail with reference to the drawings, wherein like reference numerals represent like parts and assemblies throughout the several views. Reference to various embodiments does not limit the scope of the claims attached hereto. Additionally, any examples set forth in this specification are not intended to

be limiting and merely set forth some of the many possible embodiments for the appended claims.

[0076] In general terms, this patent relates to pharmaceutical dosage forms prepared via three-dimensional (3D) printing techniques. The use of 3D printers enables the design and manufacture of novel and customized pharmaceutical dosage forms of API's that are not possible using traditional pharmaceutical methods. The use of 3D printing technology allows for the design and production of pharmaceutical dosage forms and provides advantages such as more efficient manufacturing, customizing the structure or composition of the dosage form to provide customized methods of delivering API's, customizing the structure or composition of the dosage form on a patient-by-patient basis or by classes of patients. For example, a three-dimensional printer can generate a dosage form having a customized dose based on patient's age, weight, diagnosis, symptoms, medical history, or other findings. Dosage forms can be any functional form for delivering an API such as capsules, tablets, and caplets. Additionally, the dosage form can have any suitable type of release such as a modified or delayed release of the API, controlled release of the API, immediate release of the API, or combination thereof.

[0077] Whenever appropriate, terms used in the singular also will include the plural and vice versa. For example, use of the terms "a," "and," and "the" include the plural forms as well and mean "one or more" unless stated otherwise or where the context of the related language clearly indicates otherwise. Use of the terms "or," "and," and "and/or" mean "and/or" and encompasses all possible combinations of the associated and listed items unless stated otherwise or where the context of the related language clearly indicates otherwise. The use of "comprise," "comprises," "comprising," "include," "includes," "including," "has," and "having" are interchangeable and not intended to be limiting. As such, these terms do not preclude the presence or absence of additional structures, actions, values,

or functions. For example, the term “including” shall mean “including, but not limited to.” The term “such as” also is not intended to be limiting.

[0078] The terms “substantially” and “approximately” as used herein when referring to measurable values encompass variations due to manufacturing tolerances or other slight variations that do not materially alter operation or functionality of the disclosed embodiments or embodiments otherwise covered by the claims.

[0079] The term "about," as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature, and the like, is meant to encompass variations of 10%, 5%, 1%, 0.5%, or even 0.1% of the specified amount.

[0080] As provided herein, ranges are intended to include, at least, the numbers defining the bounds of the range.

[0081] The acronym “API” represents active pharmaceutical ingredient.

[0082] The term “hydrocolloid” refers to a pharmaceutically acceptable substance that forms a gel in the presence of water. In at least some embodiments, the hydrocolloid is a thickening hydrocolloid, for example, selected from starch, xanthan, guar gum, locust bean gum, gum kayara, gum tragacanth, gum Arabic, and cellulose derivatives. In some embodiments, the hydrocolloid is a gelling hydrocolloid, for example, selected from alginate, pectin, caraggeenan, gelatin, gellan, and agar. In some embodiments, a hydrocolloid is employed in an amount of at least about 0.01% by weight, about 0.01 wt% to about 5 wt%, 0.05 wt% to about 3 wt%, or 0.1 wt% to 2 wt% of the substrate material.

[0083] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of a compound and, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the API compounds disclosed herein are capable of forming

acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. The "pharmaceutically acceptable acids" useful for preparing the pharmaceutically acceptable acid addition salts may be selected from inorganic acids or organic acids. Inorganic acids from which pharmaceutically acceptable acid addition salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which pharmaceutically acceptable acid addition salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In the case wherein the substrate composition comprises an acidic, or other anionic moiety, a "pharmaceutically acceptable cation" may be employed. In some embodiments, the pharmaceutically acceptable cation may be selected from the group consisting of Li^+, Na^+, K^+, Mg^{++}, Ca^{++}, and Zn^{++}. In some embodiments, cations are employed in an amount of about 0.001 wt% to about 5 wt%, 0.01 wt% to about 3 wt%, or about 0.1 wt% to about 2 wt% of the substrate composition.

[0084] The term "plasticizer" refers to a pharmaceutically acceptable substance added to a substrate or core composition to produce or promote plasticity and flexibility and to reduce brittleness. In some embodiments, the plasticizer is derived from United States Pharmacopoeia (USP 35, 2011) (Table 2). In some embodiments, the plasticizer is a hydrophilic plasticizer, for example, selected from glycerin, polyethylene glycols, polyethylene glycol monomethyl ether, propylene glycol, and sorbitol sorbitan solution. In some embodiments, the plasticizer is a hydrophobic plasticizer, for example, selected from acetyl tributyl citrate, acetyl triethyl citrate, castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, triacetin, tributyl citrate, triethyl citrate, methyl salicylate, ethyl salicylate, polyethylene glycol, acetyltributylcitrate, miglyol, hydrogenated oils, propylene glycol, acetyltriethylcitrate, polysorbate, castor oil, oleic acid, dibutylsebacate,

diethylphthalate, acetylated mono- and di-glycerides, or mixtures thereof. In some embodiments, plasticizer in the composition is from 0% to 30% by weight, preferably from 0.5% to 20%, more preferably from 1% to 10%, and most preferably from 1.5% to 5% by weight of the composition.

[0085] The acronym “SEDDS” refers to Self-Emulsifying Drug Delivery System.

[0086] The term “solvent” or “co-solvent” refers to a pharmaceutically acceptable solvent with low toxic potential. In some embodiments, the solvent or co-solvent is a class 3 solvent as described in the European Medicines Agency, 2010. In some embodiments, the solvent or co-solvent is selected from the group consisting of an acid (e.g., acetic acid, formic acid), an alcohol (e.g., 1-butanol, 2-butanol, ethanol, 2-methyl-1-butanol, 2-methyl-1-propanol, 1-pentanol, 1-propanol, 2-propanol), an ester (e.g., ethyl acetate, ethyl formate, isopropyl acetate, methyl acetate, propyl acetate), an ether (e.g., anisole, tert-butyl methyl ether, ethyl ether), a hydrocarbon (e.g., cumene, heptane, pentane), a ketone (e.g., acetone, methylethyl ketone), methylisobutyl ketone), or other solvent such as dimethylsulfoxide.

[0087] The term "therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease or condition, is sufficient to effect such treatment for the disease or condition. The "therapeutically effective amount" can vary depending on the compound, the disease and its severity, and the condition, age, weight, gender etc. of the subject to be treated.

[0088] The terms "treating" or "treatment" of a disease state or condition includes: (i) preventing the disease state or condition, i.e., causing the clinical symptoms of the disease state or condition not to develop in a subject that may be exposed to or predisposed to the disease state or condition, but does not yet experience or display symptoms of the disease state or condition, (ii) inhibiting the disease state or condition, i.e., arresting the development of the disease state or condition or its clinical symptoms, or

(iii) relieving the disease state or condition, i.e., causing temporary or permanent regression of the disease state or condition or its clinical symptoms.

[0089] The term “subject”, or “patient”, refers to an animal, for example a mammal, who is the object of treatment. Preferably, the patient is a human. The subject, or patient, may be either male or female.

[0090] The phrase "pharmaceutically acceptable excipient" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent or co-solvent, or solvent. Each excipient must be acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, sucrose, galactose, fructose, xylose, maltose, trehalose, sorbitol, mannitol, maltodextrins, raffinose, stachyose, fructo-oligosaccharides; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, castor oil, corn oil, Peceol®, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; (21) silica gel; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[0091] Unless otherwise specified, a value percent (%) refers to percent by weight, or wt%.

[0092] The 3D printed compositions may be formulated for any route of administration, in particular for oral, rectal, intravaginal, subcutaneous, intramuscular, or intranasal administration. The compositions may be formulated in any solid conventional form, for example, as tablets, capsules, caplets, and having a core composition comprising solutions, suspensions, dispersions, solid dispersions, syrups, gels, and emulsions.

[0093] The functional dosage forms disclosed herein may be printed via a variety of techniques, all of which may be referred to herein generically as 3D printing or additive manufacturing. Many approaches for three-dimensional printing are possible, such as printing with filaments, which heats the filament to melt it; or direct printing, which typically requires less heat than printing from a filament. Some examples of 3D printing methods or techniques include fused filament fabrication (FFF), also referred to as fused deposition modeling (FDM), in which filaments of material are heated and then extruded to deposit layers of material; hot melt extrusion (HME); binder jetting, which does not use heat and maybe advantageous if certain API's are too sensitive to heat; selective layer sintering (SLS) in which laser pulses trace the outline of an object in small particles causing the particles to heat and fuse together in a solid or semisolid form; vat polymerization or stereolithography (SLA) in which successive layers of fluid are hardened using lasers or ultraviolet rays; and polyjet printing in which droplets of material is deposited in layers and then cured with ultraviolet light. Curing during the printing process can occur at different stages during the printing process. During polyjet printing, for example, curing can occur after each layer is deposited, after a partial layer has been deposited, or even after multiple layers have been deposited. Additionally, 3D printing can include 3D printing and two-dimensional (2D) printing or additive manufacturing in which two-dimensional layers are repeatedly printed until a three-dimensional object is formed. For example, inkjet or polyjet printing of dosage forms as disclosed herein can use additive manufacturing techniques in which layers of material are deposited onto a build tray such as a template or other substrate. Some embodiments of an apparatus for

printing dosage forms might use a combination of two or more of the printing methods disclosed herein. Additionally, 3D printing of dosage forms as disclosed herein can be performed on a large scale, on a smaller scale using desktop 3D printers, or even in kiosks located at pharmacies or other convenient locations.

[0094] Referring to Figure 1, an exemplary apparatus 1 for making functional dosage forms via fused filament fabrication (FFF) is presented. Fused filament fabrication utilizes one or more mobile heated extruder heads 2 that are each fed by a continuous filament 20 of thermoplastic material. Once the filament 20 enters the extruder head 2, the filament is heated above its melting temperature (e.g. greater than 100°C) and forced out of a nozzle 3 of the extruder head 2 where the material is deposited in a predetermined fashion. The extruder head 2 is moved by an electronic controller 4 in successive horizontal planes to form a 3D object, such as the disclosed functional dosage forms. Because the filament(s) are heated to melting temperature, even if for only a short period of time, a consideration when selecting the filament materials and API's is the ability of the API to maintain its desired properties through the heating and extrusion process. Figure 1A shows a variation of the apparatus 1 in which two printer heads 2 are provided that are each fed from a continuous filament 20 of thermoplastic material. As shown, the filaments 20 are each wound on a spool. In alternative embodiments, one or more mobile heated extruders can be fed by a non-filament material, such as pellets via a hopper or feed system. Referring to Figure 2, other alternative embodiments of a 3D printing apparatus 10 for making functional dosage forms have inkjet or polyjet printing heads 12 for printing or fabrication of dosage forms.

[0095] In some applications, more than one 3D printing technique may be utilized to form a single dosage form. In some applications, a functional dosage form can be printed from a single material, as shown in the example presented at Figure 1. In other applications, a functional dosage form can be created from multiple materials. For example, a multi-head extruder can

be utilized to form a functional dosage form, from two or more separate filaments. For example, a dual-head extruder can 3D print a functional dosage form, for example a polypill, having alternating regions of a first material and a second different material, as discussed in more detail herein including with reference to Figures 3 and 4.

[0096] In at least some embodiments, a 3D printed dosage form is prepared from a substrate composition comprising a thermoplastic material. In at least some embodiments the thermoplastic material is selected from the group consisting of a hydrophilic polymer, a hydrophobic polymer, a swellable polymer, a non-swellable polymer, a porous polymer, a non-porous polymer, an erodible polymer, a non-erodible polymer. In at least some embodiments, the thermoplastic material is selected from the group consisting of polyvinyl caprolactam-polyvinyl acetate- polyethylene glycol graft copolymer 57/30/13 (e.g., SOLUPLUS®), polyvinylpyrrolidone- co-vinyl-acetate (PVP- VA), polyvinylpyrrolidone-polyvinyl acetate copolymer (PVP-VA) 60/40, polyvinylpyrrolidone (PVP), polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) 80/20, polyethylene glycol-polyvinyl alcohol graft copolymer 25/75, Kollicoat™ IR-polyvinyl alcohol 60/40, polyvinyl alcohol (PVA or PV-OH), polyvinyl acetate) (PVAc), poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1 :2: 1, poly(dimethylaminoethylmethacrylate-co-methacrylic esters), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride), poly(methyl acrylate-co- methyl methacrylate-co-methacrylic acid)7:3 : 1, poly(methacrylic acid-co- methylmethacrylate) 1 :2, poly(methacylic acid-co-ethyl acrylate) 1 : 1, poly(methacylic acid- co-methyl methacrylate) 1 : 1, poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), hyperbranched polyesteramide, hydroxypropyl methylcellulose phthalate, hypromellose phthalate, hydroxypropyl methylcellulose or hypromellose (HPMC), hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate (HPMCAS), poly(lactide-co-glycolide) (PLGA), carbomer, acrylonitrile butadiene styrene (ABS), poly(ethylene-co-vinyl acetate), ethylene-vinyl acetate copolymer, polyethylene (PE), and polycaprolactone

(PCL), hydroxyl propyl cellulose (HPC), Polyoxyl 40 Hydrogenerated Castor Oil, Methyl cellulose (MC), Ethyl cellulose (EC), Poloxamer, hydroxypropyl methylcellulose phthalate (HPMCP), Hydrogenated Castor & Soybean Oil, Glyceryl Palmitostearate, Carnauba Wax, polylactic acid (PLA), polyglycolic acid (PGA), Cellulose acetate butyrate (CAB), Colloidal Silicon, Dioxide, Sucrose, Glucose, Polyvinyl Acetate Phthalate (PVAP) and a combination thereof.

[0097] In some embodiments, the thermoplastic material is formed from one or more, or two or more monomers. In some embodiments, the monomer is selected from lactic acid, glycolic acid, dipentaerythritol, acrylic acid, methacrylic acid, methylmethacrylic acid, acrylonitrile, 1,3-butadiene, styrene, ethylene oxide, vinyl alcohol, vinyl acetate, N-vinylpyrrolidone, beta-glucose, alpha-glucose, ethylene oxide, propylene oxide, metyl vinyl ether, maleic anhydride, N-(2-hydroxypropyl)methacrylamide, caprolactone, and phthalic acid.

[0098] In at least some embodiments, the thermoplastic material is a biodegradable thermoplastic material. In at least some embodiments, the biodegradable thermoplastic material is selected from polylactic acid (PLA), starch/PLA, polycaprolactone, or starch/polycaprolactone. In at least some embodiments, the thermoplastic material is a water soluble thermoplastic material. In at least some embodiments, the water soluble thermoplastic material selected from polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), polyvinyl pyrrolidone-vinyl acetate (PVP-VA), polyvinyl alcohol (PVA), starch-PVA, N-(hydroxypropyl) methacrylamide (HPMA), or divinyl ether-maleic anhydride (DIVEMA).

[0099] In fused filament fabrication applications, the filament(s) for the printer can also be formed advantageously. One exemplary filament material is polylactic acid (PLA, also known as polylactide) which is a biodegradable thermoplastic polymer made from plant starch. One exemplary filament material is polyvinyl alcohol (PVA), a water-soluble filament. One exemplary filament material is acrylonitrile butadiene styrene

(ABS), a petroleum-based thermoplastic. In some applications, the filament can be formed from a pH responsive polymer, such as Eudragit, chitosan, or methylacrylates.

[0100] Various dosage form coatings may be employed for pH sensitive release or time controlled release of 3D printed dosage forms.

[0101] The term "enteric coat" refers to a coat that is stable at the highly acidic pH found in the stomach, but breaks down at a less acidic (relatively more basic) pH. For example, enteric coats will not dissolve in the stomach but they will in the basic pH environment present in the small intestine. Materials used for enteric coatings include polymers such as fatty acids, waxes, shellac, plastics, and plant fibers.

[0102] The term “release agent” refers to an extended release agent. An extended release agent may be used to coat the dosage form, or as a component in the substrate or core composition. In some embodiments, the release agent is selected from the group of cellulose ethers, cellulose esters polymethacrylates, wax, fatty acid, fatty alcohol, polyalkylene glycol, or mixtures thereof. However, any other suitable agent(s) that extends the release of API from the dosage form may also be used.

[0103] Representative examples of such agent includes ethylcellulose powder, aqueous dispersion of ethylcellulose (such as SURELEASE®, AQUACOAT® ECD 30) hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, methylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, cellulose acetate butyrate, cellulose acetate trimellitate, cellulose acetate, polyvinyl alcohol, polyvinyl acetate (such as KOLLICOAT SR 30D), povidone, polyethylene glycol, cetyl alcohol, stearyl alcohol, bees wax, carnauba wax, stearic acid, vinyl pyrrolidone-vinyl acetate copolymer (such as KOLLIDON VA 64, KOLLIDON SR), dimethylaminoethyl

methacrylate and other neutral methacrylic acid esters (such as Eudragit E), methacrylic acid copolymers type A (such as Eudragit L), methacrylic acid copolymers type B (such as Eudragit S), methacrylic acid copolymers type C (such as Eudragit L 30D 55), ammoniomethacrylate copolymers (such as Eudragit RL, Eudragit RS), neutral copolymer of polymethacrylic acid ester (Such as Eudragit NE 30D), or mixtures thereof. In some embodiments, the release agent is employed in an amount from about 0.1 wt% to about 3 wt%.

[0104] The term "Eudragit™ E" is referred to as a pH dependent polymer and, more specifically, an acid labile polymer and may include any dimethylaminoethyl methacrylate copolymers. Examples include Eudragit™ E and Eudragit™ E 100.

[0105] The term "Eudragit™ RL" is referred to as a pH independent polymer and may be any poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride. Examples include Eudragit™ RL, Eudragit™ RL 100, Eudragit™ RL PO, Eudragit™RL 30 D, and Eudragit™ RL 12,5.

[0106] The terms "Eudragit™ NE", "Eudragit™ RS" and "Eudragit™ NM" are referred to as pH independent polymers and may be any neutral copolymer based on ethyl acrylate and methyl methacrylate. Examples include Eudragit™NE 30 D, Eudragit™NE 40 D, and Eudragit™NM 30 D, Eudragit™RS 100, Eudragit™RS PO, Eudragit™RS 30 D, and Eudragit™RS 12,5.

[0107] The terms "Eudragit™L" and "Eudragit™S" are referred to as enteric polymers and may be any anionic copolymers based on methacrylic acid and methyl methacrylate. Examples include Eudragit™L 100, Eudragit™L 12,5, Eudragit™S 12,5 and Eudragit™S 100. The ratio of the free carboxyl groups to the ester groups is approx. 1:1 in Eudragit™L 100 and approx. 1:2 in Eudragit™S 100.

[0108] In at least some embodiments, a 3D printed dosage form is provided having a coating designed to release in a targeted portion of the gastrointestinal system of the subject following oral administration. In at least some embodiments, the Eudragit™ L series may be utilized for release in the duodenum pH>5.5 (e.g., Eudragit™ L30 D-55, Eudragit™ L100-55), or jejunum pH 6-7 (Eudragit® L100, Eudragit™ L12,5). Eudragit™ E series may be utilized for release in the stomach at pH 1-5 (e.g., Eudragit™E100, Eudragit™E12,5, Eudragit™EPO). Eudragit™ S and FS series may be employed for release in the ileum or colon pH>7.0. Eudragit™RL, RS, NE and NM series are time releases, pH independent coatings (e.g., Eudragit™ RL30D, Eudragit®RL PO, Eudragit™RL 100, Eudragit™RL 12,5, Eudragit™RS 30D, Eudragit™ PO, Eudragit™ RS 100, Eudragit™RS 12,5, Eudragit™ NE 30D, Eudragit™NE 40D, Eudragit™ NM 30D).

[0109] Filaments and/or core compositions also may be provided with an API embedded in a polymer matrix, such as polyvinyl alcohol (PVA), poly-lactic acid (PLA), PVA copolymer, acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), methoxypolyethylene glycol (MPEG), etc. For example, filaments can be utilized that are an amorphous or non-amorphous solid dispersion of an API. The API can also be formed as nano-crystals, which are then embedded into filament matrix material, such as PLGA (polylactic-co-glycolic acid). The API also may be covalently linked to the polymer matrix via a biodegradable link. Other approaches for impregnating a polymer matrix with an API also may be utilized.

[0110] Mucoadhesive polymers may be utilized in some dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. The term “mucoadhesive” refers to pharmaceutically acceptable materials that bind to the mucin layer of a biological membrane. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate

the mucus network or tissue crevices. Mucin molecule behaves as anionic polyelectrolytes at neutral pH. At low pH values, such as found in the stomach, sialic acids are protonated and as result, are not charged. Numerous hydroxyl groups of carbohydrates on mucin molecules have the potential to interact with other polymers that can form hydrogen bonds. Mucin molecules are negatively charged at neutral pH due to the presence of carboxylate and sulfate groups. In some embodiments, the mucoadhesive polymer is a synthetic polymer such as poly (acrylic acid) (PAA), hydroxypropyl methylcellulose and poly (methacrylate) derivatives, or naturally occurring polymers such as hyaluronic acid and chitosan.

[0111] Examples of API's suitable for use with the processes and configurations described herein are include BCS class I, II, III and IV API's; CNS API's such as L-Dopa, and C-Dopa; Statins and CSE-inhibitors; beta blockers; diuretics; ACE-antagonists / Sartane; Sildenafil; Phenprocoumon. Biopharmaceutics Classification System (BCS) classes are defined by the U.S. FDA Center for Drug Evaluation and Research (CDER). A BCS Class I drug has high solubility, with high permeability. A BCS class II drug has high permeability, and low solubility. A BCS Class III drug has high solubility and low permeability. A BCS Class IV drug has low solubility and low permeability. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an adminstered dose, based on mass-balance or in comparison to an intravenous reference dose. A drug substance is highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 at 37 °C. BCS classification of certain APIs may be found in FDA.gov, or in WHO Proposal to Waive In Vivo Bioequivalence Requirements for the WHO Model List of Essential Medicines Immediate Release, Solid Oral Dosage Forms, 2005.

[0112] In at least some embodiments, a 3D printed dosage form is provided that includes an effective amount of a BCS Class I API. Examples of BCS Class I API's include one or more of acetylsalicylic acid, allopurinol, amiloride hydrochloride, amitriptyline hydrochloride, amlodipine,

amodiaquine (base), amoxicillin, ascorbic acid, chloroquine phosphate, chloroquine sulfate, diazepam, digoxin, DL-methionine, doxycycline hydrochloride, ethinylestradiol, fluconazole, folic acid, lamivudine, levodopa, carbidopa, levonorgestrel, lithium carbonate, metoprolol, metronidazole, morphine sulfate, nicotinamide, norethisterone, paracetamol, phenobarbital, phenoxymethylpenicillin potassium salt, potassium iodide, prednisolone, primaquine diphosphate, proguanil hydrochloride, promethazine hydrochloride, propranolol hydrochloride, propylthiouracil, pyridoxine hydrochloride, quinine bisulfate, quinine sulfate, ranitidine hydrochloride, riboflavin, pyrazinamide, salbutamol sulfate, sildenafil citrate, stavudine, sumatriptan,valproic acid sodium salt, warfarin sodium salt, and zidovudine.

[0113] In at least some embodiments, a 3D printed dosage form is provided that includes an effective amount of a BCS Class II API. Examples of BCS Class II API's include one or more of aceclofenac, bicalutamide, carbamazepine, carvedilol, clotrimazole, cinnarizine, danazol, dapsone, estradiol, exetimibe glibenclamide, fenofibrate, griseofulvin, ibuprofen, itraconazole, ketoconazole, mefenamic acid, naproxen, nevirapine, nifedipine, nitrofurantoin, nomegestrol acetate, phenytoin sodium salt, piroxicam, praziquantel, rifampicin, sulfamethoxazole, trimethoprim, and verapramil hydrochloride. For BCS class II drugs having high permeability and low solubility the critical process may be drug dissolution.

[0114] In at least some embodiments, a 3D printed dosage form is provided that includes an effective amount of a BCS Class III API. Examples of BCS Class III API's include one or more of abacavir, aciclovir, atenolol, benznidazole, biperiden hydrochloride, captopril, chloramphenicol, cimetidine, glyceryl trinitrate, chlorphenamine hydrogen maleate, chlorpromazine hydrochloride, ciprofloxacin hydrochloride, clomifene citrate, clomipramine hydrochloride, cloxacillin sodium, codeine phosphate, didanosine, enalapril, ergocalciferol, erythromycin stearate, erythromycin succinate, ethambutol hydrochloride, ethambutol, ferrous salt, folic acid, glyceryl trinitrate, hydralazine hydrochloride, hydrochlorothiazide, isoniazid,

isosorbide dinitrate, levamisole hydrochloride, levothyroxine sodium, metformin hydrochloride, methyldopa, metoclopramide hydrochloride, morphine sulfate, neostigmine bromide, nifurtimox, penicillamine, pyrazinamide, ranitidine hydrochloride, thiamine hydrochloride, spironolactone, triclabendazole, and zinc sulfate.

[0115] In at least some embodiments, a 3D printed dosage form is provided that includes an effective amount of a BCS Class IV API. Examples of BCS Class IV API's include one or more of acetazolamide, albendazole, azithromycin, cefixime, clofazimine, diloxanide furoate, efavirenz, furosemide, glibenclamide, indinavir sulfate, ivermectin, lopinavir, mebendazole, mefloquine hydrochloride, nelfinavir mesilate, niclosamide, pyrantel embonate, pyrimethamine, pyrimethamine, ritonavir, saquinavir, spironolactone, sulfasalazine, and triclabendazole.

[0116] In some embodiments, the API is a drug that is may be titrated by the physician following administration. In some embodiments, the API is for treating attention deficit hyperactivity disorder (ADHD). Examples of API's for treating ADHD include amphetamine, amphetamine sulfate, dextroamphetamine, dextroamphetamine sulfate, dextroamphetamine sulfsaccharate, dexmethylphenidate, dexmethylphenidate HCl, lisdexamfetamine dimesylate, methylphenidate, clonidine, clonidine HCl, guanfacine HCl, atomoxetine HCl, nortryptiline HCl, desipramine HCl, imipramine HCl, bupropion HCl, and any pharmaceutically acceptable salt thereof. In some embodiments, the API is for treating hypothyroidism. Examples of API's for treating hypothyroidism include levothyroxine and levothyroxine sodium. In some embodiments, the API is an antidepressant. Examples of API's for treating depression include agomelatine, amitriptyline, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, imipramine, lithium citrate, lofepramine, mianserin, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, trazodone, venlafaxine, and vortioxetine. In at least some embodiment, the API is for treating hyperkinetic movement disorders such as Huntington's disease,

Tourette syndrome, tardive dyskinesia, and hemiballismus. An example of an API for treating hyperkinetic movement disorders is tetrabenazine. In some embodiments, the API is for treating pain. Examples of API's for treating pain include alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, brifentanil, buprenorphine, butorphanol, carfentanil, clonitazene, codeine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxyaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorhine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, mirfentanil, morphine, morphine-6-glucuronide, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nociceptin/orphanin FQ (N/OFQ), normo[phi]hine, no[phi]ipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, remifentanil, sufentanil, tapentadol, tramadol, trefentanil, tilidine, or any opioid having agonist activity at an opioid receptor belonging to the phenanthrene, morphinan, benzomorphan, methadone, phenylpiperidine, propionanilide 4-anilidopiperidine, 4-aryl piperidines, and 4-Heteroarylpiperidines class, any opioid having agonist activity at an opioid receptor having the same pentacyclic nucleus as nalmefene, naltrexone, buprenorphine, levorphanol, meptazinol, pentazocine and dezocine.

[0117] In at least some embodiments, a 3D printed dosage form is provided that includes an effective amount of an API having limited water solubility of no more than about 10 mg/ml, 5 mg/ml, 4 mg/ml, 3 mg/ml, or no more than 1 mg/ml in water at 25 °C. In an example embodiment, oral 3D

printed dosage forms exhibit controlled and sustained release of API when compared to traditional hard HPMC capsules.

[0118] In some example embodiments, a 3D printed dosage form is provided having a substrate composition or a core composition comprising an active pharmaceutical ingredient and a water soluble linear polymer. In some example embodiments, the water soluble linear polymer is selected from one or more of a polyethylene glycol (PEG) and/or a methoxypolyethylene glycol (MPEG). In at least some embodiments, a core composition is provided comprising a polyethylene glycol (PEG) or methoxypolyethylene glycol (MPEG) having a solubility in water at 20 °C of 60 to 100 wt%, or about 70 to about 80 wt%. In at least some embodiments, the core composition comprises a PEG or MPEG having a melting range of from about 15 °C to about 65 °C, about 27 °C to about 60 °C, or about 35 °C to about 46 °C. In at least some embodiments, the core composition comprises a water soluble linear polymer in an amount of at least about 20 wt%, at least about 30 wt%, or at least about 50 wt% compared to the weight of the core composition. In at least some embodiments, the core composition comprises a water soluble linear polymer in an amount of from about 20 wt% to about 99.9 wt%, about 30 wt% to about 98 wt%, or about 40 wt% to about 95 wt%, compared to the total weight of the core composition. In at least one example embodiment, a core composition is provided comprising an active pharmaceutical ingredient and from about 40 wt% to about 50 wt%, or about 90 wt% to about 95 wt% of a polyethylene glycol. In at least some embodiments, the polyethylene glycol is selected from a polyethylene glycol 540, 1000, 1450, 3350, 4000, 4600, 8000, or a blend thereof. In example embodiments, the polyethylene glycol is selected from polyethylene glycol 540 (a 41/59 wt % blend of PEG 300 and PEG 1450, melting range 38 to 41 °C), polyethylene glycol 1000 (having about 22.3 oxyethylene units, melting range 35 to 40 °C), or polyethylene glycol 1450 (having about 32.5 oxyethylene units, melting range 42 to 46 °C). In at least some embodiments, the active pharmaceutical ingredient is dissolved in the substrate or core composition. In some compositions, the substrate or

core composition is a homogenous composition. In at least some embodiments, the substrate or core composition does not include particles. In at least some embodiments, the substrate or core composition is in the form of a liquid, dispersion, emulsion, solid, or fused solid. In at least some embodiments, the substrate or core composition is a filament composition.

[0119] In at least some embodiments, the substrate or core composition is provided comprising a preservative. Preservatives may be selected from any pharmaceutically acceptable preservative known in the art. In at least some embodiments, the preservative is selected from butylated hydroxyanisole (BHA), butylated hydroxy toluene (BHT), sodium benzoate, potassium sorbate, ethylenediaminetetraacetic acid (EDTA) or salts thereof, parabens (such as methyl, ethyl, propyl and butyl p-hydroxybenzoic acids esters) or mixtures thereof. In at least some embodiments, the preservative is present in the composition at from 0 to about 2 wt%, about 0.001% to about 1 wt%, about 0.005% to about 0.5%, or about 0.01% to about 0.1% of a preservative based on the weight of the composition.

[0120] In at least some embodiments, a substrate or core composition is provided comprising a surfactant. The surfactant may serve as an emulsifier or dispersing agent to enhance homogeneity of the composition. In at least some embodiments, the surfactant helps avoid phase separation of the composition in the liquid state. In at least some embodiments the surfactant is selected from any pharmaceutically acceptable ionic surfactant or a nonionic surfactant as known in the art. In at least some embodiments, the surfactant is a nonionic surfactant. In at least some embodiments the core composition comprises a nonionic surfactant that is polyoxyethylene (40) stearate (e.g., MYRJ™-52), polyoxyl 40 hydrogenated castor oil (e.g., CREMOPHOR™ RH), caprylocaproyl macrogol-8 glycerides (e.g., LABRASOL™), PEG 400, polysorbate 80 (e.g.,TWEEN™ 80), propylene glycol monocaprylate (e.g., Caproyl™ 90), propylene glycol monolaurate (e.g., Lauroglycol™ 90), 2-(2-ethoxyethoxy)ethanol (e.g., Transcutol™). In

embodiments, the core composition comprises from 0 to 70 wt%, 1 to 60 wt%, 10 to 50 wt%, or 20 to 45 wt% of a nonionic surfactant.

[0121] In at least some embodiments, the core composition comprises a SEDDS composition. In example embodiments, the SEDDS composition comprises an API, a substrate, a surfactant, and optionally a pharmaceutically acceptable excipient. In at least some embodiments, the API is a BCS Class II API. In at least some embodiments, the substrate is a water soluble linear polymer. In at least some embodiments, the surfactant is a nonionic surfactant. In at least some embodiments, the excipient is a diluent or co-solvent such as water or an oil. In example embodiments, the SEDDS composition comprises from 0.1 to 40 wt% API, 20 to 95 wt% of a substrate thermoplastic polymer, 1 to 60 wt% of a surfactant, and 0 to 20% of a pharmaceutically acceptable diluent or co-solvent. In example embodiments, the SEDDS composition comprises from 0.5 to 20 wt% API, 30 to 50 wt% of a substrate thermoplastic polymer, 5 to 50 wt% of a surfactant, and 1 to 10% of a pharmaceutically acceptable diluent or co-solvent.

[0122] In at least some embodiments, a core composition is provided further comprising a pharmaceutically acceptable excipient. For example, Figures 3 and 4 illustrate a functional dosage form 100, which can be formed by a FFF process to have a specified geometry (e.g. shape, height, width, length, volume, surface area, ratio of volume to surface area, etc.) optimized for a particular application. Software can be utilized to calculate the shape and size of the functional dosage form 100 depending on the desired API dose. As shown, the functional dosage form 100 is provided with a generally obround capsule shape with rounded sides and edges at an average length, l_{100}, an average height, h_{100}, and an average width, w_{100}, to result in an outer surface area and volume of the dosage form 100. The geometry of the dosage form 100 can be modified to suit any particular application. Examples of shapes for dosage form 100, and all other described dosage forms described herein, include standard convex (bisect not flush, quadrisect

flush, straight-through bisect), compound cup, convex with bevel, flat-faced plain, flat-faced bevel-edged (bisect, qudrasect), flat-faced radiused edged, lozenge, modified ball, core rod type (hole in center), capsule, modified capsule, oval, bullet, arrowhead, triangle, arc triangle, square, pillow (arc square), rectangle, modified rectangle, diamond, pentagon, hexagon, octagon (natural edge), heart, half-moon (D shape), and almond.

[0123] The functional dosage form 100 can be entirely formed from a single material or can be formed form a plurality of materials to form a polypill. Where multiple materials are used, many configurations are possible for physically arranging the materials to form the functional dosage form 100. For example, the materials could be arranged in layers in a horizontal, vertical, or concentric fashion. In the example shown at Figures 3 and 4, the functional dosage form 100 is formed from a first material defining a first layer 102 and a third layer 106 and from a second material defining a second layer 104 and a fourth layer 108. Although four layers are shown, any number of desired layers may be utilized. In the example shown, the layers 102 – 108 are of substantially equal size or volume. However, the layers 102 -108 could be provided with unequal sizes or volumes. Additionally, in the example shown, each of the layers 102 - 108 has at least one exposed edge. However, the dosage form 100 could be formed such that only the layers associated with the first or second materials are externally exposed with the other layer encapsulating that layer. Furthermore, the dosage form 100 shown at Figures 3 and 4 could be provided with an additional encapsulating layer that entirely covers each of the layers 102-108.

[0124] With continued reference to Figures 3 and 4, many materials and layer arrangements may be utilized to form the functional dosage form 100. For example, each of the layers 102-108 could be formed from a unique material, in which case a four head FFF printer could be utilized to form the dosage form 100. In the example shown, the first and third layers 102, 106 are formed from a first material and the second and fourth layers

104, 108 are formed from a second material. In at least one example, the first material is a PLA material and the second material is a PVA material. An API may be embedded into one or both of the first and second materials. An example of a suitable dosage form 100 is described in more detail herein, including with reference to Example 1 in the *Examples* section of this specification.

[0125] In an example embodiment, the functional dosage form shown at Figures 3 and 4 can be designed and printed to be suitable for buccal delivery. Such an embodiment enables a compounded pharmacy approach to prepare custom blends such as multiple drug substances at custom ratios for personalized medicine applications. Such an embodiment also might enable delivery of a custom dose based on weight or age requirements, which might be useful in different applications such as pediatrics. Another advantage of this system would be the ability to incorporate taste-masking technologies into the dosage form.

[0126] Referring now to Figures 5 and 6, several technologies have been used to yield gastric retentive capsules/tablets. These systems typically use mucoadhesive strategies, low density configurations in order to float the formulations, or expanding formulations that block passage into the GI tract. Additionally, at least some embodiments use 3D printing to make capsule or tablets having an API and a hollow cavity. A hollow or cavity can be a fully hollow cavity formed by a void having no intervening elements as illustrated in Figures 5 and 6. In various embodiments, the void is fully enclosed or has a small passage or orifice between the void and the outer surface of the dosage form. Alternatively, the hollow or cavity has intervening elements within the void such as an internal lattice structure that forms a low density lattice structure region or repeating patterns of particular cell shapes or cell types that form a low density void region. An advantage of such embodiments is that the dosage form can be made with a material that has a density higher than the aqueous or other fluid in the target bodily cavity, but the overall density of the dosage form has a density lower than

the fluid. An example of such a fluid is gastric fluid. Some embodiments can be tested in a fluid having a density approximating gastric fluid having a density slightly above 1 g/ml, such as a fluid having a density between about 1.0022 g/ml and about 1.0024 g/ml.

[0127] As illustrated in the figures, an example embodiment of a functional dosage form 200 has an outer shell 202 defining an interior hollow cavity 204. The hollow cavity 204 allows the functional dosage form 200 to float in an aqueous environment even though the outer shell 202 may be formed from a material having a density greater than that of the aqueous environment. As such, the increased volume of the dosage form 200 caused by the interior cavity 204 enables the dosage form 200 to have gastric retentive properties. In the example shown, the printed outer shell 202 has an average length, l_{202}, an average width, w_{202}, and an average height, h_{202}, to give the functional dosage form 202 a first volume and first outer surface area. The interior hollow cavity 204 has an average length, l_{204}, an average width, w_{204}, and an average height, h_{204}, giving the cavity a second volume and defining a thickness, t_{202}, of the outer shell 202.

[0128] During use, the resulting hollow capsule dosage form 200 will float and slowly erode to release the API in the stomach. The dosage form surface area, the wall thickness , t_{202}, and the solubility of the material forming the outer shell 202 are variables affecting the timing of when the capsule will disolve to a point where the interior cavity 204 is exposed to the aqueous environment and no longer buoyant. As discussed above, the API could be incorporated through nano-crystals or amorphous solid dispersion (using hot melt extrusion) or the API could be covalently linked to the polymer through a biodegradeable polymer link. An example of this might be L-Dopa or SD-1077 as this API is amenable to polymer incorporation and a sustained gastric delivery of this compound has a clinical benefit. Specifically, hot melt extrusion techniques may be employed to provide 3D printed core amorphous solid dispersions. Processing is typically done at elevated temperatures (>100 °C) for very short duration (seconds) for

preparation of amorphous solid dispersions of drug substances. This technique may be employed to prepare drug-polymer sustems for direct 3D printing.

[0129] In an alternative to the single cavity shown at Figures 5 and 6, tablets can be prepared with multiple controlled cavities that can be ultilized to achieve the similar floating or sustained release purpose. Referring to Figures 7 and 8, a functional dosage form 300 having a plurality of interior cavities is presented. As shown, dosage form 300 is printed with a first material to form a body 302 with an average length, l_{302}, average width, w_{302}, and average height, h_{302}, to define a first volume. The body 302 is printed such that a plurality of hollow cavities 304 are defined that cumulatively define a second volume. The combined total second volume of the hollow cavities 304 enable the first volume of the body 302 to make the dosage form 300 buoyant in an aqueous environment. In the particular example shown, the dosage form 300 is provided with 54 spherically shaped interior cavities 304. However, the number, size, and shape of the cavities 304 can vary and can be customized to suit any particular application provided the end result is a body first volume that enables the dosage form 300 to be buoyant in an aqueous environment. As noted above, the hollow cavity can be formed as a low density region by printing an internal lattice network with void areas within the dosage form rather than having discrete fully hollow cavities.

[0130] Referring to Figures 9 and 10, the dosage form 300 can be printed with one or more additional internal cavities or cavities for holding a material with one or more APIs. In such instances, a controlled dissolution profile can be achieved in combination with the buoyant gastric retentive features described above. An example of a suitable gastric retentive dosage form in accordance with the foregoing description is described in more detail herein, including with reference to Example 8 in the *Examples* section of this specification.

[0131] Capsule formulations have been commercialized which are designed to slowly dispense its contents when they come in contact with the aqueous environment of the stomach, and thus deliver a controlled release of API.

[0132] In at least some embodiments, a 3D printed dosage form is provided having (1) an outer shell formed from a substrate, wherein the outer shell comprises at least one compartment, or at least two compartments; (2) a core composition comprising an active pharmaceutical ingredient residing in at least one of the compartments; and (3) at least one orifice in the outer shell.

[0133] In example embodiments, the substrate is selected from PVA or PLA. For example, a caplet dosage form 400 can be printed using a dual head extruder in which one head builds an outer shell 402 of a slowly dissolving hydrophilic polymer such as PVA or PLA, while the other nozzles simultaneously prints an inner core 404 of water soluble polymer core composition matrix containing the API. In alternative emboidment, the inner core 404 can be injected into a void defined by the outer shell 402. As illustrated in the figures, a single compartment functional dosage form 400 configured as an osmotic pump having an inner core 404 surrounded by an outer shell 402 is presented. In the example shown, the printed outer shell 402 has an average length, l_{402}, an average width, w_{402}, and an average height, h_{402}, to give the functional dosage form 402 a first volume and first outer surface area. The inner core 404 has an average length, l_{404}, an average width, w_{404}, and an average height, h_{404}, giving the inner core a second volume and defining a thickness, t_{402}, 402T of the outer shell 402. In at least one example, l_{402} is approximately 21.6 millimeters (mm), w_{402},402W is approximately 7.64 mm for a total volume of approximately 0.67 milliliters (ml), wherein *h*402 is approximately 7.64mm, l_{404} is approximately 19.6 mm, w_{404} is approximately 5.64 mm, and h_{404} is approximately 5.64 mm for an internal volume of approximately 0.623 ml.

[0134] In at least one example, the dosage form caplet 400 is printed by a FFF 3D printer with the outer shell comprised of either PVA or PLA. The two polymers exhibit different behaviors when exposed to aqueous environments, with PVA swelling and dissolving and the PLA requiring erosion of the polymer. In at least one example, the caplets 400 can be printed to include a SEDDS formulation of CEP-701. In at least one example, the outer shell 402 is printed with a 3D printer and the inner core is later filled by injecting a dosage of at least one pharmaceutically active ingredient and/or pharmaceutically acceptable excipients. An outer cap can be affixed to the outer shell 402 to retain the API within the outer shell 402 after filling. Examples of osmotic pump dosage forms in accordance with the foregoing description and Figures 9 and 10 are described in more detail herein, including with reference to Examples 2 and 6 in the *Examples* section of this specification.

[0135] The system can be designed to have one or more controlled openings 406 in the outer shell to allow for a controlled release of the contents. The controlled opening 406 can be printed to include the inner core material such that the inner core material has an exterior exposure. In at least one example, the controlled opening has a diameter of approximately 2 mm. In at least one example, the controlled opening is covered with an additional cap 408 which can be formed from a third material different from the outer shell material and the inner core material. An example of a cap 408 is shown at Figure 10. Examples of osmotic pump dosage forms having a cap 408 are described in more detail herein, including with reference to Examples 4 and 5 in the *Examples* section of this specification. The third material can be sensitive to a certain condition (e.g. pH) before dissolving and exposing the inner core material at the controlled opening 406 to control dissolution at different pH levels. In at least one example, the cap 408 material is formed by a Eudragit L100-55 film made by a Eudragit and Ethanol slurry for an acidic release at a pH above 5.5. In at least one example, the cap 408 material is formed from a Eudragit EPO film made by Eudragit and an Ethanol slurry for a basic release at a pH of

between 1 and 5. In at least one example, the controlled opening 406 is plugged with a fourth printed material rather than being plugged by the material forming the inner core.

[0136] In certain embodiments, the dosage form comprises a gas-generating component loaded into the orifice. In certain embodiments, the gas-generating component is selected from the group consisting of water-soluble carbonates, sulphites, bicarbonates, sodium carbonate, sodium bicarbonate, sodium metabi sulphite, calcium carbonate, and combinations thereof, which on contact with gastric fluid releases carbon dioxide or sulphur dioxide gas. In at least some embodiments, the gas-generating component is a combination of sodium bicarbonate and organic acid (e.g., citric acid, tartaric acid etc). In at least some embodiments, the material is magnesium carbonate ($MgCO_3$). In at least one example, a dosage form is created by printing, with a four-headed printer, the outer shell 402 from a first material, printing the inner core 404 from a second material, printing a plug within the opening 406 from a third material, and printing a cap 408 from a fourth material, wherein the first, second, third, and fourth materials are all different from each other.

[0137] In an alternative construction, a capsule or tablet blank shell 402 with controlled openings 406 and cavity sizes could be fabricated to deliver one or more semi-solid or liquid formulations comprised of a drug solution or drug particle suspension. This system could be filled with a self-emulsifying drug delivery system (SEDDS) of one or more API's and give a controlled ratio and release profile that is customized for the therapeutic conditions of the system.

[0138] In at least one example, the dosage form 400 can be provided with an additional weak point designed plug 410 for obtaining two-phase dissolution profile. An example of an osmotic pump dosage form having a weak point designed plug 410 is described in more detail herein, including with reference to Example 3 in the *Examples* section of this specification. In at least some embodiments, the weak point plug is prepared from a

substrate material that is more hydrophilic than the outer shell substrate material. The plug 410 can be formed by printing the plug 410 out of a material that is different than that used for the outer shell 402 or can be printed from the same material as the outer shell 402, but in a perforated or otherwise reduced structural integrity configuration that exposes the inner core 404 to the exterior. In at least some example embodiments, the plug is made from a porous polymer, an erodible polymer, a pH sensitive polymer or natural occurring material such as shellac. In at least some embodiments, the plug is made from a material selected from the group consisting of water soluble polymers, erodible or dissolvable polymers, wax like materials and saccharides or any materials mentioned above. In at least some embodiments, the weak point plug comprises PVA and the outer shell comprises PLA.

[0139] Testing under standard USP II dissolution of the disclosed functional dosage form 400 in comparison to a traditional HPMC hard capsule shows a controlled and sustained release of CEP-701 compared to the traditional capsule.

[0140] Although the functional dosage form 400 is shown having a single inner core 404, functional dosage forms including multiple compartments and inner cores are possible. For example, a variation of the dosage form 400 is shown at Figures 11 and 12. The dosage form 500 shown at Figures 11 and 12 has two inner cores 504a, 504b separated by an intermediate wall 502a of the outer shell 502 is shown, each configured as an osmotic pump is shown. As shown, each of the inner cores 502a, 502b are substantially equal in size, volume, and surface area. However, the dosage form 500 can be configured such that the inner cores 502a, 502b are configured differently from each other. Similar to the dosage form 400, the dosage form 500 can be provided with caps 508a, 508b to respectively cover controlled openings 506a, 506b, as shown at Figure 12. In at least some embodiments, the opening, or orifice, is a controlled size having a diameter of from approximately 0.1 mm to approximately 6 mm,

approximately 0.5 mm to approximately 5 mm, approximately 0.75 mm to approximately 3 mm, or approximately 1 mm to approximately 2 mm. In at least some embodiments, the opening or orifice is in a controlled shape, such as a circular opening, oval opening, square opening, diamond shape opening, or triangular opening. The wall thickness surrounding each inner core 502a, 502b may be the same or different to create the desired release profile. The total volume and/or surface area of each inner core 502a, 502b also may be the same or different to create the desired release profile. The inner cores 502a, 502b also may be formed from the same material or a different material. In the latter case, an osmotic pump polypill is formed.

[0141] In at least some embodiments, each inner core 504a, 504b can be filled with the same or different API's. Additionally, the cover controlled openings 506a, 506b can have plugs formed by the same material or different materials that dissolve at different rates in a given environment. Similarly, the caps 508a, 508b can be formed by the same material or different materials that dissolve at different rates in a given environment. In yet other embodiments, one opening (e.g., 506a) and can be covered by a cap, (e.g., 508a) while the other opening (e.g., 506b) is not covered by a cap. An advantage of these embodiments is that a single dosage form can deliver one or more API's at different rates, or delivery of an API from one inner core (e.g., 504a) can be delayed relative to delivery of an API from the other inner core (e.g., 504b). Yet another application is that a single dose can be used to deliver API's to different body cavities. For example, a dosage form that does not have a cap over one opening (e.g., 506a) can rapidly delivers an API from one inner core (e.g., 504a) while the dosage form is in the stomach while a cap (e.g., 508b) over the other opening (e.g., 506b) delays delivery of the other API from the other inner core (e.g., 504b) until the dosage form passes from the stomach to the intestine.

[0142] In yet other possible embodiments, the dosage form 500 may be provided with a single inner core and a hollow cavity such that the dosage form 500 is buoyant in an aqueous solution. In such cases, the

location, shape, and size of the hollow cavity can be controlled such that the controlled openings are oriented in a desired direction. In one example, one or both of the inner cores 502a, 502b are printed as a low density region, for example via a lattice network, such that the dosage form is buoyant in an aqueous solution. In other embodiments, one or both of the inner cores 502a, 502b can be partially filled within the body, thereby leaving a fully hollow cavity region to give the dosage form buoyancy.

[0143] In at least one example, an anti-HIV drug combination dosage form 500 is formed according to Figure 11 or 12, by printing Ritonavir as a first inner core 504a and by printing Darunavir ethanolate as a second inner core 504b, wherein the volume ratio of the first inner core 504a to the second inner core 504b is substantially 6:1.

[0144] In another example, an anti-Parkinson's disease drug combination dosage form 500 is formed according to Figure 11 or 12, by printing levodopa or deulevodopa as a first inner core 504a and is by printing carbidopa as a second inner core 504b, wherein the volume ratio of the first inner core 504a to the second inner core 504b is substantially 4:1. An example osmotic pump dosage form in accordance with the foregoing description and Figure 11 is described in more detail herein, including with reference to Example 7 in the *Examples* section of this specification. The dosage form 500 also may be configured such that only one inner core 504a, 504b is provided with features that enable operation as an osmotic pump with the other core functioning as a standard dosage form. Dosage forms including more than two inner cores are also possible.

[0145] Referring to Figures 13 and 14, the dosage forms could be designed and printed that incorporate the delivery options described above but have additional functionality or triggered release options built into the dosage form. An example of this would be a caplet with an outer shell containing a pH responsive polymer (i.e. Eudragit, chitosan or methylacrylates) that is designed to swell or release its contents at the appropriate pH. The figures illustrate an example functional dosage form

600 having the features of dosage form 400 and such additional features. The dosage form 600 includes a plurality of pH swellable projections or spikes that grow in response to an appropriate pH condition. Once grown, the projections 610 act as a mucoadhesive to improve gastric retention. Although the projections 610 are shown as uniformly shaped conical spikes, the projections can be configured to have different shapes and can be provided with additional branch-like sub-projections. Additionally, the projections 610 can be provided with different shapes on different sides of the dosage form 600.

[0146] During the manufacturing process, the responsive polymer that swells or releases its contents can be segments of an additional layer printed over the outer surface of the dosage form. Alternatively, the outer wall or surface of the dosage form can be printed with different materials in which at least one of the materials is responsive polymer.

[0147] Figure 15 illustrates an array of 3D printed functional dosage forms 700 configured as mini tablets is shown. 3D printing an array of functional dosage forms itself to the preparation of customized dosages to titrate drug dose to a specific level, which is beneficial for a variety of dosing options including pediatrics. This embodiment can be enabled by printing a series of mini-tablets or miniature dosage forms from a common polymer filament that contains a known weight of API per gram of the polymer filament. A series of doses could be printed by a pharmacist based on a patient's weight using a standard CAD drawing stored in the system. In at least one example, the mini-tablets 700 are printed from a PVA filament with a diameter of approximately 2 mm. As illustrated in Figure 16, an alternative option would be to print a dosing spoon or device 800 outfitted with a body 802 and a sliding cover 804. The dosing device 800 can be configured with a handle 806 that supports a dispensing portion 808 having a plurality of recesses 810 for receiving the mini-tablets 700. The recesses are arranged in an array corresponding to the array of functional dosage forms illustrated in Figure 15. Additionally, the device 800 can also function as a build tray

when printing the dose forms wherein each does form is printed in a separate recess simultaneously printing the dose forms and arranging them in the array. As illustrated in Figure 17, the cover 804 can slid over the body 808 to expose a desired number of mini-tablets 700 such that the desired dosage is made available. This formulation approach would overcome many of the issues with current mini-tablet use, such as special manufacturing equipment, content uniformity issues, material loss (yields), and ease of handling and dosing.

[0148] Figure 17 shows an alternative dispenser 800' having a body 802' with a handle portion 806' extending from a dispensing portion 808'. In contrast to the dispenser shown at Figures 15 to 17, the API containing functional dosage forms 702' are printed onto the dispensing portion 808' in an array 700' rather than being placed into recesses. As shown, each dosage form 702' is connected to the dispensing portion 808' via a neck portion 704' which can be broken when it is desired to remove a dosage form 702' for consumption. The functional dosage forms 702' and the neck portion 704' can be printed from the same material or from different materials. In one example, the body 802' of the dispenser is first printed, followed by printing of the individual neck portions 704' after which the functional dosage forms 702' are printed.

[0149] Referring to Figure 18, multiple examples of dosage forms 900a-900d in the form of tablets having various geometries are shown. The different geometries can have different erosion or release rates, and can be customized to provide different delivery rates. The geometries also may be customized to provide erosion or release rates that vary over time and have a particular erosion or release profile. The tablets can have sustained release of the API, delayed release of the API, or both delayed and sustained release of the API. Dosage form 900a is shown as having a cubic form. Dosage form 900b is shown as having a pyramid form with a four-sided base. Dosage form 900c is shown as having a tablet or cylindrical form. Dosage form 900d is shown as having a spherical form. Dosage form

900e is shown as having a toroidal form. Many other shapes are possible. An advantage of the 3D printing apparatuses and method disclosed herein is that they can print dosage forms having different geometries such as those illustrated in Figure 18. Additionally dosage forms can be rapidly printed without the need to make different molds or forms so that a tablet having a particular erosion or release rate or erosion or release profile can be more easily and quickly determined through trial and error. In alternative embodiments, such 3D printing of dosage forms can be used to print implants having different geometries.

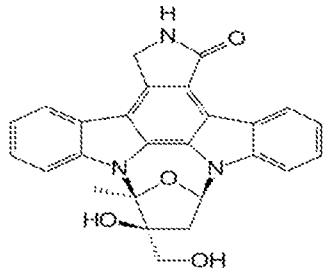
[0150] 3D printing has demonstrated its ability to be used to print biodegradeable implants for tissue scaffolding applications. The technology could also be used to print scaffoldings having API's as disclosed herein such that the scaffolding also functions as a 3D printed dosage form. The 3D printing of dosage forms as disclosed herein also can be used to 3D print customized drug delivery implants or Depo formulations that would control release of API's over a reproducible time frame. The drug could be extruded with the polymer as an amorphous solid dispersion, nano-crystals or even attached to the polymer via a bio-cleavable linker. An example of this technology would be to print a spike made of a biocompatible or erodible polymer that contained nano-crystals or amorphous drug substance. An alternative option would be to print a hollow (e.g., straw like) or porous (e.g., sponge like) cylinder which could be filled with a SEDDS formulation allowing for a slow and sustained delivery of the drug substance.

Examples

[0151] Example 1. Powder filled capsule dosage forms and API with limited water solubility

[0152] CEP-701 is a tyrosine kinase inhibitor with limited solubility in water of ~0.3 ug/mL. CEP-701 is classified as a Biopharmaceutics Classification System (BCS) Class II molecule having high permeability, low

solubility, as defined by the U.S. FDA Center for Drug Evaluation and Research (CDER). The chemical structure of CEP-701 is shown below.



[0153] Pharmacokinetic studies performed with CEP-701 in powder fill, or micronized drug in powder fill in traditional rapidly dissolving hydroxypropyl methylcellulose (HPMC) capsules showed poor exposure (low AUC) of drug substance following oral administration to dogs, when compared to CEP-701 in formulated solution in HPMC capsules (high AUC) as shown in Figure 19A.

[0154] Specifically, three formulations of CEP-701 were prepared and finished in capsule formulations. Formulation A contained drug substance CEP-701 as powder filled hard gelatine capsule. Formulation B was micronized drug substance CEP-701 in powder filled capsule. Formulation B was 50 mg CEP-701 mixed with 5 mg Sodium CMC and 5 mg SLS. Formulation C was CEP-701 in formulated solution with 25 mg/ml solution of CEP-701 in a 50/50 (weight/weight) mixture of polypropylene glycol and Polysorbate 80. Each formulation was compared to capsule formulation having a 20 mg dose in a 0.625 mL fill. The dosage forms were administered orally to dogs. Mean AUC for CEP-701 post oral dosing in dogs was determined for Formulations A, B and C as shown in Figure 19A.

[0155] Formulation C (formulated solution) provided significantly increased AUC drug exposure compared to Formulation A (powder fill) or B (micronized powder fill), as shown in Figure 19A. Specifically, the mean AUC for CEP-701 was substantially increased at least 5 times following oral

administration to dogs of Formulation C (formulated solution filled capsule) compared to Formulation A (powder filled capsule) or Formulation C (micronized powder fill capsule), as shown in Figure 19A. The capsule filled with a CEP-701 powder formulation, or a micronized powder formulation, did not exhibit appropiate absorption following oral administration to dogs. Therefore, alternative dosage forms for administering Class II drugs such as CEP-701 as a formulated solution were developed.

[0156] Example 2. Osmotic Pump with orifice/ Diffusion Control Functional Dosage Forms

[0157] Osmotic caplets 400 as described in Figure 9 were printed by FDM 3D printer with the outer shell 402 comprised of either polyvinyl alcohol (PVA) or poly-lactic acid (PLA). The two polymers exhibit different behavior when exposed to aqueous environments, with PVA swelling and dissolving and the PLA requiring erosion of the polymer.

The printed caplets were filled by syringe with a core 404 composition comprising active pharmaceutical ingredient 25 mg CEP-701 in 500 mg of a self-emulsifying drug delivery system (SEDDS) formulation according to Table 1.

[0158] 3D printed caplet shells 402 according to Figure 9 were prepared having external size length 402L: approximately 21.6 mm; height 402H of approximately 7.64 mm; and width 402W of approximately 7.64 mm. Inner core 404 size (internal capacity) was length of approximately 19.6 mm; height of approximately 5.64 mm; width of approximately 5.64 mm; and volume: of approximately 0.623 mL. The caplet wall thickness was approximately 0.82 mm. Caplets included an orrifice of approximately 2 mm in diamter. In comparison, capsule size 0 has overall length of approximately 21.6 mm, external diameter of approximately 7.64 mm, and volume of approximately 0.67 mL.

[0159] Caplet core 404 formulation containing CEP-701 was prepared according to Table 1 comprising a self-emulsifying drug delivery system (SEDDS) core formulation comprising active pharmaceutical ingredient (API), polyethylene glycol 1000 (PEG-1000) as dispersing agent, and polyoxyethylene (40) stearate (MYRJ-52), a neutral surfactant.

[0160] Table 1. SEDDS Formulation of CEP-701

Material	Amount (wt%)	Purpose
CEP-701	5.0%	API
water	8.0%	Diluent or co-solvent
PEG-1000	43.5%	Dispersing agent Substrate
MYRJ-52	43.5%	Surfactant

Capsule shells 402 were filled with Formulation of Table 1 via caplet orifice using a syringe for proof of concept studies. 500 mg of SEDDS (25 mg CEP-701) was loaded into each caplet blank via syringe through caplet orifice.

[0161] Average dissolution profiles of filled CEP-701 3D printed PVA (n=3) and PLA (n =3) caplets were determined by using USP apparatus II (paddle) and compared to historical data used traditional HPMC capsules (n = 6) as shown in Figure 19B. Dissolution media (900 mL): 0.5% sodium lauryl sulfate (SLS) having a pH of 7.0 – 9.5 also known as sodium dodecyl sulfate (SDS), an anionic surfactant dissolution media.

[0162] As shown in Figure 19B, HPMC capsule comprising CEP-701 in SEDDS formulation rapidly dissolved, compared to the 3D printed caplets comprising PVA or PLA shell which both exhibited controlled and sustained

release of CEP-701. The PVA caplets released faster than the PLA caplets in 0.5% SLS.

[0163] The PVA caplet shell exhibited at least about 75% release of the CEP-701 within 60 minutes, and about 95% release of the CEP-701 within about 75 minutes, as measured by in-vitro dissolution in a USP Apparatus II (paddle) at 50 rpm in 500 ml 0.5% SLS at 37°C.

[0164] The PLA caplet shell exhibited at least about 20% release of CEP-701 within about 75 minutes, as measured by in-vitro dissolution in a USP Apparatus II (paddle) at 50 rpm in 500 ml 0.5% SLS at 37°C.

[0165] In comparison, the traditional HPMC capsule exhibited about 100% release of CEP-701 within about 20 minutes.

[0166] Therefore, 3D printed caplets comprising PVA or PLA shell having 2 mm diameter orifice both exhibited controlled and sustained release of CEP-701 in SEDDS formulation compared to the traditional HPMC capsule filled with CEP-701 in SEDDS formulation.

[0167] Example 3. Osmotic Pump with orifice and weak point plug/ Diffusion Control Functional Dosage Forms

[0168] 3D printed PLA caplets 400 as shown in FIG. 10, were designed having a PLA capsule shell 402 with an orifice 406 and with or without a weak point PVA plug 410 for getting 2-phase controlled dissolution. 3D printed PLA caplets were prepared in a similar fashion to Example 2, except having a 1 mm orifice 406, with a core 404 fill of CEP-701 SEDDS formulation according to Table 1, and having a PVA plug to create a weak point in the dosage form. The external dimensions in the PLA caplet shell 402 were used according to example 2, except a PVA plug 410 of 0.5 mm length, 5 mm width and 5 mm height was employed. Dissolution studies were performed in 0.5% SLS by the method of example 2. Dissolution profiles with and without the PVA plug are shown in Figure 20A. As shown in FIG. 20A, release of CEP-701 in SEDDS formulation with PVA plug

exhibits about 15% release over 2 hours, about 65% release over 4 hours and about 100% release over about 8 hours. The PLA caplet having 1 mm diameter orifice and PVA plug exhibited a period of slow release between 0 to 2 hours of about 15% release, followed by a period of moderate release between about 2 to about 4 hours of about 65% release, followed by a period of slow release from about 4 to about 8 hours of about 100% release. In comparison, the PLA caplet having 1 mm orifice without PVA plug exhibited about 10% release at about 2 hours, about 40% release at about 4 hours, with about 95% release after 16 hours, and about 100% release after about 24 hours. By employing a weak point PVA plug in the PLA caplet in addition to the orifice, dissolution profiles were tailored to increase rate of controlled release of the poorly water soluble drug.

[0169] Example 4. Osmotic Pump with Controlled release sealing cap/ Diffusion Control Functional Dosage Forms

[0170] 3D printed PLA caplets 400 were prepared according to Example 2 having a 2 mm orifice 406, with a core 404 fill of CEP-701 SEDDS formulation according to Table 1. A slurry of Eudragit L100-55 in ethanol was used to form a Eudragit L100-55 film seal cap 408 over the orifice of the 3D printed caplet, as shown in Figures 10 and 20B. Dissolution studies were performed per USP apparatus II (paddle) by over a period of 4 hours with simulated gastrointestinal fluid (SGF, 0.1 N HCl) pH 1.1, or simulated intestinal fluid (SIF, 0.5% SLS) pH 6.8. Figure 21A shows dissolution over 4 hours in SGF (pH 1.1). PLA caplet with 2 mm orifice without sealing (control) exhibited greater than about 90% release of CEP-701 at 4 hours in SGF. In contrast, PLA caplet with 2 mm orifice sealed with Eudragit L100-55 exhibited less than about 15% release of CEP-701 at 4 hours in SGF.

[0171] Figure 21B shows dissolution over 4 hours in SIF (pH 6.8). PLA caplet with 2 mm orifice without sealing (control) exhibited greater than about 90% release of CEP-701 at 4 hours in SIF. In contrast, PLA caplet with 2 mm orifice sealed with Eudragit L100-55 exhibited about 40% release

of CEP-701 at 4 hours in SIF. The example shows that by combining the 3D printed osmotic dosage form with Eudragit L-100-55 coating, the controlled dissolution period can be significantly extended to exhibit no more than about 60% release over a period of 4 hours using PLA caplet shell in SIF (pH 6.8), or no more than about 20% over 4 hours in SGF (pH 1.1).

[0172] Example 4A. Osmotic Pump with Controlled release sealing cap/ Diffusion Control Functional Dosage Forms

[0173] 3D printed PLA caplets 400 were prepared according to Example 2 having a 2 mm orifice 406, with a core 404 fill of 50 mg Sumatriptan formulation in the form of an 80.3 mg/g suspension in PEG-1450. A slurry of Eudragit L100-55 in ethanol was used to form a Eudragit L100-55 film seal cap 408 over the orifice of the 3D printed caplet, as shown in Figures 10 and 20B. Dissolution studies were performed per USP apparatus II (paddle) by over a period of 24 hours with simulated gastrointestinal fluid (SGF, 0.1 N HCl) pH 1.1, or simulated intestinal fluid (SIF, 0.5% SLS) pH 6.8. Figure 25A shows dissolution over 24 hours in SGF (pH 1.1) compared to SIF (pH 6.8). PLA caplet with 2 mm orifice with L-100 55 sealing showed less than about 2% release of sumatriptan at 24 hours in SGF. In contrast, PLA caplet with 2 mm orifice sealed with Eudragit L100-55 exhibited greater than about 90% release of sumatriptan within 8 hours in SIF.

[0174] Figure 25A shows dissolution over 24 hours in SIF (pH 6.8) and SGF (pH 1.1). PLA caplet with 2 mm orifice sealed with Eudragit 100-55 exhibited greater than about 90% release of summatriptan at 8 hours in SIF. In contrast, the same type of PLA caplet with 2 mm orifice sealed with Eudragit L100-55 exhibited <5% release of sumatriptan at 24 hours in SGF. The example shows that by combining the 3D printed osmotic dosage form with Eudragit L-100-55 coating, the controlled dissolution period can be significantly extended to exhibit no more than about 5% release over a period of 24 hours using PLA caplet shell in SGF (pH 1.1).

[0175] Example 5. Osmotic Pump with Plug and Controlled release cap coating/ Diffusion Control Functional Dosage Forms

[0176] 3D printed PLA caplets were designed to allow drug release only at acidic conditions, e.g. upon exposure to simulated gastric fluid (SGF). 3D printed PLA caplets prepared according to Example 2 having a 2 mm orifice, with a core fill of CEP-701 SEDDS formulation according to Table 1. $MgCO_3$ plug was used to plug the orifice. A slurry of Eudragit EPO in ethanol was used to form a Eudragit EPO film seal cap over the orifice of the 3D printed caplet, as shown in FIG. 20C. Upon exposure to SGF (pH 1.1), the orifice is exposed within 2 hours. However, in the simulated intestinal fluid (SIF, pH 6.8) the orifice is still sealed but swelled after 2 to 3 hours (data not shown).

[0177] Example 5A. Osmotic Pump with Plug and Controlled release cap coating/ Diffusion Control Functional Dosage Forms

[0178] 3D printed PLA caplets 400 were prepared according to Example 2 having a 2 mm orifice 406, with a core 404 fill of 50 mg Sumatriptan formulation in the form of an 80.3 mg/g suspension in PEG-1450. $MgCO_3$ plug was used to plug the orifice. A slurry of Eudragit EPO in ethanol was used to form a Eudragit EPO film seal cap over the orifice of the 3D printed caplet, as shown in FIG. 20C. Upon exposure to SGF (pH 1.1), the orifice is exposed within 1 hour. However, in the simulated intestinal fluid (SIF, pH 6.8) the orifice is still sealed after 24 hours.Dissolution studies were performed per USP apparatus II (paddle) over a period of 24 hours with simulated gastrointestinal fluid (SGF, 0.1 N HCl, pH 1.1), or simulated intestinal fluid (SIF, 0.5% SLS, pH 6.8). Figure 25B shows dissolution over 24 hours in SGF (pH 1.1) compared to SIF (pH 6.8). PLA caplet with 2 mm orifice with Eudragit EPO/$MgCO_3$ sealing showed less than about 2% release of sumatriptan at 24 hours in SIF. In contrast, PLA caplet with 2 mm orifice sealed with Eudragit EPO/$MgCO_3$ exhibited greater than about 90% release of sumatriptan within 8 hours in SGF.

[0179] Figure 25B shows dissolution over 24 hours in SIF (pH 6.8) and SGF (pH 1.1). PLA caplet with 2 mm orifice sealed with Eudragit EPO/$MgCO_3$ exhibited greater than about 90% release of summatriptan at 8 hours in SGF. In contrast, the same type of PLA caplet with 2 mm orifice sealed with Eudragit EPO/$MgCO_3$ exhibited <5% release of sumatriptan at 24 hours in SIF. The example shows that by combining the 3D printed osmotic dosage form with Eudragit EPO/$MgCO_3$ coating, the controlled dissolution period can be significantly extended to exhibit no more than about 5% release over a period of 24 hours using PLA caplet shell in SIF (pH 6.8)

[0180] Example 6. 3D Printed osmotic pump with different orifice size

[0181] 3D printed PLA caplets 400 were prepared according to Example 2, FIG. 10 having either a 1 mm or a 2 mm diameter orifice 406, with a core 404 fill of CEP-701 SEDDS formulation according to Table 1. Dissolution was performed in 0.5% SLS. Dissolution profile is shown in FIG. 22. The PLA caplet having a 2 mm orifice exhibited about 50% release over about 1 hour, whereas the caplet having a 1 mm diameter orifice exhibited about 25% release over about 1 hour. This example shows orifice size can be adjusted to regulate controlled release profile in 3D printed caplets.

[0182] Example 7. 3D Printed osmotic pump with Dual Compartment

[0183] Dual compartment 3D printed PLA caplets were printed having two internal compartments according to FIG. 11 to allow fill with two different active pharmaceutical ingredients. External dimensions of the caplet were 21.6 mm length, 7.64 mm width, and 7.64 height. The first compartment 504a had dimensions 20 mm length, 5.99 mm width and 5.99 mm height with an orifice 506a of 2 mm diameter. The second compartment 504b was 5 mm in length, 5.99 mm width, and 5.99 mm height with an orifice 506b having a 2 mm diameter. The wall thickness was 1.32 mm.

[0184] A 4:1 wt ratio of TEV-50939 (deuterated L-Dopa) to Carbidopa was employed in a single dosage form. The first compartment was filled with 100 mg TEV-50939 formulation and the second compartment was filled with 25 mg Carbidopa formulation. Each drug was suspended in polyethylene glycol 1450 at a concentration of 80.3 mg/mL drug substance. TEV-50939 is a Levodopa formulation and may be useful to treat Parkinson's Disease. Carbidopa is a drug given to people with Parkinson's disease to inhibit peripheral metabolism of levodopa, and or prevent nausea as a side effect of levodopa when given alone. Dissolution studies were performed in 0.5% SLS in a similar fashion to Example 2. FIG. 23 shows release profiles of TEV-50939 (solid line) and carbidopa (dashed line). Each dissolution curve is an average of 3 caplets and measures release of TEV-50939 (mg) and carbidopa (mg). The dual chamber caplets released approximately 100% of TEV-50939 and Carbidopa within 12 hours. This example shows 3D printed caplets can be employed for simultaneous controlled sustained release of two different drugs.

[0185] Example 8. 3D Printed Floating Caplet for Gastric Retention

[0186] Dual compartment 3D printed PLA caplets were printed having two internal compartments according to FIG. 12. The caplet was designed with a hollow core to float by sealing one compartment. The caplet has external dimensions of 24 mm length, 8.64 mm height, and 8.64 mm width. The first internal compartment was 12 mm in length, 6.64 mm width and 6.64 mm height with a 2 mm diameter orifice. The second compartment was 5 mm length, 5.99 mm width and 5.99 mm height. The second compartment contained only air and was sealed without an orifice. The wall thickness was 1.32 mm. The first compartment was filled with TEV-50939 suspended in polyethylene glycol 1450 at a concentration of 80.3 mg/mL drug substance. Dissolution studies were performed in 0.1 N HCl SGF, and otherwise according to methods of example 2. FIG. 24 shows the dissolution profile of an average of 3 caplets (n=3). Rapid release of TEV-50939 occurred within the first hour and reached 100% within 8 hours.

[0187] The various embodiments described above are provided by way of illustration only and should not be construed to limit the claims attached hereto. Those skilled in the art will readily recognize various modifications and changes that may be made without following the example embodiments and applications illustrated and described herein, and without departing from the true spirit and scope of the following claims.

WHAT IS CLAIMED IS:

1. A filament for feeding a 3D printer, the filament comprising:
a substrate material, wherein the substrate material comprises greater than 40 wt% of a water soluble linear polymer; and
an active pharmaceutical ingredient (API) integrated into the substrate material.

2. The filament of claim 1, wherein the substrate material is selected from the group consisting of: polyvinyl alcohol (PVA), poly-lactic acid (PLA), PVA copolymer, acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), methoxypolyethylene glycol (MPEG), and combinations thereof.

3. The filament of claim 1, wherein the API comprises an amorphous solid dispersion or a crystalline solid dispersion within the substrate material.

4. The filament of claim 1, wherein the API comprises nano-crystals and the nano-crystals are embedded into the substrate material.

5. The filament of claim 1, wherein the API is covalently linked to the polymer matrix via a biodegradable link

6. The filament of claim 1, wherein the substrate material consists of polyvinyl alcohol and a setting system, and the setting system consists of hydrocolloids or mixture and cations.

7. The filament of claim 6, wherein the substrate material contains polyvinyl alcohol in an amount of about 90% to about 97% by weight, water in an amount of about 2% to about 7% by weight, hydrocolloids in an amount of at least about 0.01% by weight, and cations in an amount of about 0.001% to about 5% by weight.

8. The filament of claim 1, wherein the substrate material comprises at least one of a copolymer and a plasticizer.

9. The filament of claim 8, wherein the substrate material comprises a hydrocolloid and/or a release agent.

10. The filament of claim 9, wherein the substrate material is configured for free-radical polymerization.

11. The filament of claim 9, wherein the substrate material comprises a monomer, a plasticizer, and a release agent.

12. The filament of claim 11, wherein the substrate material comprises the release agent in an amount from about 0.1 wt% to about 3 wt%.

13. A pharmaceutical dosage form comprising:

a drug substance dosage containing capsule defining a first container compartment;

wherein the capsule is formed out of or comprises layers comprising gelatinized gelatin, HPMC, PVA, PLA, acid labile polymer, anionic copolymers based on methacrylic acid and methyl methacrylate,or Copolymers thereof.

14. The pharmaceutical dosage form of claim 13, further comprising a drug substance dosage within the first container compartment.

15. The pharmaceutical dosage form of claim 14, wherein the capsule has a wall thickness of between approximately 0.3 mm and approximately 0.5 mm.

16. The pharmaceutical dosage form of claim 14, wherein the capsule comprises:

side walls defining the first container compartment, the side walls tapering in a conical shape;

an end portion, the end portion being open to the first container compartment; and

an opposite end portion, the opposite end portion being closed and comprising a generally hemispherical end wall, the generally hemispherical end wall comprising a central part, the central being generally flat.

17. The pharmaceutical dosage form of claim 16, wherein the generally hemispherical end wall defining an opening for receiving a plug.

18. The pharmaceutical dosage form of claim 14, wherein the drug dosage substance is a formulation comprising an active pharmaceutical ingredient (API), a dilutent, a dispersing agent, and a surfactant.

19. The pharmaceutical dosage form of claim 18, wherein the API is CEP-701, the dilutent is water, the dispersing agent is PEG-1000, and the surfactant is MYRJ-52.

20. The pharmaceutical dosage form of claim 19, wherein the API is present in the drug dosage substance at about 5 wt%, the diluent or co-solvent is present in the drug dosage substance at about 8 wt%, the dispersing agent is present in the drug dosage substance at about 43.5 wt%, and the surfactant is present in the drug dosage substance at about 43.5 wt%.

21. The pharmaceutical dosage form of claim 14, further comprising a second container compartment separated from the first container compartment.

22. The pharmaceutical dosage form of claim 21, wherein a portion of the side walls defining the first container compartment has a thickness different than a portion of the side walls defining the second container compartment.

23. A process for forming a capsule wherein the capsule is formed via 3D printing from at least one component material, the process comprising:

preheating at least one first component filament material to a temperature above a gelation temperature of the first component filament material;

localized and layered dispensing of said gelatinized material through a nozzle to form at least a first part of a capsule, the first part defining a first container compartment;

filling the first container compartment with a dosage of at least one pharmaceutically active ingredient, pharmaceutically acceptable excipients, or combinations thereof; and

forming at least a second part of the capsule to enclose the first container compartment.

24. The process of claim 23, further comprising:

forming at least a third part of the capsule from the first component filament material, the third part defining a second container compartment.

25. The process of claim 23, wherein filling the first container compartment includes dispensing through a nozzle the at least one pharmaceutically active ingredient, pharmaceutically acceptable excipients, or combinations thereof.

26. The process of claim 23, wherein the first component filament material is comprises gelatinized gelatin, HPMC, PVA, PLA, or Copolymers thereof.

27. The process of claim 23, wherein localized and layered dispensing of said gelatinized material through a nozzle comprises forming a capsule wall thickness between approximately 0.3 mm to approximately 0.5 mm.

28. The process of claim 23, wherein:

dispensing the first filament material to form a generally conical wall defining the first container compartment, the generally conical wall comprising an end portion, the end portion being open to the first container compartment; and

forming a second part of the capsule comprises dispensing the first filament material to form an opposite end portion of the generally conical wall, the second end portion comprising a generally hemispherical wall, the generally hemispherical wall comprising a generally flat central portion.

29. The process of claim 28, further comprising forming an opening in the generally hemispherical end wall, the opening configured and arranged to receive a plug.

30. The process of claim 23, wherein the at least one pharmaceutically active ingredient and/or pharmaceutically acceptable excipients is a formulation comprising an active pharmaceutical ingredient (API), a dilutent, a dispersing agent, and a surfactant.

31. The process of claim 30, wherein the API is CEP-701, the diluent or co-solvent is water, the dispersing agent is PEG-1000, and the surfactant is MYRJ-52.

32. The process of claim 31, wherein the API is present in the formulation at about 5 wt%, the diluent is present in the formulation at about 8 wt%, the dispersing agent is present in the formulation at about 43.5 wt%, and the surfactant is present in the formulation at about 43.5 wt%.

33. A 3D printed functional dosage form comprising:

a body printed from a first material including a first API, the first material having a density higher than that of water;

the body defining at least one internal hollow cavity; and

wherein the body is buoyant in aqueous solution.

34. The 3D printed functional dosage form of claim 33, wherein the at least one internal hollow cavity is a single internal hollow cavity.

35. The 3D printed functional dosage form of claim 33, wherein the at least one internal hollow cavity includes a plurality of internal hollow cavities.

36. The 3D printed functional dosage form of claim 35, wherein at least some of the plurality of internal hollow cavities have a generally spherical shape.

37. The 3D printed functional dosage form of claim 33, wherein the first material comprises:

a substrate material, wherein the substrate material comprises greater than about 40 wt% of a water soluble linear polymer; and

the active pharmaceutical ingredient (API) is integrated into the substrate material, wherein the API is a BCS Class II compound.

38. The 3D printed functional dosage form of claim 37, wherein the substrate material is selected from the group consisting of: polyvinyl alcohol (PVA), poly-lactic acid (PLA), PVA copolymer, acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), methoxypolyethylene glycol (MPEG), and combinations thereof.

39. A 3D printed functional dosage form comprising:

a plurality of tablets printed from a first material including an API, each tablet having a diameter of approximately 3 mm or less.

40. A 3D printed dispensing device comprising:

a handle portion;

a body potion connected to the handle portion, the body portion including a plurality of recesses for holding a plurality of dosage forms; and

a cover connected to the body portion, the cover being movable with respect to the body to expose a predetermined number of the recesses in the body portion.

FIG. 1

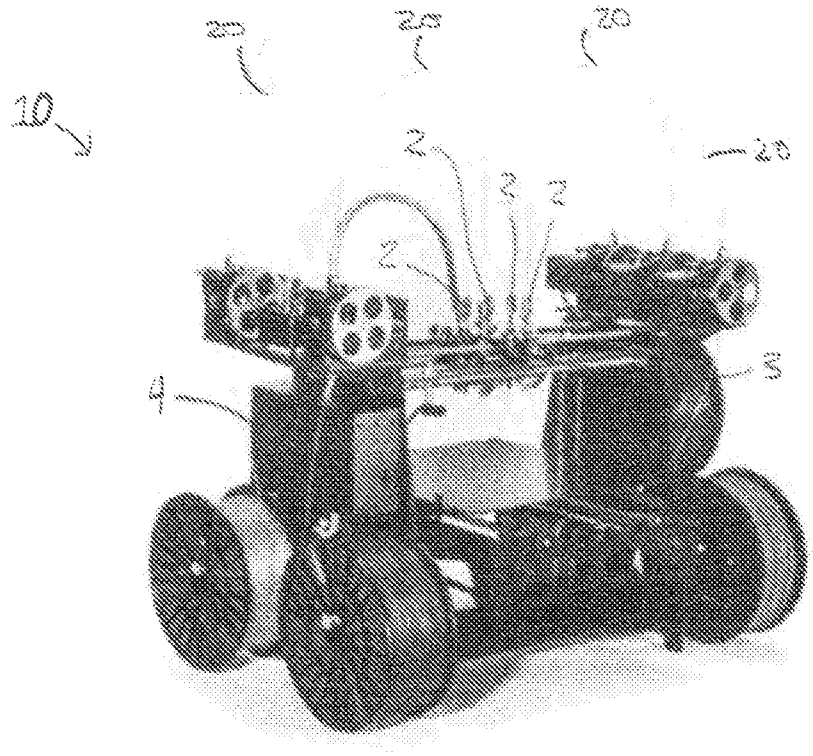


FIG. 1A

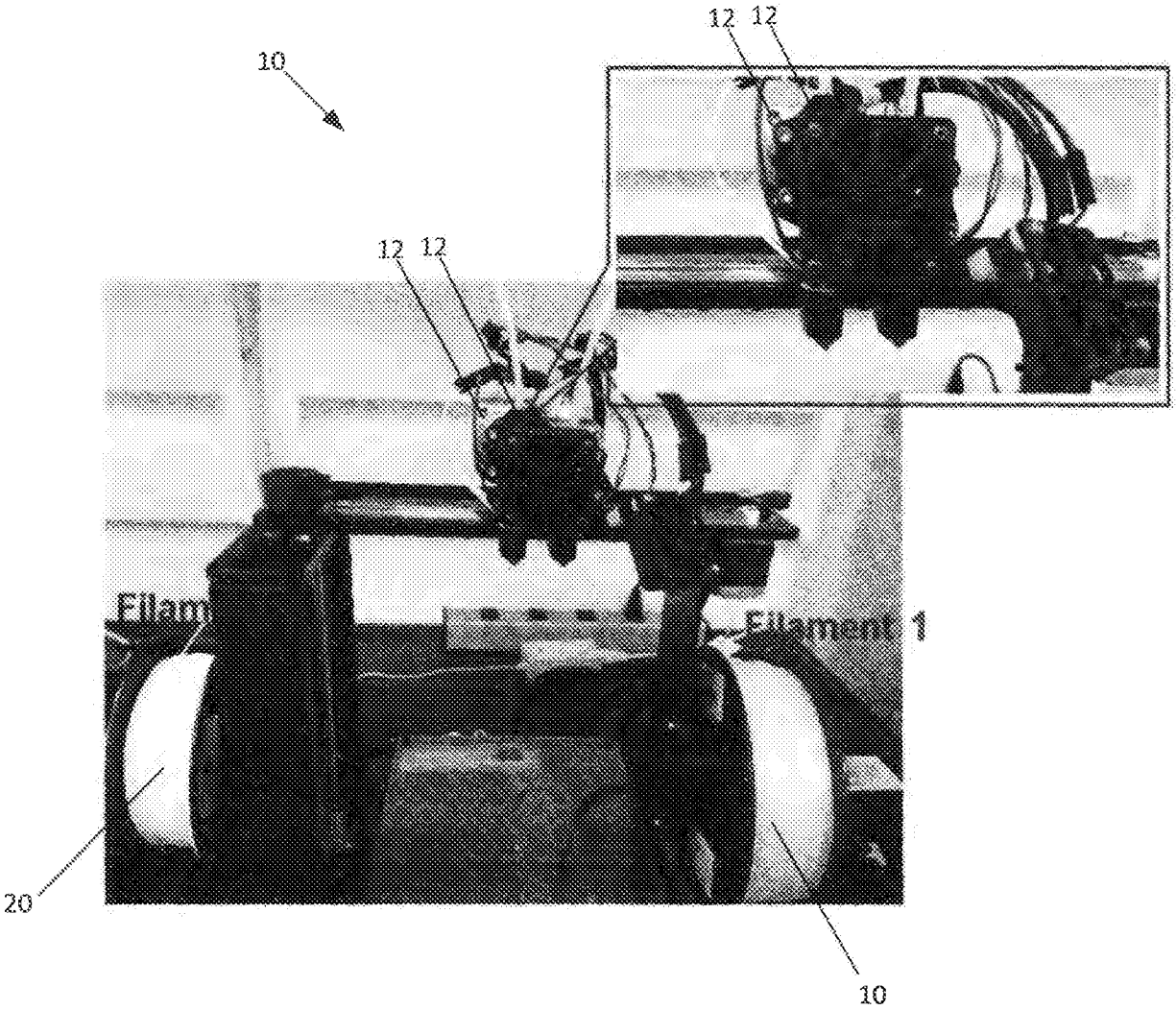


FIG. 2

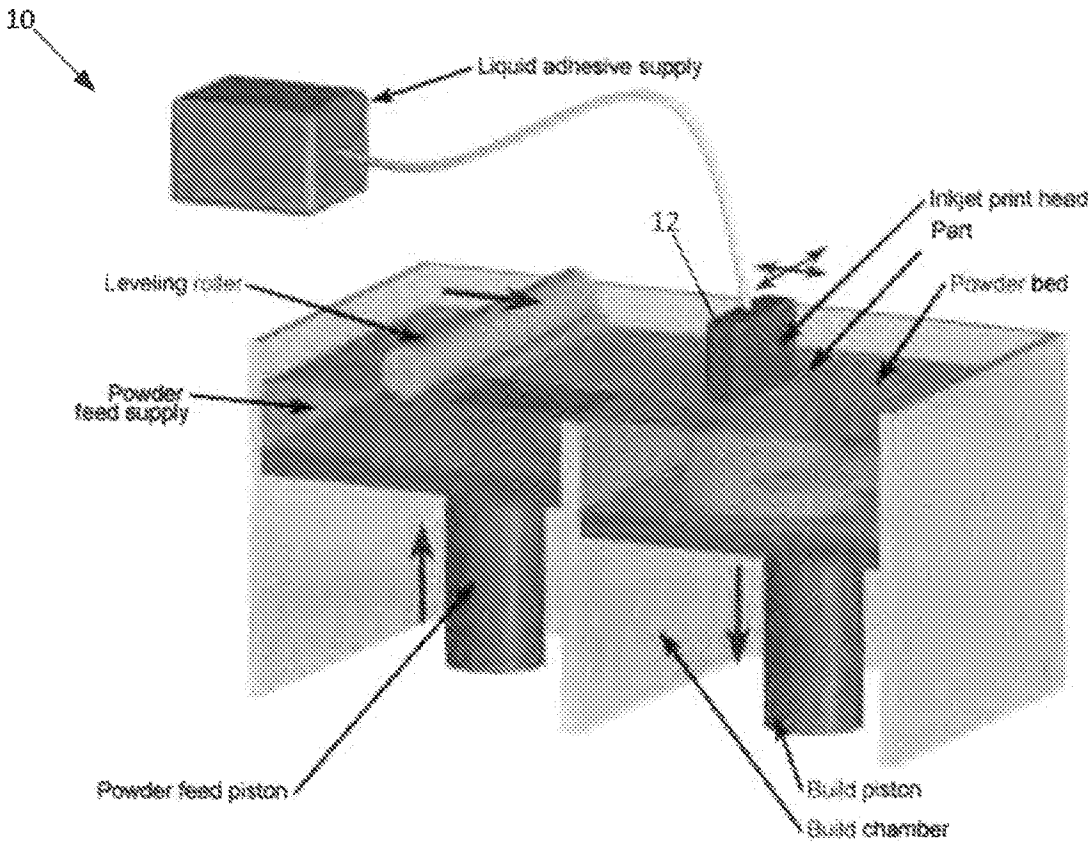

10
Liquid adhesive supply
12
Inkjet print head
Part
Leveling roller
Powder bed
Powder
feed supply
Powder feed piston
Build piston
Build chamber

FIG. 3

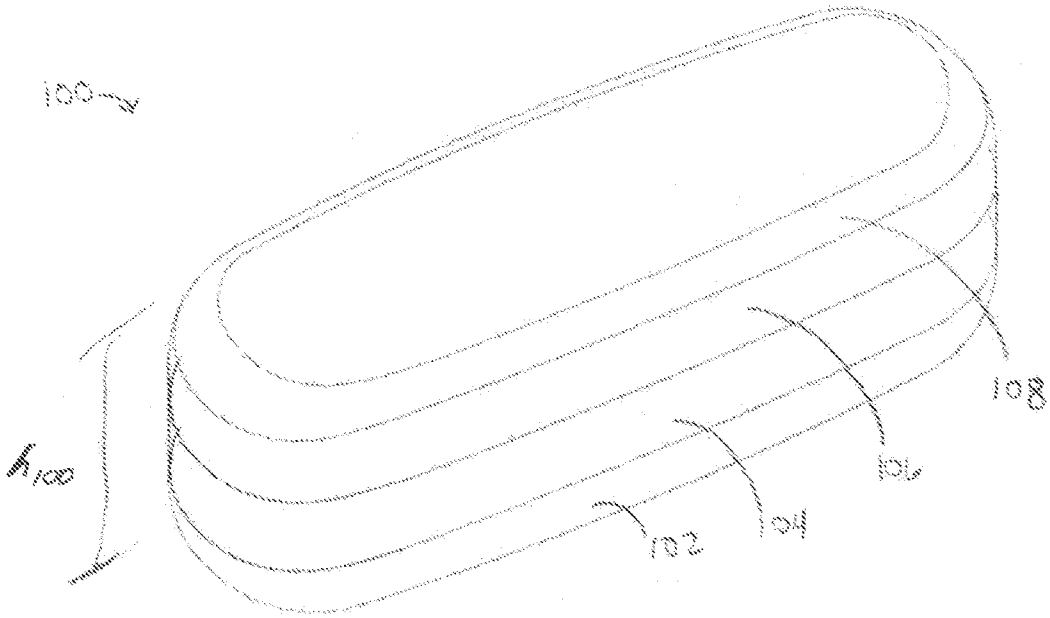


FIG. 4

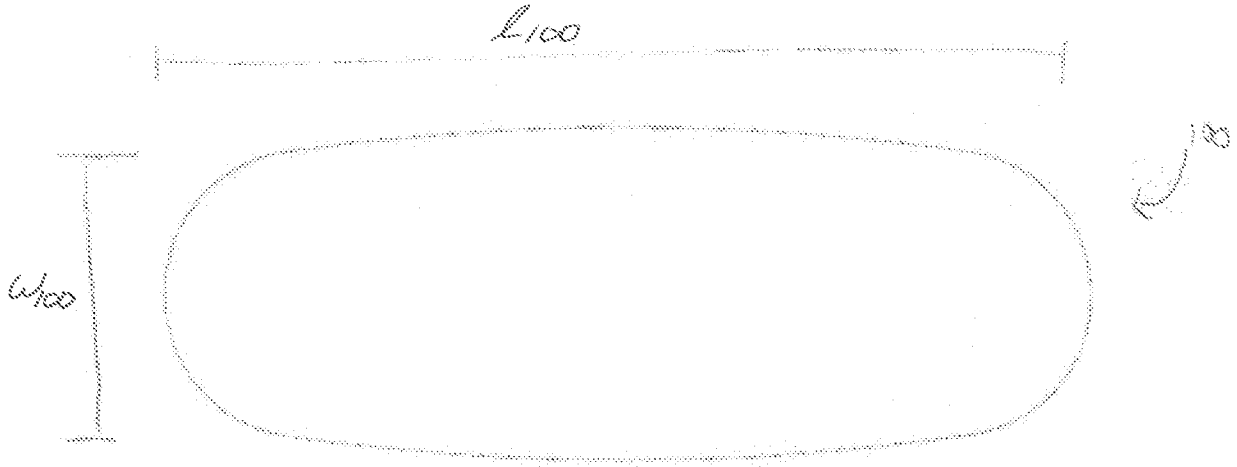


FIG. 5

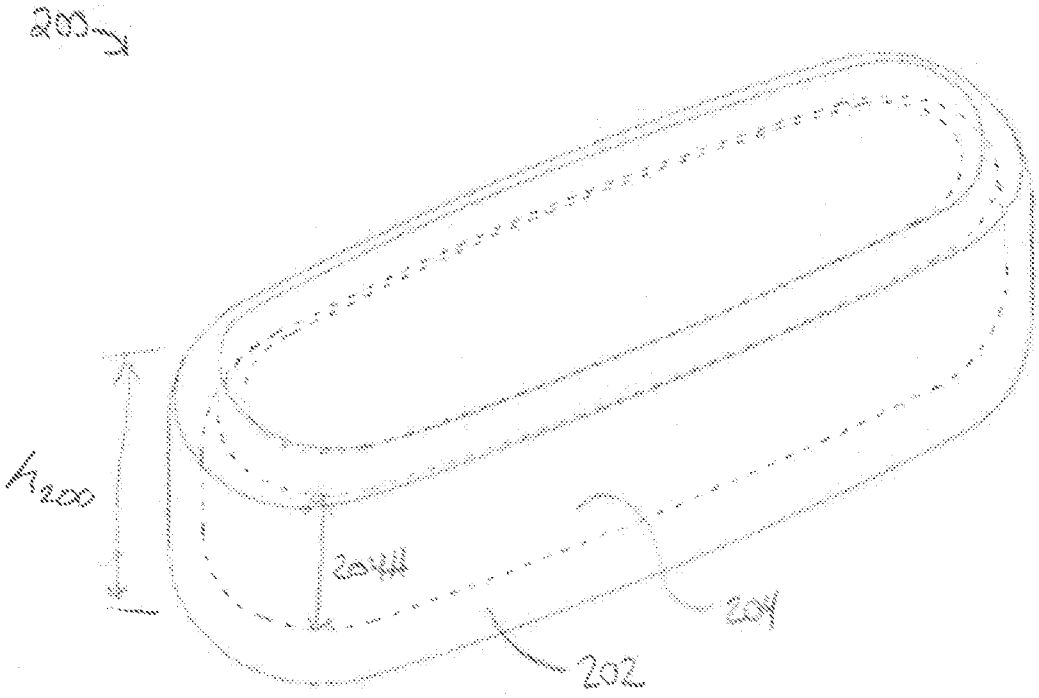


FIG. 6

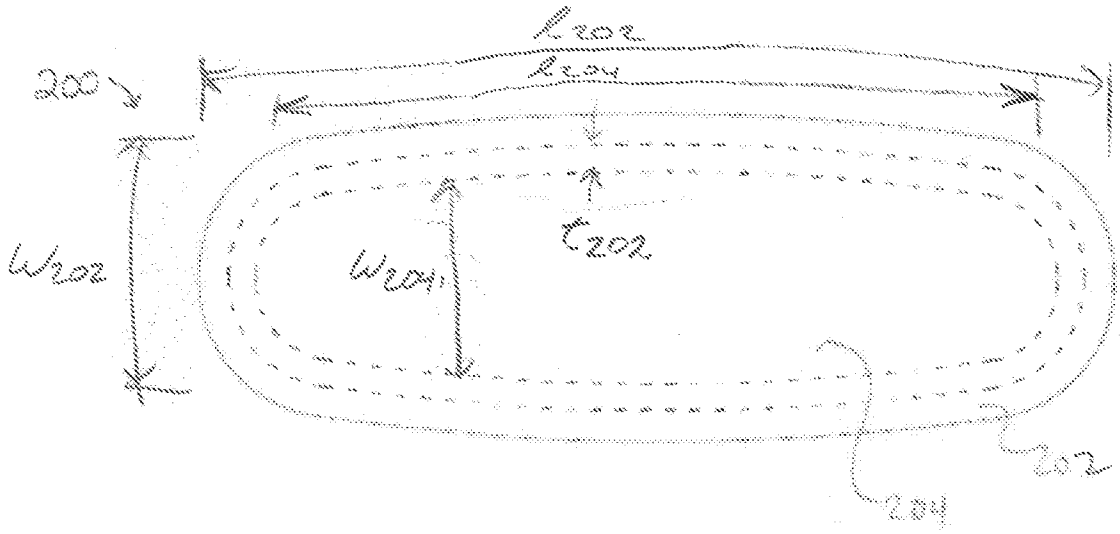


FIG. 7

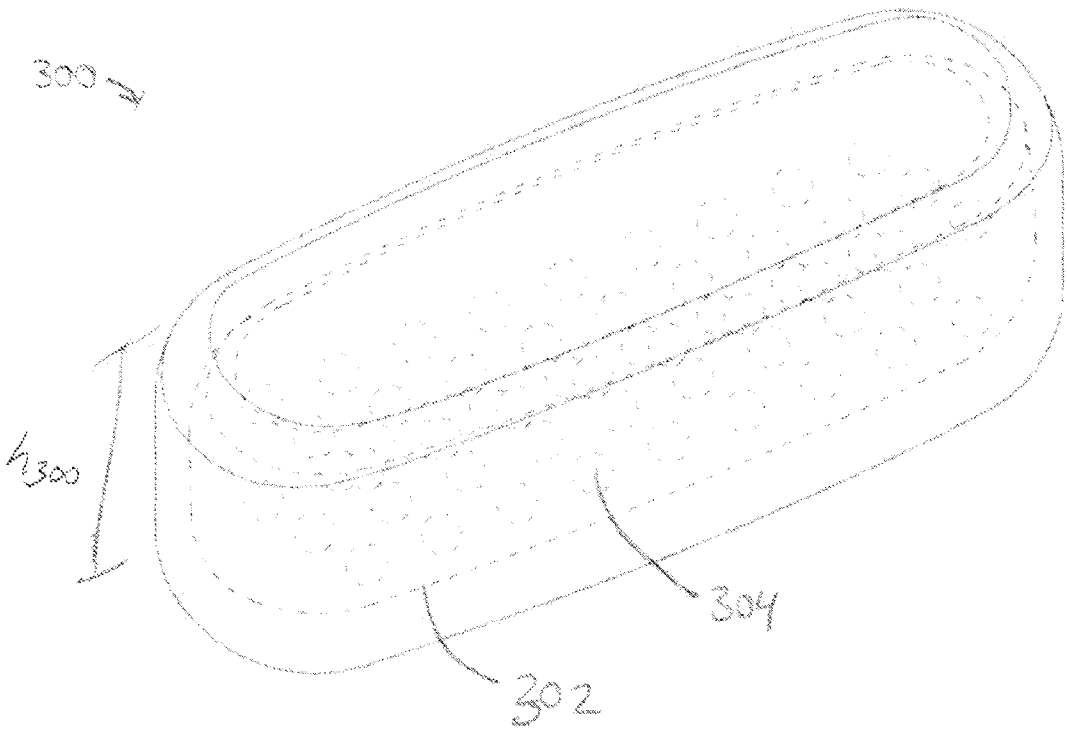


FIG. 8

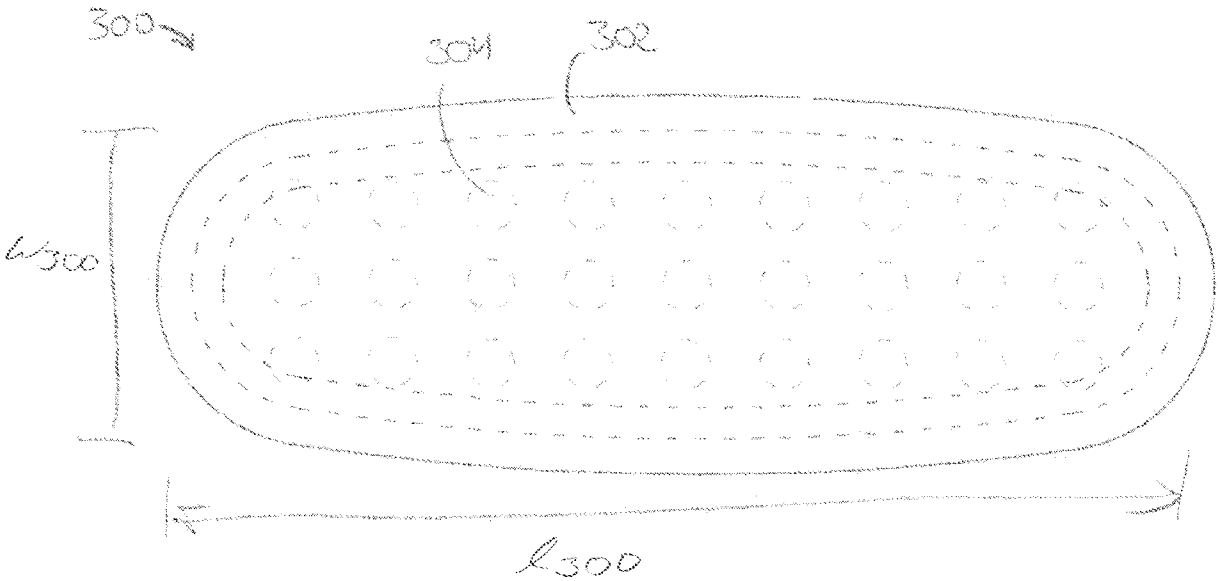
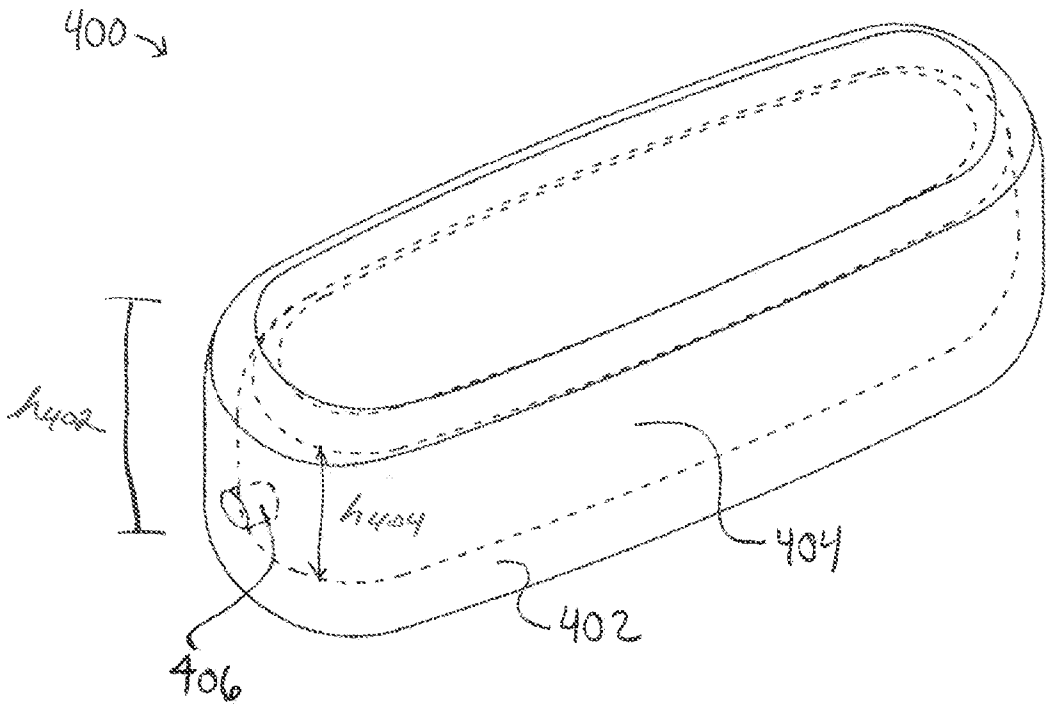


FIG. 9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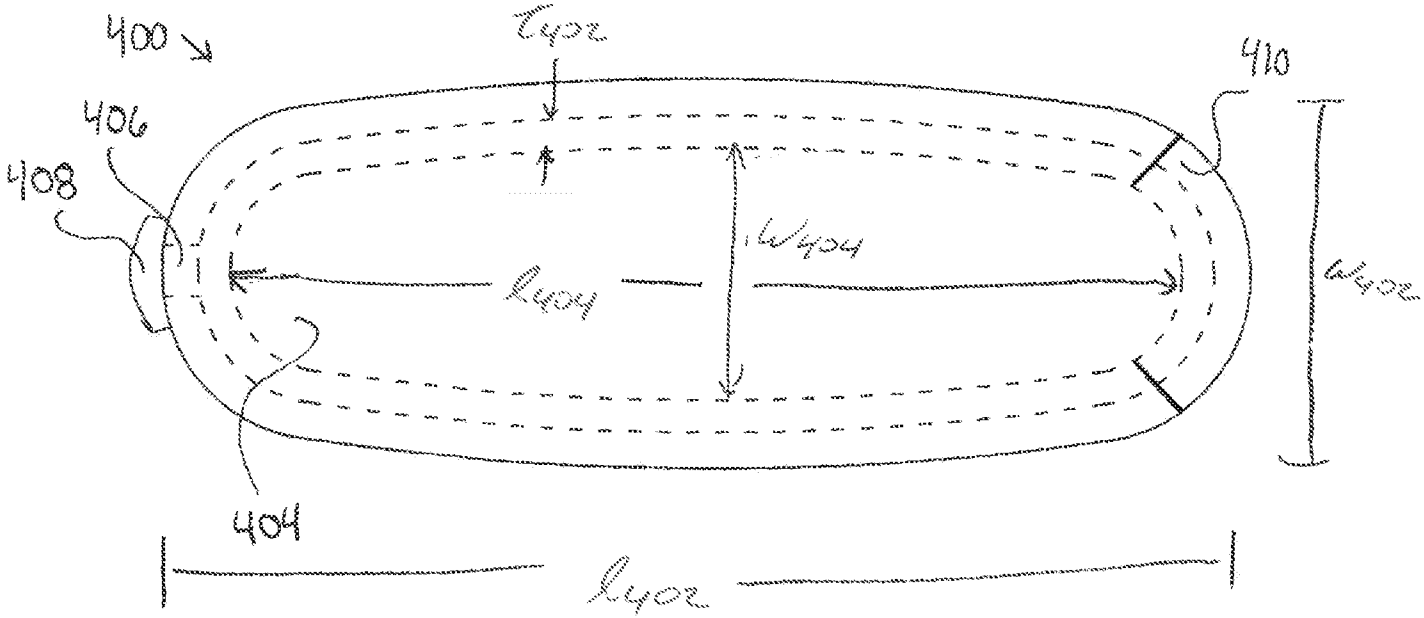
406

FIG. 10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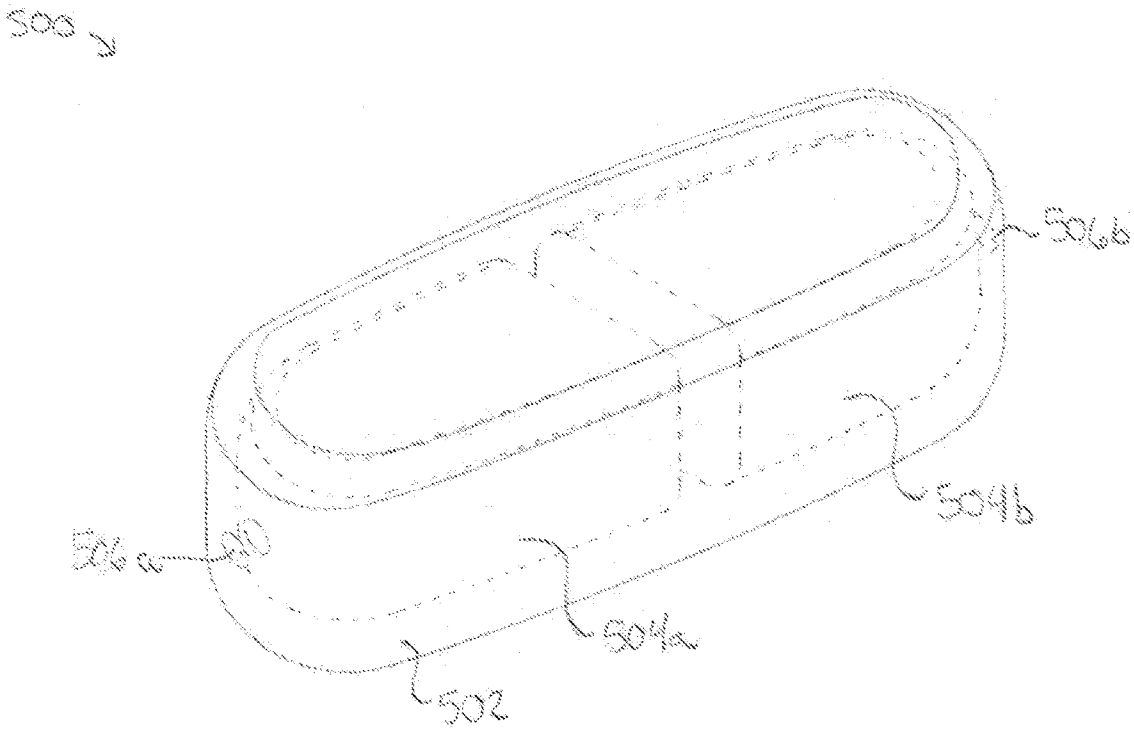
ℓ_{404}
w_{402}
404
ℓ_{402}

FIG. 11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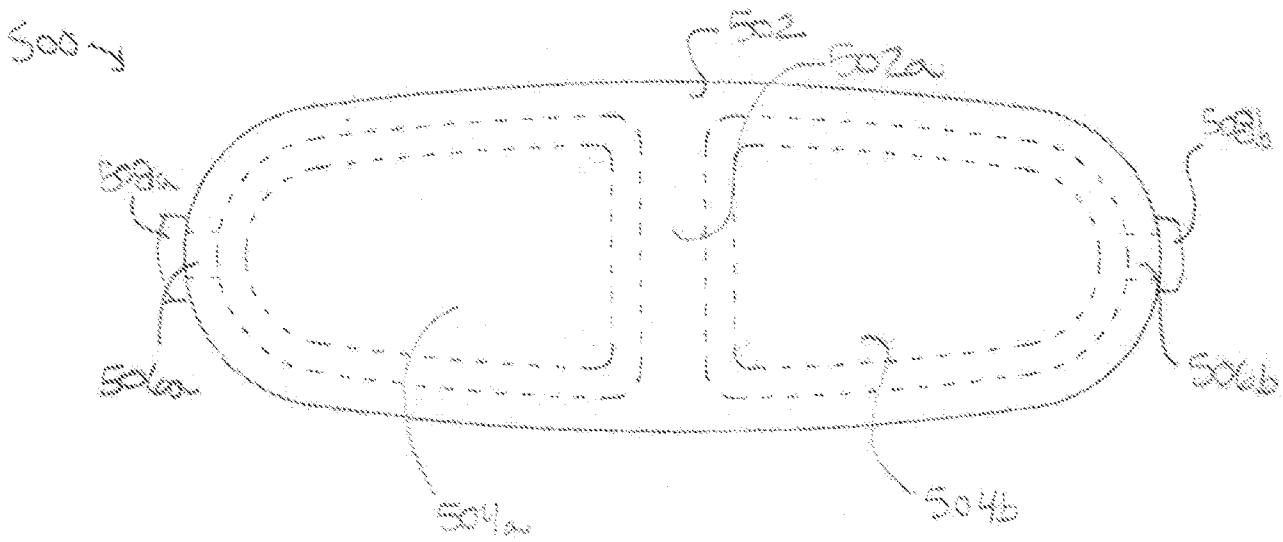
504a
502

FIG. 12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502
502a
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504b
504a
504b

FIG. 13

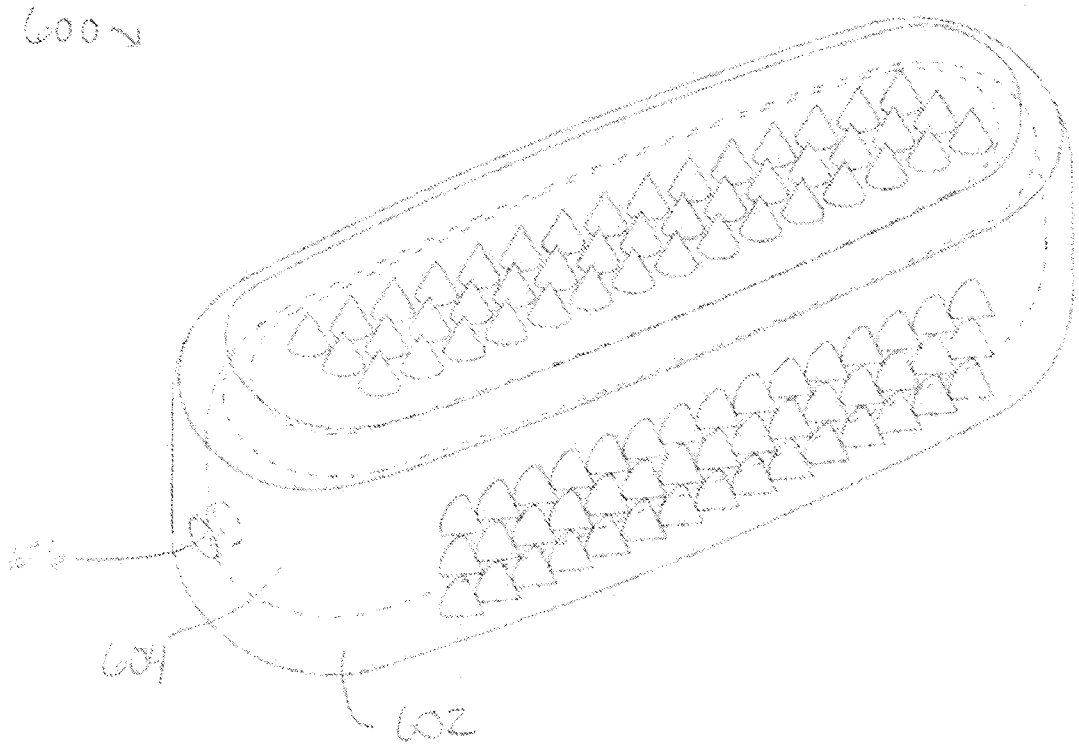


FIG. 14

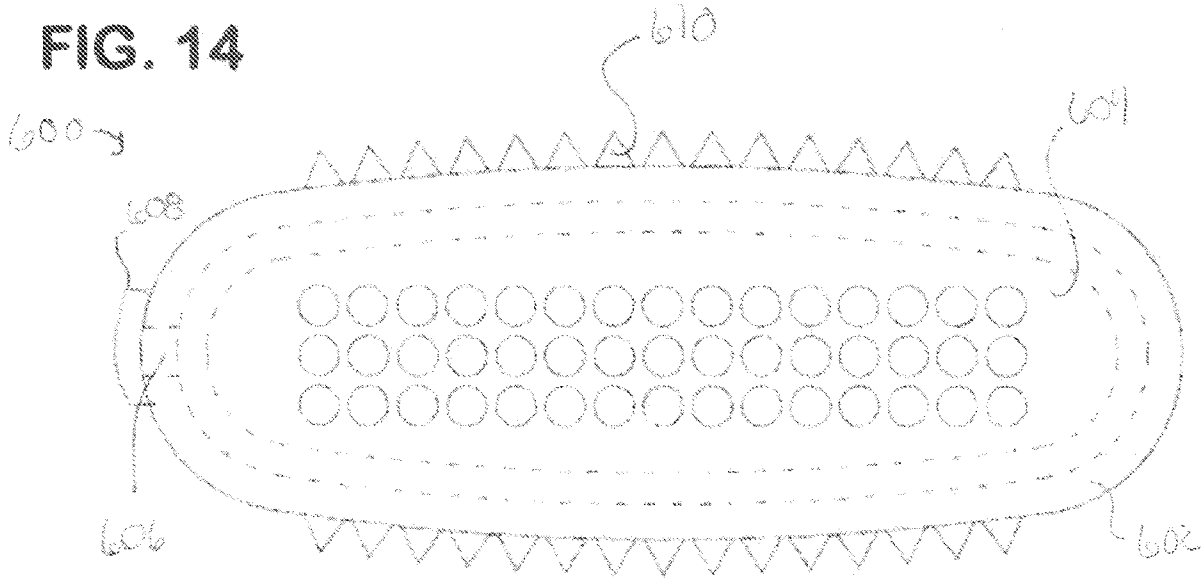


FIG. 15

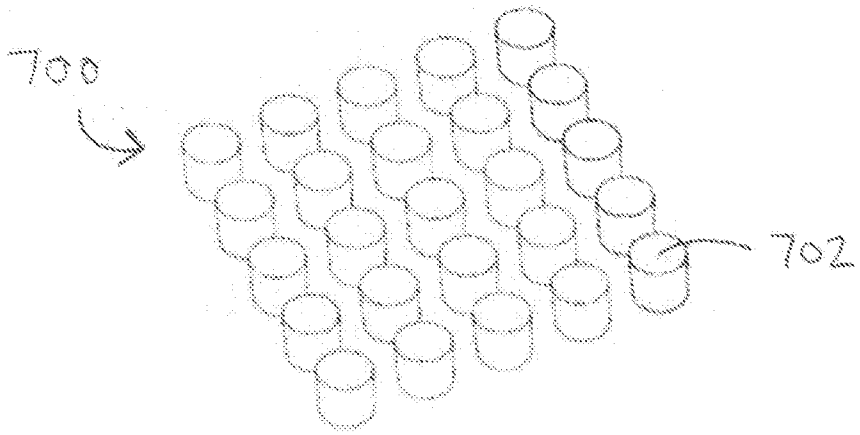


FIG. 16

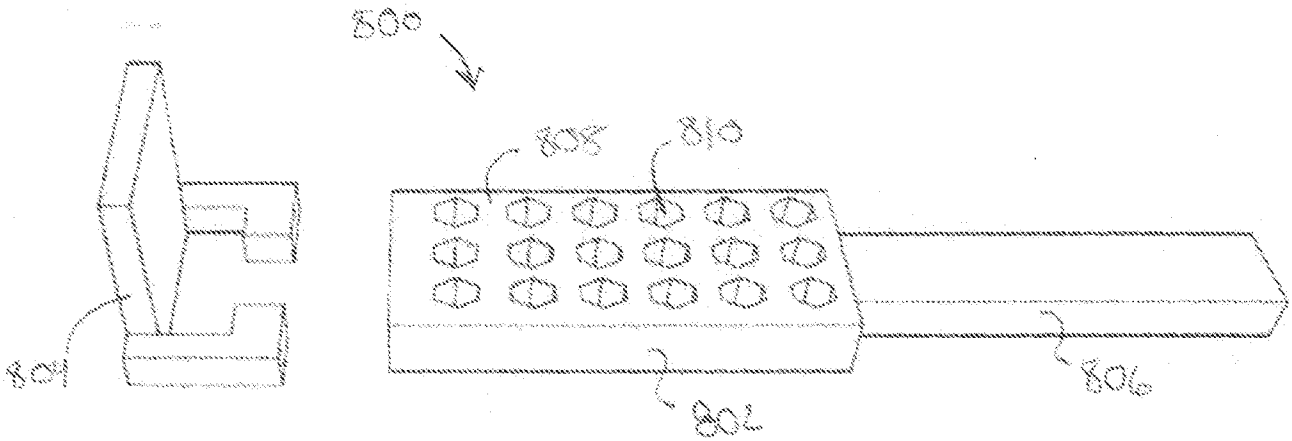


FIG. 17

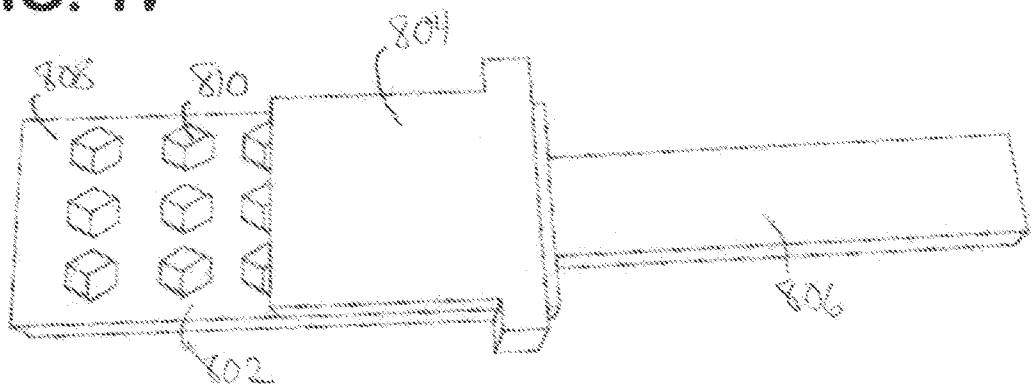


FIG. 17A

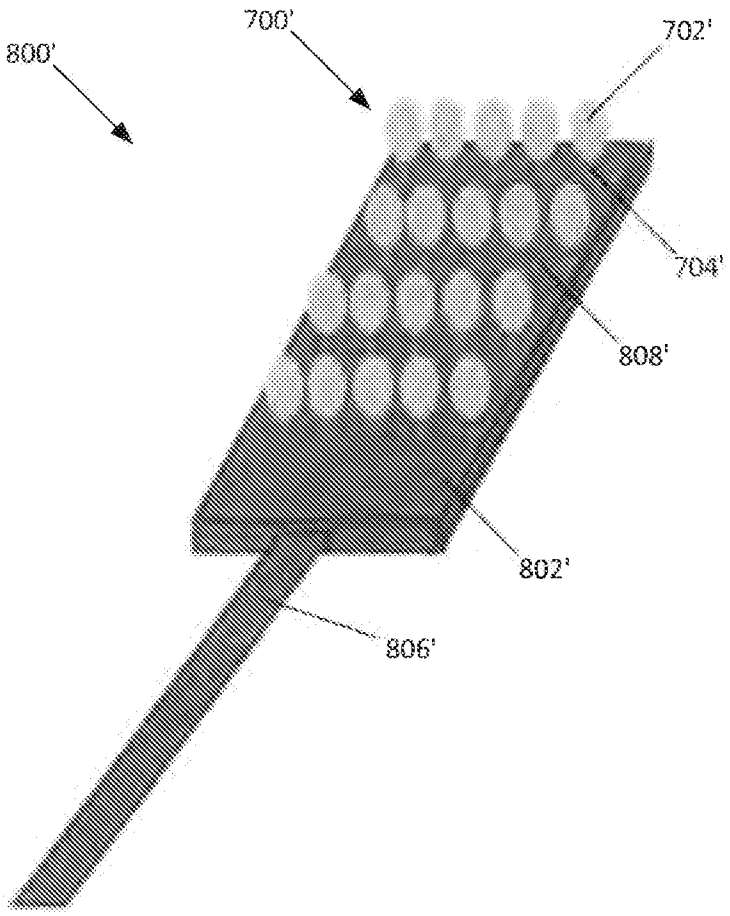
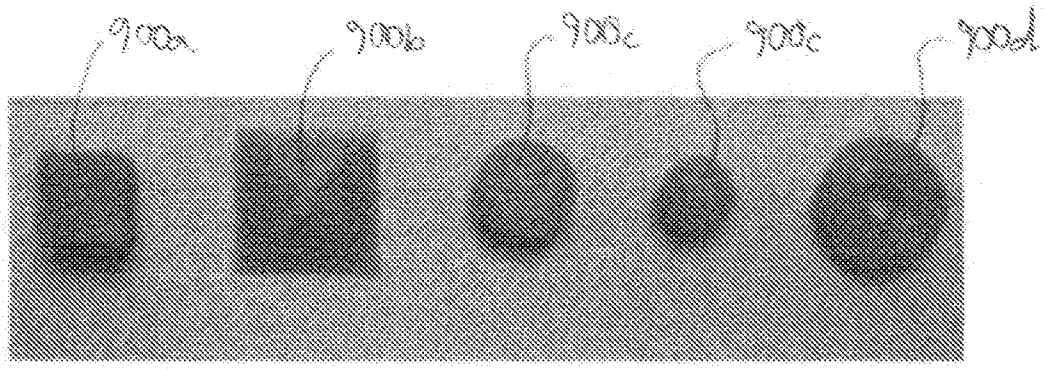


FIG. 18



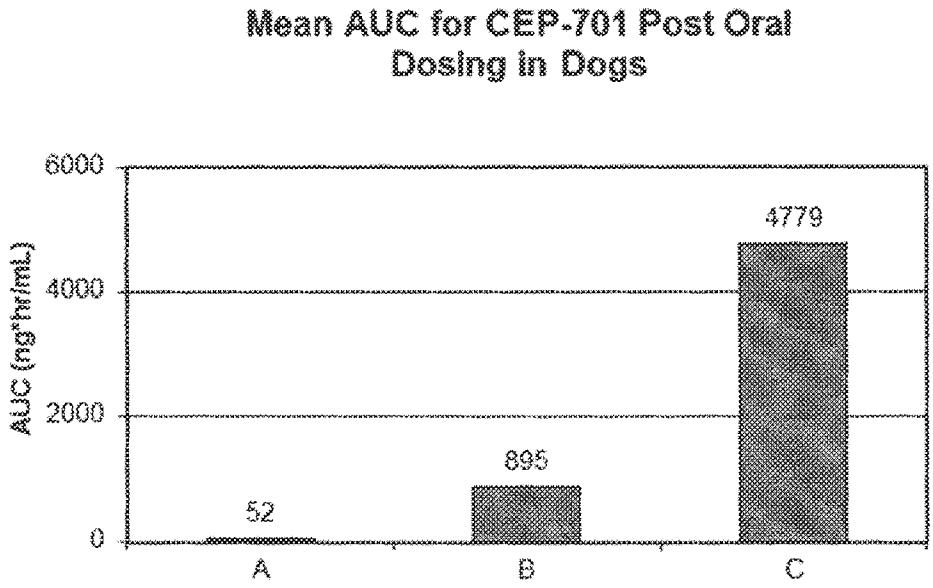

Mean AUC for CEP-701 Post Oral Dosing in Dogs
AUC (ng*hr/mL)
6000
4000
2000
0
52
895
4779
A
B
C

FIG. 19A

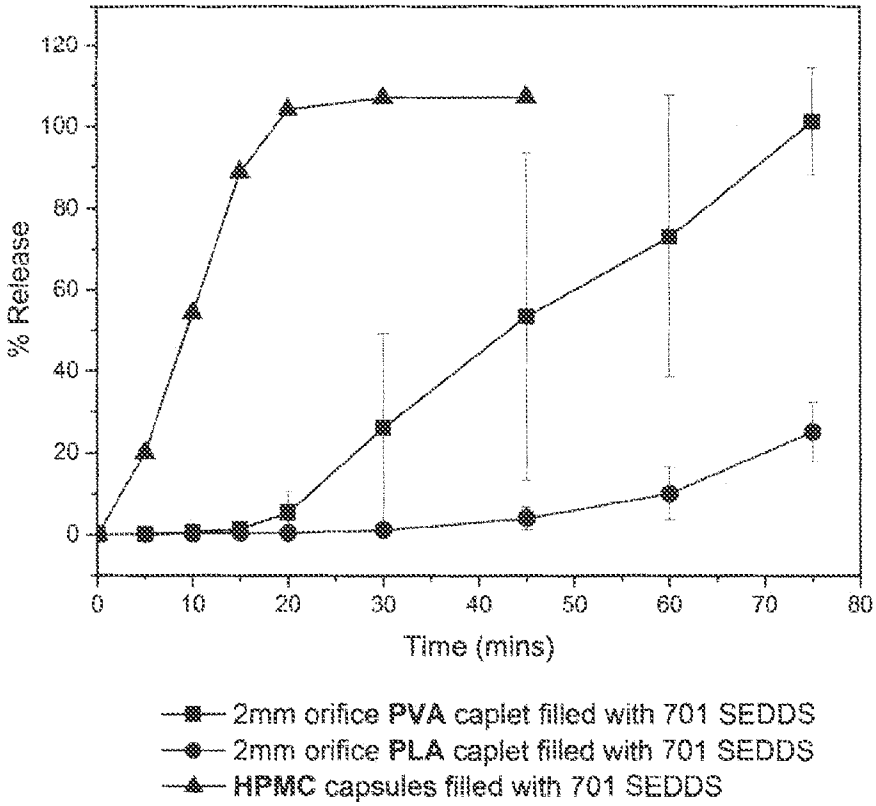

% Release
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Time (mins)
2mm orifice PVA caplet filled with 701 SEDDS
2mm orifice PLA caplet filled with 701 SEDDS
HPMC capsules filled with 701 SEDDS

FIG. 19B

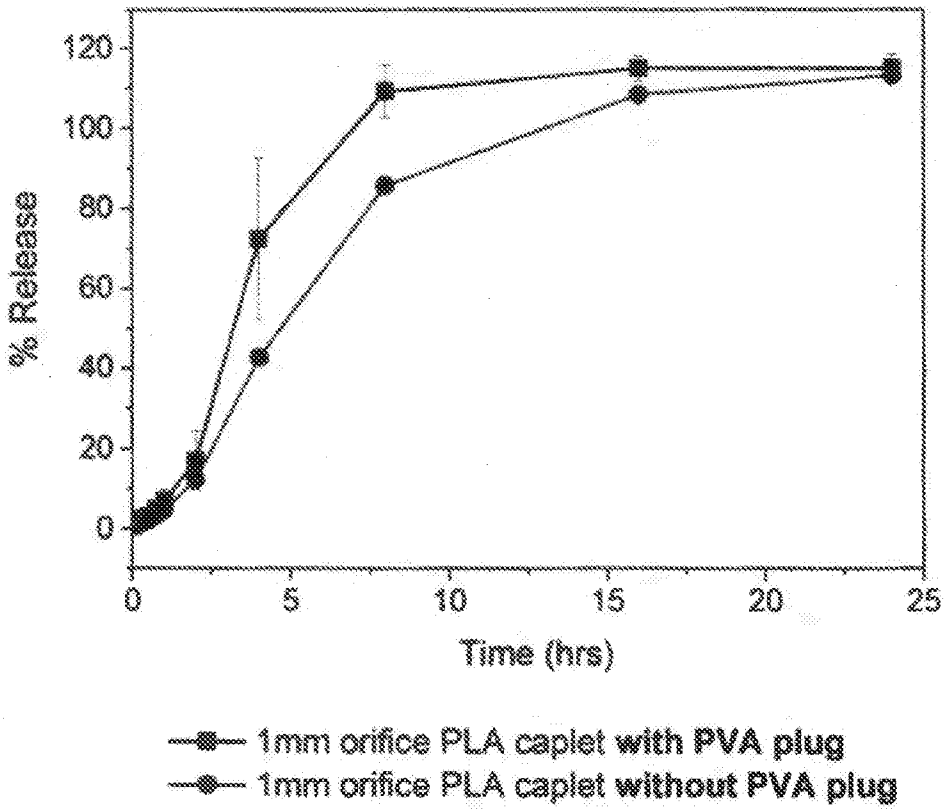


FIG. 20A

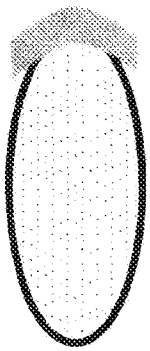


FIG. 20B

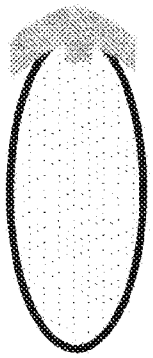


FIG. 20C

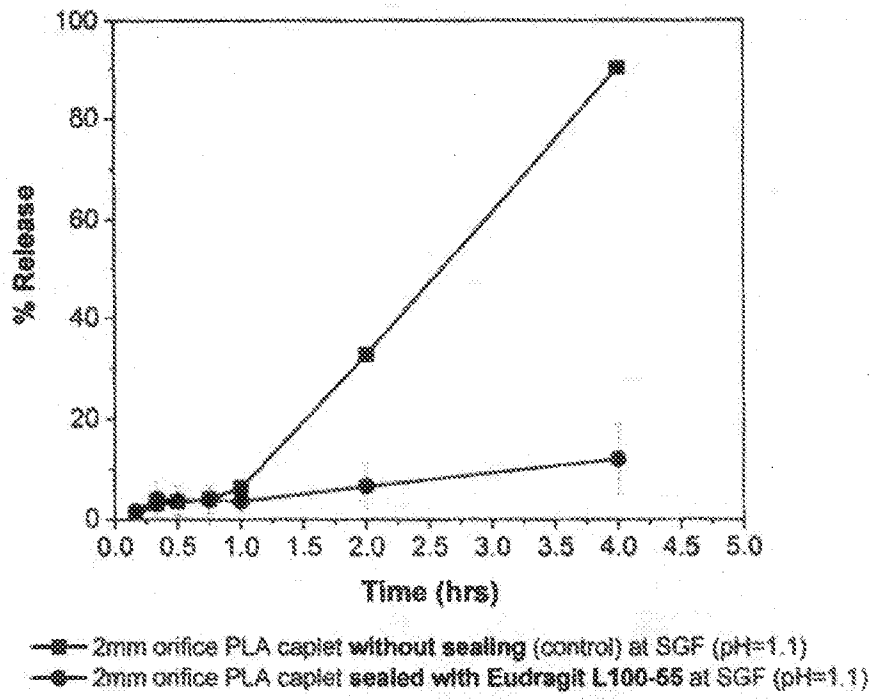


FIG. 21A

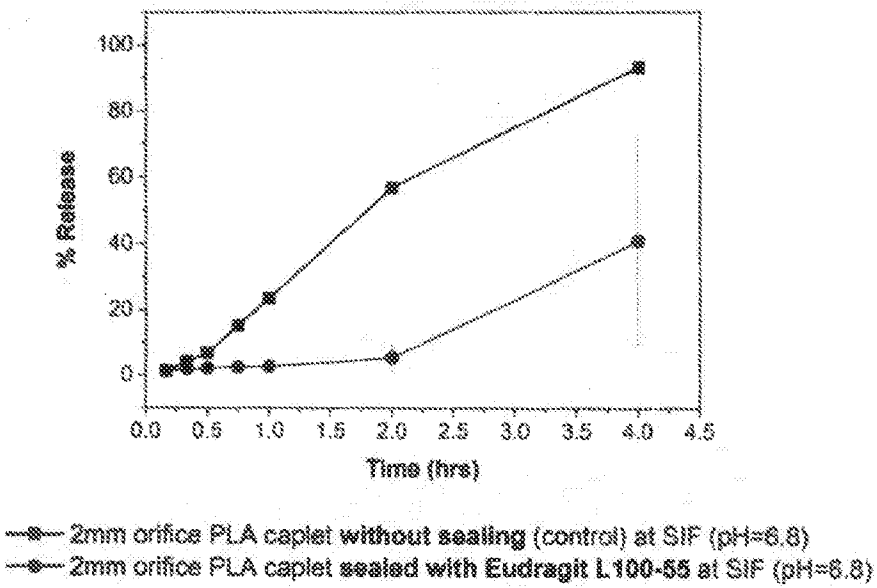


FIG. 21B

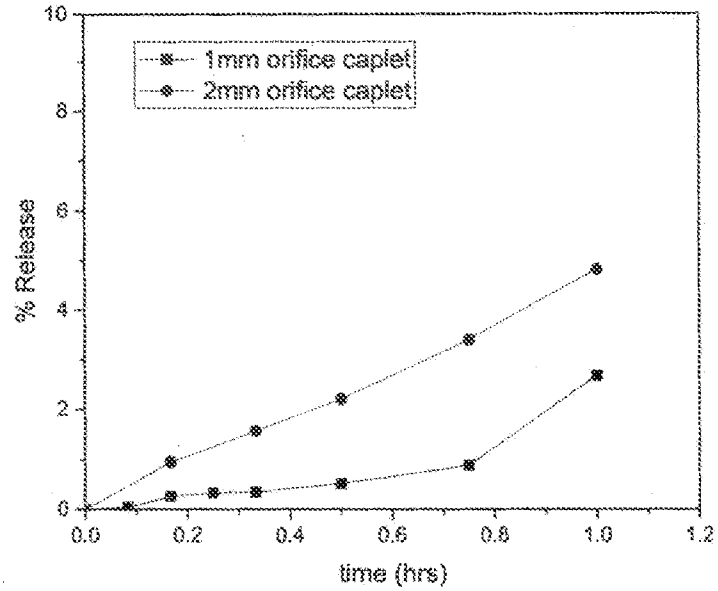

1mm orifice caplet
2mm orifice caplet
% Release
time (hrs)
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
1.2

FIG. 22

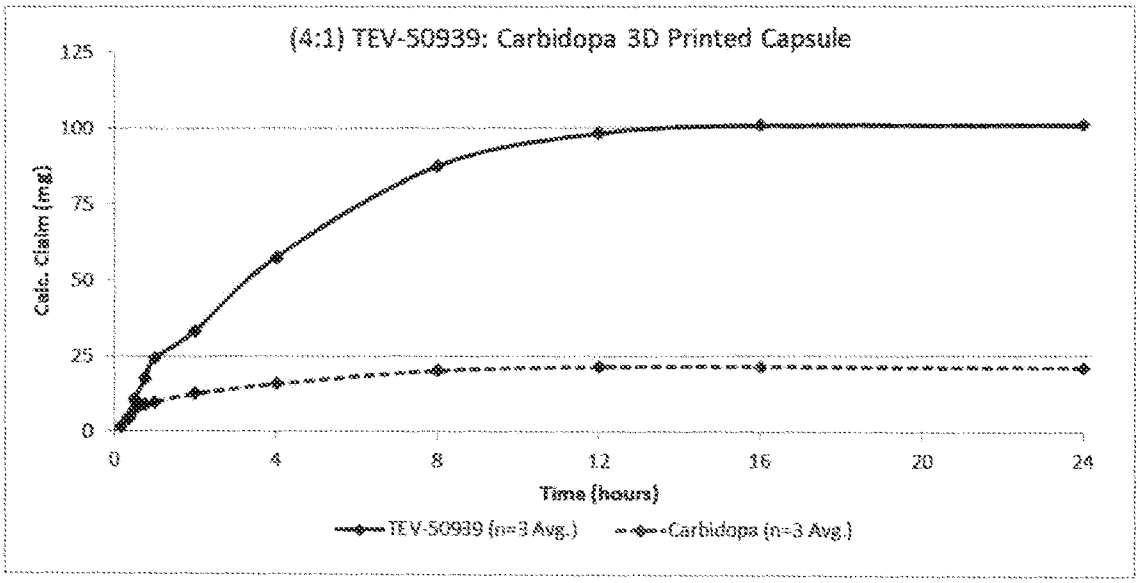

(4:1) TEV-50939: Carbidopa 3D Printed Capsule
Calc. Claim (mg)
Time (hours)
TEV-50939 (n=3 Avg.)
Carbidopa (n=3 Avg.)
0
25
50
75
100
125
0
4
8
12
16
20
24

FIG. 23

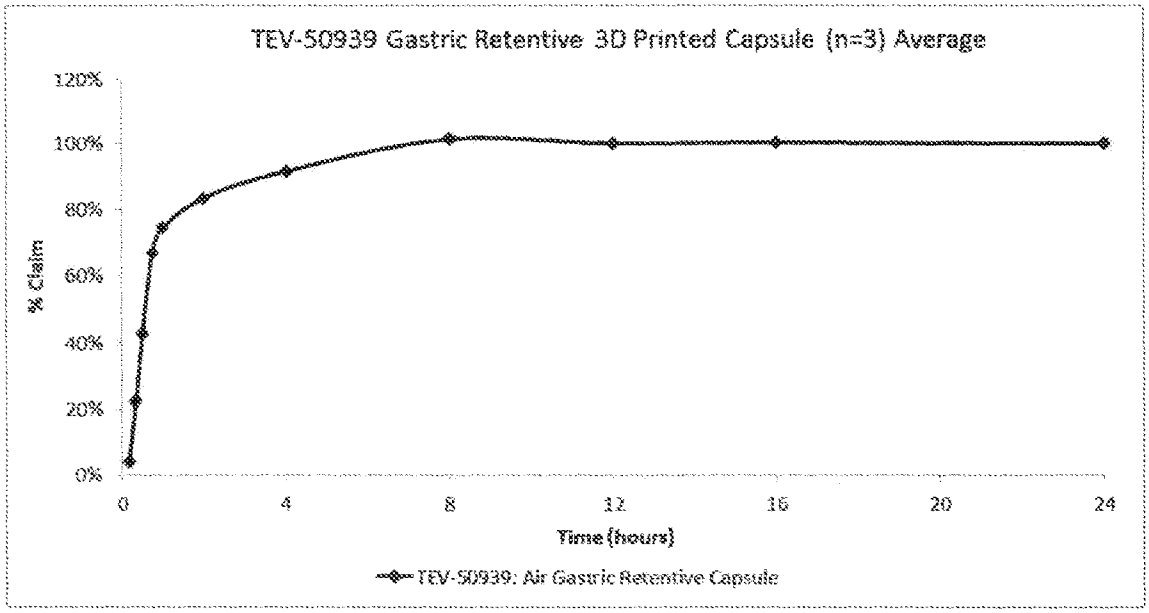

TEV-50939 Gastric Retentive 3D Printed Capsule (n=3) Average
120%
100%
80%
60%
40%
20%
0%
% Claim
0
4
8
12
16
20
24
Time (hours)
TEV-50939: Air Gastric Retentive Capsule

FIG. 24

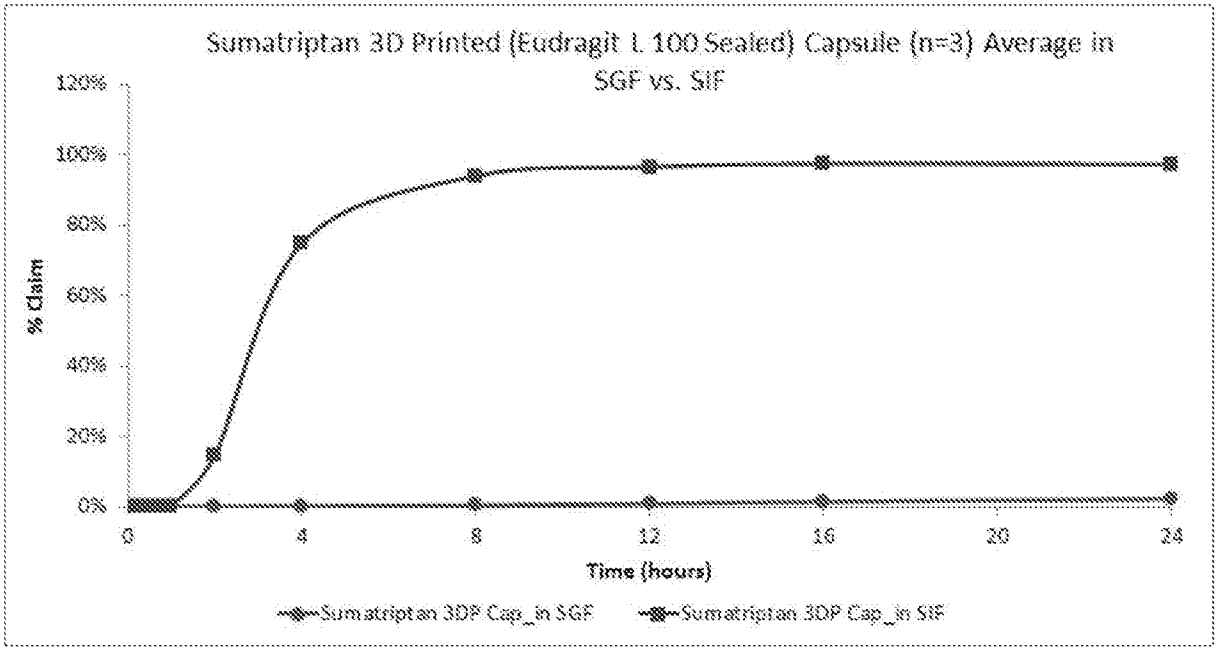


Figure 25A

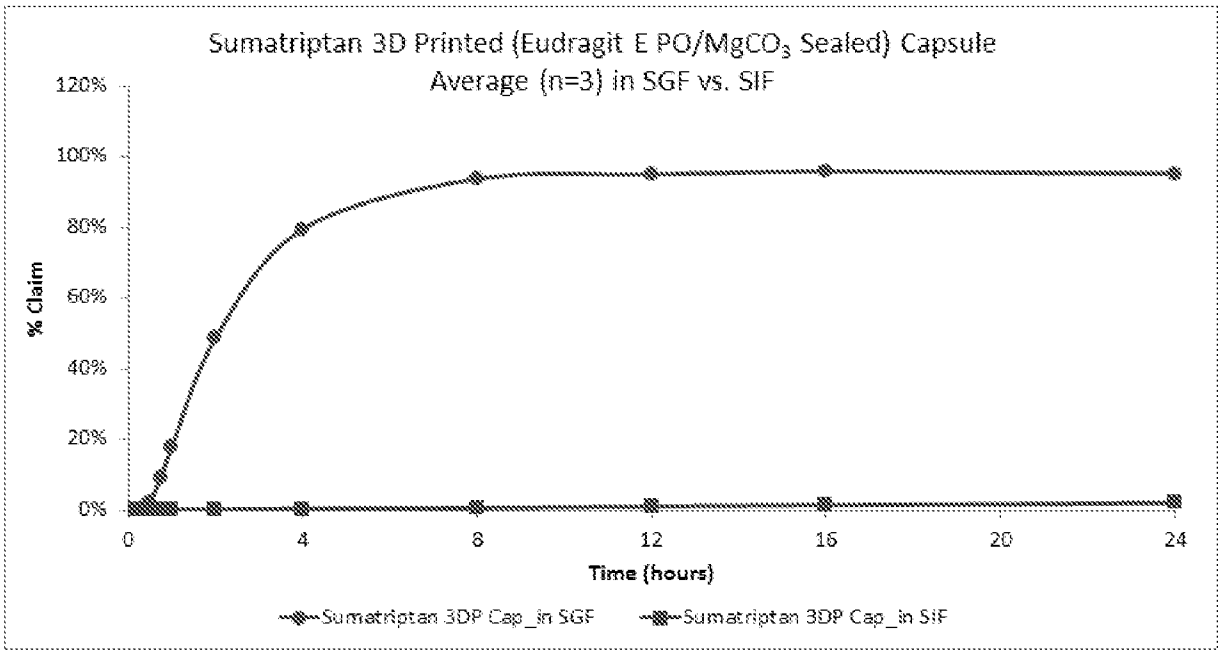


Figure 25B