Abstract:
A stable solid pharmaceutical dosage form for oral administration. The dosage form includes a substrate that forms at least one compartment and a drug content loaded into the compartment. The dosage form is so designed that the active pharmaceutical ingredient of the drug content is released in a controlled manner.
DOSAGE FORMS AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Applications Serial Nos. 62/170,645, filed June 3, 2015, and 62/313,092, filed March 24, 2016, the entire disclosures of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention generally relates to a pharmaceutical dosage form and controlled release of biologically active agents, diagnostic agents, reagents, cosmetic agents, and agricultural/insecticide agents.

BACKGROUND

[0003] Pharmaceutical drug products must be manufactured into dosage forms in order to be marketed for use. Conventional dosage forms typically involve a mixture of active pharmaceutical ingredients and inactive components (excipients), along with other non-reusable materials such as a capsule shell. Categories of dosage forms include liquid dosage forms (e.g., solutions, syrups, elixirs, suspensions and emulsions), solid dosage forms (e.g., tablets, capsules, caplets and gel-caps), and semi-solid dosage form (e.g., ointments and suppositories), among which solid dosage forms are more advantages to administer drugs in systemic effect through oral route.

[0004] Tablets are most commonly used solid dosage forms, which shows more benefits in terms of manufacturing, packaging and shipping, and easy to identify and swallow. After being administered into a living organism, a tablet undergoes interplay with the body in exerting pharmaceutical effects. The active pharmaceutical ingredient must be released from the tablet before being absorbed into the blood circulation. The pharmaceutical ingredient then disperses, disintegrates or dissolves throughout the fluids and tissues of the body.

During drug absorption, disposition, metabolism, and elimination process, dosage forms play a critical role in determining the release profile and bioavailability of the drugs. Therefore, there is a continuing needs for developing dosage forms that provides controlled drug delivery systems, which may offer desired drug plasma levels, reduced side effects as well as improved patient compliance.
BRIEF SUMMARY OF THE INVENTION

[0005] In one aspect, the present disclosure provides a dosage form including a substrate forming at least one compartment and a drug content loaded into the compartment. In certain embodiments, the drug content is operably linked to the substrate. In certain embodiments, the drug content is detached from the substrate and freely movable in the compartment.

[0006] In certain embodiments, the substrate is made from a thermoplastic material 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 certain embodiments, the thermoplastic material is selected from the group consisting of polyvinyl caprolactam-poly vinyl acetate-polyethylene glycol graft copolymer 57/30/13, 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(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic 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 (HMPC), hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate (HPMCAS), poly(lactide-co-glycolide) (PLGA), carborner, poly(ethylene-co-vinyl acetate), ethylene-vinyl acetate copolymer, polyethylene (PE), and polycaprolactone (PCL), hydroxy propyl cellulose (HPC), Polyoxy 40 Hydrogenerated Castor Oil, Methyl cellulose (MC), Ethyl cellulose (EC), Poloxamer, hydroxypropyl methylcellulose phthalate (HPMCP), Poloxamer, Hydrogenated Castor & Soybean Oil, Glycerol 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.

[0007] In certain embodiments, the compartment has a shape selected from the group consisting of a pie shape, a cone shape, a pyramid shape, a cylindrical shape, a cubic or
cuboidal shape, a triangular or polygonal prism shape, a tetrahedron and a combination thereof.

[0008] In certain embodiments, the first drug content is in a form of nanoparticles, microneedles or forms a net.

[0009] In certain embodiments, the drug content comprises an active pharmaceutical ingredient (API). In certain embodiments, the API is selected from the groups consisting of local anesthetics, antiepileptic drugs and anticonvulsants, anti-Alzheimer’s disease drugs, analgesics, antipodalagric, anti-hypertensive drugs, antiarrhythmic drugs, diuretic drugs, drugs for treating liver diseases, drugs for treating pancreatic diseases, antihistamine drugs, anti-allergic drugs, glucocorticoid drugs, hormone drugs and contraceptive drugs, hypoglycemic drugs, anti-osteoporosis drugs, antibiotics, sulfonamides, quinolones, and other synthetic antibacterial drugs, anti-tuberculosis drugs, antiviral drugs, anti-neoplasm drugs, immune-modulators, cosmetically active agents and traditional Chinese medicine. In certain embodiments, the API is a biologically active agent, a diagnostic agent, a reagent for scientific research, a cosmetic agent, or an agricultural/insecticide agent.

[0010] In certain embodiments, the drug content further comprises an excipient. In certain embodiments, the excipient is made from materials selected from the group consisting of cocoa butter, polyethylene glycol (PEG), sucrose, glucose, galactose, fructose, xyloselactose, maltose, trehalose, sorbitol, mannitol, maltodextrins, raffinose, stachyose, fructo-oligosaccharides, water-soluble oligomers and polymers and a combination thereof.

[0011] In certain embodiments, the compartment has an aperture that is blocked and/or sealed by a plug. In certain embodiments, the plug is made from a porous polymer, an erodible polymer, a pH sensitive polymer or natural occurring material such as shellac. In certain embodiments, the plug is made from a material selected from the group consisting of water-soluble polymers, erodible or dissolvable polymers, wax like materials or saccharides or any materials mentioned above.

[0012] In certain embodiments, the dosage form comprises a gas-generating component loaded into the first compartment. In certain embodiments, the gas-generating component is selected from the group consisting of water-soluble carbonates, sulphites, bicarbonates, sodium carbonate, sodium bicarbonate, sodium metabisulphite, calcium carbonate, and combinations thereof, which on contact with gastric fluid releases carbon dioxide or sulphur dioxide gas. In certain embodiments, the gas-generating component is a combination of sodium bicarbonate and organic acid (e.g., citric acid, tartaric acid etc).
In another aspect, the present disclosure provides a dosage form including a substrate forming at least a first compartment and a second compartment. The dosage form includes a first drug content loaded into the first compartment and a second drug content loaded into the second compartment.

In certain embodiments, the first compartment and the second compartment are connected. In certain embodiments, the first compartment and the second compartment are disconnected.

In certain embodiments, the first drug content is the same as the second drug content. In certain embodiments, the first drug content is different from the second drug content.

In certain embodiments, the first compartment has a first aperture that is covered by a first plug, and the second compartment has a second aperture that is covered by a second plug. In certain embodiments, the first plug is more permeable than the second plug. In certain embodiments, the first plug erodes faster than the second plug.

In certain embodiments, the first compartment is enclosed by a first wall, and the second compartment is enclosed by a second wall.

In certain embodiments, the first wall is thicker than the second wall. In certain embodiments, the first wall is more permeable than the second wall. In certain embodiments, the first wall erodes faster than the second wall.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1A shows a conventional dosage form comprising a drug content.

FIG. 1B illustrates the release profile of the dosage form of FIG. 1A when administered to a subject.

FIG. 1C shows the plasma drug level when the dosage form of FIG. 1A is administered to a subject.

FIG. 1D shows the plasma drug level of a controlled release dosage form having the zero-order drug release profile when administered to a subject.

FIG. 2A shows an exemplary dosage form having a substrate that forms a compartment with a drug content loaded into the compartment.

FIG. 2B shows the release of the API from the dosage form illustrated in FIG. 2A.

FIG. 3 shows an exemplary dosage form having a substrate that forms a compartment with another dosage form loaded into the compartment.
FIG. 4A shows an exemplary dosage form having a substrate forming a compartment of pie shape.

FIG. 4B shows an exemplary dosage form having a substrate forming multiple compartments containing various sized openings.

FIG. 4C shows an exemplary dosage form having a substrate forming an angled compartment.

FIG. 4D shows an exemplary dosage form having a substrate forming multiple compartments of different radius.

FIG. 4E shows an exemplary dosage form having a substrate forming multiple compartments of different geometric-shape that can be used to modulate release rate of the API.

FIG. 5 shows the cross section of an exemplary dosage form having a pie-shaped compartment.

FIG. 6 shows an exemplary dosage form having a substrate that forms layers with drug content in the form of nanoparticles dispersed between the layers.

FIG. 7 shows an exemplary dosage form having a substrate that forms a compartment with a microneedle-shaped drug content loaded into the compartment.

FIG. 8A shows an exemplary dosage form having a substrate forming a compartment loaded with a drug content. The drug content forms a network. The substrate is made of a material that dissolves between 1-5 minutes, and the drug content dissolves in seconds.

FIG. 8B shows the quick release of the API from the dosage form illustrated in FIG. 8A.

FIG. 9 shows an exemplary dosage form having a substrate forming a plurality of column-shaped compartments. Each compartment is loaded with one drug content. The release of the drug content can be controlled by the number and size of the compartments.

FIG. 10A shows an exemplary dosage form having a substrate forming three column-shaped compartments. Each compartment is loaded with one drug content. Each drug content has a plug that blocks the aperture of each compartment.

FIG. 10B shows an exemplary dosage form having a multiple-layered substrate with drug content embedded into each layer.

FIG. 10C shows the consequential release of the drug content from the dosage form illustrated in FIG. 10A or 10B.
Fig. 10D shows the plasma drug level of the controlled release dosage form illustrated in Fig. 10A or 10B when administered to a subject.

Fig. 11 is a schematic workflow for using of a three-dimensional printer for preparing patient specific dosage form.

Fig. 12A shows an exemplary dosage form having a three-layered substrate with different drug content embedded into each layer.

Fig. 12B illustrates the release of three APIs from the dosage form illustrated in Fig. 12A.

Fig. 13A shows an exemplary dosage form having a substrate forming three compartments, each of which loaded with one drug content. The release profile of the drug content can be controlled by the dissolution rate of the drug content.

Fig. 13B illustrates the release profile of the APIs from the dosage form illustrated in Fig. 13A.

Fig. 14A shows an exemplary dosage form having a substrate having three pie-shaped segments, with drug content embedded into each segment.

Fig. 14B shows an exemplary dosage form having a substrate having three pie-shaped segments wrapped with a shell structure.

Fig. 14C shows the release profile of the APIs from the dosage forms illustrated in Fig. 8A and Fig. 8B.

Fig. 15A shows an exemplary dosage form having a substrate forming a compartment filled with a drug content. A second API is embedded in the substrate and is released when the substrate dissolves.

Fig. 15B shows the controlled release of the APIs from the dosage form illustrated in Fig. 15A.

Fig. 16A shows an exemplary dosage form having a substrate forming three column-shaped compartments. Each compartment is loaded with one drug content. Each drug content has a plug that blocks the opening of each compartment. The release of the drug content in each compartment can be controlled by the permeability, degradability or erodibility of the plug.

Fig. 16B shows the release profiles of the APIs from the dosage form illustrated in Fig. 16A.

Fig. 17A shows an exemplary dosage form having a substrate forming four compartments. Each compartment is loaded with a drug content.
FIG. 17B shows the release of the APIs from a dosage form having a substrate consisted of four drug content embedded segments.

FIG. 17C shows the controlled release of the APIs from the dosage form illustrated in FIG. 17A.

FIG. 18A is a schematic diagram of the drug form having a substrate forming a pie-shaped compartment.

FIG. 18B is a photograph of a drug release processes of the drug form illustrated in FIG. 18A.

FIG. 18C shows release percentage curve of benzoic acid and PEG8000 from the dosage form of FIG. 18A.

FIG. 19A shows the perspective view of a dosage form that contains two compartments.

FIG. 19B shows the cross-sectional view of the dosage form of FIG. 19A.

FIG. 19C shows an exemplary release profile of the dosage form of FIG. 19A.

FIG. 19D shows another exemplary release profile of the dosage form of FIG. 19A.

DETAILED DESCRIPTION OF THE INVENTION

In the Summary of the Invention above and in the Detailed Description of the Invention, and the claims below, and in the accompanying drawings, reference is made to particular features (including method steps) of the invention. It is to be understood that the disclosure of the invention in this specification includes all possible combinations of such particular features. For example, where a particular feature is disclosed in the context of a particular aspect or embodiment of the invention, or particular claim, that feature can also be used, to the extent possible, in combination with and/or in the context of other particular aspects and embodiments of the invention, and in the invention generally.

The term "comprises" and grammatical equivalents thereof are used herein to mean that other components, ingredients, steps, etc. are optionally present. For example, an article "comprising" (or "which comprises") components A, B, and C can consist of (i.e., contain only) components A, B, and C, or can contain not only components A, B, and C but also one or more other components.

Where reference is made herein to a method comprising two or more defined steps, the defined steps can be carried out in any order or simultaneously (except where the context excludes that possibility), and the method can include one or more other steps which
are carried out before any of the defined steps, between two of the defined steps, or after all the defined steps (except where the context excludes that possibility).

[0066] Where a range of value is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictate otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0067] The term "at least" followed by a number is used herein to denote the start of a range beginning with that number (which may be a range having an upper limit or no upper limit, depending on the variable being defined). For example, "at least 1" means 1 or more than 1. The term "at most" followed by a number is used herein to denote the end of a range ending with that number (which may be a range having 1 or 0 as its lower limit, or a range having no lower limit, depending upon the variable being defined). For example, "at most 4" means 4 or less than 4, and "at most 40%" means 40% or less than 40%. In this disclosure, when a range is given as "(a first number) to (a second number)" or "(a first number)-(a second number)," this means a range whose lower limit is the first number and whose upper limit is the second number. For example, 2 to 10 millimeters means a range whose lower limit is 2 millimeters, and whose upper limit is 10 millimeters.

[0068] It will be appreciated that for simplicity and clarity of illustration, where appropriate, reference numerals have been repeated among the different figures to indicate corresponding or analogous elements. In addition, numerous specific details are set forth in order to provide a thorough understanding of the embodiments described herein. However, the embodiments described herein can be practiced without these specific details. In other instances, methods, procedures and components have not been described in detail so as not to obscure the related relevant function being described. Also, the description is not to be considered as limiting the scope of the implementations described herein. It will be understood that descriptions and characterizations of the embodiments set forth in this disclosure are not to be considered as mutually exclusive, unless otherwise noted.

Controlled Release Dosage Form

[0069] Conventional solid dosage forms, e.g., compressed tablets, are composed of a substrate where active drug ingredients is dissolved or embedded (FIG. 1A). Currently conventional solid dosage forms exhibit first-order drug release profile (FIG. 1B) where the
plasma level of the drug increases rapidly to an extremely high level after administration and then decreases exponentially (see FIG. 1C). This poses disadvantages such as minimal therapeutic efficacy due to reduced drug levels or drug toxicity which can occur at high concentrations. This type of drug release does not allow for appropriate plasma drug level balance. The instant invention relates to modified or controlled release oral drug delivery system, which offers advantages over conventional systems, including increased patient compliance, selective pharmacological action, reduced side effects and reduced dosing frequency. Controlled release offers prolonged delivery of drugs and maintenance of plasma levels within a therapeutic range. For example, a drug delivery system exhibiting zero-order drug release profile (FIG. 1D) allows for a constant quantity of drug to be release over an extended period of time, resulting in uniform and sustained drug delivery. As a result, zero-order release profile may be desired in antibiotic delivery, the treatment of hypertension, pain management, antidepressant delivery and numerous other conditions that require constant plasma drug levels.

Therefore, one aspect of the present disclosure provides a stable solid pharmaceutical dosage form for oral administration, which has a controlled release profile. In certain embodiments, the dosage form includes a substrate forming at least one compartment and a drug content loaded into the compartment. The dosage form is so designed that the release of the active pharmaceutical ingredient of the drug content can be controlled, e.g., by opening the compartment in a predetermined manner.

A. Substrate

As used herein, "substrate" refers to a structure in which a drug is enclosed or embedded. The substrate of a dosage form of the instant invention can be of any size and shape that are suitable for oral administration. In certain embodiments, the substrate is a flat round tablet having a diameter of around 2 mm, 3 mm, 4 mm, 5 mm, 6 mm, 7 mm, 8 mm, 9 mm, 10 mm, 11 mm 12 mm. In certain embodiments, the substrate is an oval tablet having a dimension of around a mm x b mm, wherein a is 5 to 15 and b is 2 to 10. In certain embodiments, the substrate has a capsule shape.

In certain embodiments, the substrate is made of a hydrophilic polymer (e.g., hydroxypropylmethylcellulose (UPMC) and poly(ethylene oxide) (PEO)), a hydrophobic polymer (e.g., ethylcellulose (EC)), a swellable polymer, a non-swellable polymer, a porous polymer, a non-porous polymer, an erodible polymer, or a non-erodible polymer.
In certain embodiments, the dosage form has a monolithic substrate. In certain embodiments, the substrate consists of several pieces, each piece made of the same or different material.

In certain embodiments, the substrate is made of a thermoplastic material. As used herein, a "thermoplastic material" refers to a material having the ability to be shaped using heat and pressure. In certain embodiments, the thermoplastic materials may, for example, be hydrophilic, gel-forming materials, from which drug content release proceeds mainly by diffusion, or hydrophobic materials, from which drug content release proceeds mainly by diffusion from the pores in the substrate. Polymers, particularly cellulose ethers, cellulose esters and/or acrylic resins can be used as hydrophilic thermoplastic materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are suitable for use as thermoplastic materials. Physiologically acceptable, hydrophobic materials that are known to the person skilled in the art, such as mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof may be used as thermoplastic material. Substrate prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also envisioned.

In certain embodiments, the thermoplastic material is selected from the group consisting of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, 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), poly(vinyl 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(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic 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 (HMPC), hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate (HPMCAS), poly(lactide-co-glycolide) (PLGA), carbomer, poly(ethylene-co-vinyl acetate),
ethylene-vinyl acetate copolymer, polyethylene (PE), and polycaprolactone (PCL), hydroxyl propyl cellulose (HPC), Poloxol 40 Hydrogenated Castor Oil, Methyl cellulose (MC), Ethyl cellulose (EC), Poloxamer, hydroxypropyl methycellulose phthalate (HPMCP), Poloxamer, 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.

Properties and sources of various thermoplastic materials are listed in Table 1. In certain embodiments, the thermoplastic material allows the dosage form to be made using an additive method such as fused deposition modeling (FDM). In certain embodiments, the substrate can be made by using a three-dimensional printer (3D printer) configured to extruding the thermoplastic material. Typically, the thermoplastic material is melted in the 3D printer before being extruded to form the substrate. In certain embodiment, appropriate extruders include without limitation, single or twin screw extruders with the temperature within the extruder at a range from 50°C to 180°C and from 80° to 140°C. In general, the extrusion process can be conducted at temperatures 10° to 40°C above the glass transition (Tg) of the thermoplastic material. Once at a suitable temperature for use in the three-dimensional printer, the thermoplastic material can be deposited to the three-dimensional printing surface. The shape and size of the substrate and the compartment fabricated by the thermoplastic material can be controlled by programing the three-dimensional printing process.

In certain embodiments, the material of the substrate can be so selected to control the release profile of a drug. For example, the substrate is made of a material having desired erosion/dissolution rate, permeation rate so that when administered the compartment can be opened in a predetermined manner, and the drug content is release from the compartment at desired rate. In certain embodiments, the substrate is erodible or dissolvable and is embedded with an active pharmaceutical ingredient (API). The API is released when the substrate is eroded or dissolved

The release of the drug content can also be controlled by adjusting the thickness of the substrate. For example, the substrate forming a compartment is made of a soluble material. The opening of the compartment, thus the release of the drug content loaded within can be controlled by adjusting the thickness of the walls that enclose the compartment. The thicker the wall, the slower the compartment is open, and the later the drug content is released.
B. Compartment

In certain embodiments, the dosage form disclosed herein contains at least one compartment within the substrate. As used herein, "compartment" refers to a space, part or room marked or partitioned off by the substrate. A compartment can be closed or be open (e.g., having an aperture or a passageway). A compartment can be of any geometry suitable for loading drug contents. In certain embodiments, the compartment has a shape selected from the group consisting of a pie shape, a cone shape, a pyramid shape, a cylindrical shape, a cubic or cuboidal shape, a triangular or polygonal prism shape, a tetrahedron and a combination thereof.

In certain embodiments, containing a compartment in the dosage form can increase its retention in the gastro intestinal tract. FIG. 2A illustrates an exemplary dosage form having a substrate forming a compartment where drug content is loaded. Referring to FIG. 2A, a dosage form 100 has a compartment 102 formed by a substrate 101. A drug content 103 is loaded in the compartment 102 by linking to the internal wall of the compartment 102. The compartment 102 can provide a floating effect to the dosage form and thereby extend its residence time in the stomach or in an aqueous or acidic environment. The residency time can be a function of the erosion/dissolution rate of the materials of the substrate and result in a sustained release of API as shown in FIG. 2B.

FIG. 3 illustrates another exemplary dosage form with increased residence in the gastro intestinal tract. Referring to FIG. 3, a dosage form 200 has a configuration that the compartment 202 contains a second dosage form 203 (e.g., a tablet) freely moving within the compartment 202. The gastro intestinal residence time of a dosage form is limited. Using floating systems can allow the dosage form to stay in stomach and continuously release the drug at the upper part of GI tract and maximize the absorption in small intestine.

In certain embodiments, the shape of the compartment is uniquely created so that the drug content can be released at a controlled rate. In certain embodiments, the compartment has a shape selected from the group consisting of a wedge shape, a pie shape, a cone shape, a pyramid shape, a cylindrical shape, a cubic or cuboidal shape, a triangular or polygonal prism shape, a tetrahedron and a combination thereof.

In one embodiment, the compartment of the dosage form has different geometric shape. FIG. 4A shows an exemplary dosage form having a substrate forming a compartment of pie shape. FIG. 4B shows an exemplary dosage form having a substrate forming multiple compartments containing various sized openings. FIG. 4C shows an
exemplary dosage form having a substrate forming an angled compartment. FIG. 4D shows an exemplary dosage form having a substrate forming multiple compartments of different sized radius.

[0087] The shape of the compartment can be used to control the release profile of the dosage form. For example, R.A. Lipper and W.I. Higuichi described a delivery system that provides zero-order release profile, which is illustrated in FIG. 5. FIG. 5 shows a cross-sectional view of the delivery system having a pie-shaped compartment. The compartment communicates with the environment through a small opening. The compartment is loaded with a drug content that dissolves to release an API. The API is then released to the environment through the small opening. The dissolution rate of the drug content positively correlates to the area of the dissolution boundary of the drug content (the interface between the drug content and the space of the compartment). On the other hand, the diffusion rate of the API into the environment is negatively correlates to the diffusion path length \( \lambda \). As a result, as the drug content dissolves, the area of the dissolution boundary increases, and the dissolution rate of the drug content increases. On the other hand, the diffusion path length \( \lambda \) increases as the drug content dissolves. So the API released in the compartment needs to be transported a longer length to diffuse out of the dosage form. It is assumed that the dosage form can be so designed to provide a zero-order release kinetics (R.A. Lipper and W.I. Higuichi (1977) Analysis of theoretical behavior of a proposed zero-order drug delivery system. J. Pharm Sci 66(2): 163-4; D. Brooke and R. J. Washkuhn (1977) Zero-order drug delivery system: theory and preliminary testing. J Pharm Sci. 66(2): 159-162).

[0088] C. Drug Content

[0089] As used herein, the term "drug content" refers to a composition comprising one or more active ingredient, including active pharmaceutical ingredient (API), cosmetic agent, biological agent, diagnostic agent and reagent for scientific experiments.

[0090] As used herein, an API refers to an ingredient in a pharmaceutical drug that is biologically active. In certain embodiments, the API is selected from the groups consisting of local anesthetics, antiepileptic drugs and anticonvulsants, anti-Alzheimer's disease drugs, analgesics, antipodagric, anti-hypertensive drugs, antiarrhythmic drugs, diuretic drugs, drugs for treating liver diseases, drugs for treating pancreatic diseases, antihistamine drugs, anti-allergic drugs, glucocorticoid drugs, sex hormone drugs and contraceptive drugs, hypoglycemic drugs, anti-osteoporosis drugs, antibiotics, sulfonamides, quinolones, and other
synthetic antibacterial drugs, anti-tuberculous drugs, antiviral drugs, anti-neoplasm drugs, immune-modulators, cosmetically active agents, traditional Chinese medicine (TCM) and TCM extracts.

[0091] In certain embodiments, the API is selected from the groups consisting of (R)-folitixorin, lidocaine, 11-di-deutero-ethyltinoleate, 16-dehydro-pregnenolone, 17-beta-estradiol, 2-iminobiotin, 3,5-diiodothyropropionic acid, 5-fluoro-2-deoxycytidine, 6-mercaptopurine, edotretide, abacavir, abalone haemocyanin, abametapir, abediterol, abemaciclib, abexinostat, abiraterone, acalabrutinib, acamprosate, acamprosatecalcium, acarbose, acebilustat, aceclidine, aceclofenac, acehytisine hydrochloride, acemannan, aceneuramic acid, acetaminophen, acetyl cysteine, acetylsalicylic acid, aciclovir, acipimox, acitazanolast, acitretin, aclidinium, aclidinium bromide, acolbifene, alectinib, alendronate, alendronate sodium, alendronate sodium hydrate, alendronic acid, alfadex, alferenta, alfuzosin, allantoin, allisartanisopropoxil, allopurinol, almotriptan, alogliptin, alprazolam, alprostadil, alprostadil alfadex, altretamine, alattopane, aluminunm sulfate, alvocidib, amantadine, amantadine hydrochloride, ambrisentan, ambroxol, amcasertib, amfetamine, amfetamine polistirex, amifampridine, amifampridine phosphate, amifostine, amikacin, amiloride, aminolevulinic acid, aminolevulinic acid hydrochloride, aminopterin, amidarone, amisulpride, amitifadine hydrochloride, amitriptyline, amlexanox, amlodipine, amlodipine, amlodipinebesilate, amlodipine besylate, amlodipine camsylate, amlodipine maleate, amlodipine nicotinate, amlodipine orotate, ammonium lactate, amodiaquine, amorolfine, amosulalol, amoxicillin, amoxicillin hydrate, amphetamine, amphetamine aspartate, amphetamine...
sulfate, amphotericinB, amphotericinB cholesteryl sulfate, amphotericinB lipid complex, ampicillin sodium, ampiroxicam, amrinone, amrubicin, amtolmetinguacil, anacetrapib, anaglaptin, anagrelide, anamorelin, anastrozole, ancrod, androgen, andrographolide, anecortave, anidulafungin, aniracetam, anistreplase, anlotinib, antazoline, antiandrogens, antineoplaston A-10, antineoplaston AS2-1, antofloxacin hydrochloride, antroquinonol, apabetalone, apalutamide, apatinib mesylate, apaziquone, apilimod mesylate, apixaban, apomorphine, apomorphine hydrochloride, apremilast, aprepitant, apricitabine, aramchol, aranidipine, araretaconazole, araretaconazol enitrate, arbaclofen, arbaclofen placarbil, arbekacin, arbekacin sulfate, ardeparin sodium, arformoterol, argatroban, arhalofenate, arimoclomol, aripiprazole, aripiprazole lauroxil, armodafinil, arsenic trioxide, arsenious acid, artefenomel mesylate, artemether, artemotil, arteminol, arterolane maleate, artesunate, Artiss, asapiprant, asenapine, asimadoline, astodrimer, astragaloside, azelastine, azelastine hydrochloride, azelnidipine, azilsartan, azilsartan medoxomil potassium, azilsartan trimethylethanolamine, azimilide, azithromycin, azithromycin lactobionate, aztreonam, aztreonam lysine, azudine, baclofen, bafetinib, Baicalein, baicalin, BAK-freelatanoprost, balofloxacin, balsalazine, balsalazide sodium, bambuterol, barasertib, barbital, baricitinib, baridipine, barsanidol, batetefenterol succinate, bazedoxifene, beclabuvir, beclometasone dipropionate, bedaquiline, bedoradrine, belinostat, beloranib, belotecan, bempedoic acid, benapenem, benazepril, bencycloquidium bromide, bendamustine, bendamustine hydrochloride, benidipine, benzerazide, bentamapimod, benzalkonium chloride, benzhydrocodone, benznidazole, benzocaine, benzoylperoxide, benzydamineHCL, bepotastine, bepotastine calcium dihydrate, bepotastine salicylate, beractant, beraprost sodium, besifloxacin, besifovir, besipirdine, beta-elemene, beta-histidine, betaine anhydrous, betamethasone,
betamethasone butyrate propionate, betamethasonedipropionate, betamethasone valerate,
betamipron, betaxolol, betaxolol hydrochloride, betanechol, betrixaban, bevacizumab,
bexagliflozin, bexarotene, bezafibrate, biafungin, biapenem, bicalutamide, bicizar,
bictegravir, bicyclol, bilastine, bimatoprost, binimetinib, biotin, birabresibdihydrate,
biskalcitrate potassium, bismuth subgallate, bismuthyl ecabet, bisnorcymserine,
bisoprolol, bisoprolol fumarate, bitespiramycin, bixalomer, bleomycin, blonanserin,
boanmycin hydrochloride, boceprevir, bortezomib, bosentan, bosentan hydrate,
bosutinib, bovactant, brexiprazole, briclib Sodium, brilacidin, brimapitide, brimonidine, brincidofovir,
brinzolamide, brivanibalaninate, brivaracetam, brivudine, brolucizumab, bromapen, bromfenac sodium, bromocriptine,
bronchostat, brotizolam, biyostatin-1, bucindolol, bucladesine, budesonide, budipine, buflomedil, bulaquin, bunazosin, buparlisib, bupivacaine, bupivacaine hydrochloride, buprenorphine, buprenorphine hydrochloride, busulfan, busulfex, butenafine, butorphanol tartrate, butylphthalide, cabazitaxel, cabergoline, cabotegravir, cabozantinib S-malate, cadazolid, cadrofloxacin, caffeine, caffeine citrate, cafnea, cafusertib hydrochloride, calcipotriol, calcitriol, calcium acetate, calciumfolinate, calcium levofolinate, calcium polycarbophil, calsurf, camicinal, camostat mesylate, camptothecin, cariprazine, carisbamate, carprofen, carprofen hydrochloride, carprofen sodium, cefepime, cefepime dihydrochloride, cefetanepivoxil hydrochloride, cefiderocol, cefilavancin, cefminox, cefoperazone, cefoperazone sodium, cefoselis, cefotaxime, cefotaxime sodium, cefotiam, cefozopran, cefpirome, cefpodoxime, cefprozil, ceftaroline, ceftaroline fosamil, ceftazidime, ceftibuten, ceftobiprole medocaril, ceftolozane sulfate,
ceftriaxone, ceftriaxone sodium, cefuroxime, cefuroxime sodium, celecoxib, celgosivir, celiprolol, cellprotect, celenstin, cenicriviroc, censavudine, centanafadine, cephalosporin, ceralifimod, cerdulatinib, ceritinib, ceriumnitrate, cetraxate, cefuroxime sodium, celecoxib, cefuroxime sodium, celecoxib, celgosivir, celiprolol, cellprotect, celenstin, cenicriviroc, censavudine, centanafadine, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, ceftriaxone, ceftriaxone sodium, cefuroxime, cefuroxime sodium, celecoxib, celgosivir, celiprolol, cellprotect, celenstin, cenicriviroc, censavudine, centanafadine, cephalosporin, ceralifimod, cerdulatinib, ceritinib, ceriumnitrate, cetraxate, cefuroxime sodium, celecoxib, cefuroxime sodium, celecoxib, celgosivir, celiprolol, cellprotect, celenstin, cenicriviroc, censavudine, centanafadine, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, ciclosporin, cidofovir, cidoxepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide maleate, chlorprosone, cino-
darinaparsin, darunavir, dasabuvir, dasatinib, dasotraline, daunorubicin, decitabine, decuprate, defactinib, deferasirox, deferiprone, deferoxamine mesylate, deflazacort, deflexifol, delafloxacin, delamanid, delapril, delapril hydrochloride, delavirdine, denibulin, deoxyandrographolide, dermatansulfate, desflurane, desipramine hydrochloride, desloratadine, desmopressin, desmopressin acetate, desogestrel, desonide, desvenlafaxine, deudextromethorphan hydrobromide, deuterated levodopa, deuteratedvenlafaxine, deutetrabenazine, dexamethasone, dexamethasone acetate, dexamethasone cipocilate, dexamethasone palmitate, dexamethasone sodium phosphate, dexamfetamine, dexanabinol, dexferrum, dexketoprofen trometamol, dexlansoprazole, dexametomidine, dexmethyphenidate, dexpramipexole, dextroamphetamine saccharate, dextroamphetamine sulfate, dextromethorphan, dextromethorphan hydrobromide, dextropropoxyphene, diacerein, diamorphine hydrochloride, dianhydrogalactitol, diazepam, diazoxidecholine, diclofenac, diclofenac potassium, diclofenac sodium, diclofenamide, diclofenamid, diclopiroplatin, didanosine, dienogest, difluprednate, digoxin, dihomogamma-linolenic acid, dihydroergocristine, dihydroergotamine, dihydroergotamine mesylate, diltiazem, diltiazem hydrochloride, dimesna, dimethyl fumarate, dimiracetam, dinoprostone, diphenylcyclopropenone, dipraglurant, dipyriramole, diquafosoltetra sodium, dirithromycin, disulfenton sodium, disulfiram, dithranol, d-methadone, docarpamine, docetaxel, dociparstat, docosanol, dofetilide, dolasetron, dolutegravir, domiperidone, donafenib tosylate, donepezil, donepezil hydrochloride, dopamine, doravirine, doripenem, dorzolamide, dorzolamide hydrochloride, dosmalfate, doxacurium chloride, doxazosin, doxazosin mesylate, doxepin hydrochloride, doxercalciferol, doxifluridine, doxofylline, doxorubicin, doxorubicin hydrochloride, doxycycline, doxycycline hyelate, doxylamine succinate, dronabinol, dronedarone, drospirenone, droxidopa, D-tagatose, duloxetine, duloxetine hydrochloride, dutasteride, duvelisib, ebastine, eberconazole, ebson, ecabet, econazolenitrate, ecopipam, edaravone, edivoxetine, edonerpic maleate, edoxaban, efatutazone, efavirenz, efinaconazole, effornithine, efonidipin hydrochloride, egualen sodium, eicosapentaenoic acid monoglycerides, elafibrinanor, elagolix, elamipretide, elbasvir, eldecicalcit, eleclazine, elesclomol sodium, eletriptan,
eliglustattartrate, elobixibat, eltrombopag, eluxadoline dihydrochloride, elvitegravir, emdogain, emedastine, emeramide, emixustat, emodipside, empagliflozin, emricasan, emtricitabine, enalapril, enalaprilmaleate, enasidenib, encenicline, enclomifene citrate, enorafenib, endoxifen, enobosarm, enoxacin gluconate, enoxaparin sodium, enprostil, entacapone, entasobulin, entecavir maleate, entinostat, entospletinib, entrectinib, enzalutamide, enzastaurin, epacadostat, eperisone, epetram, ephedrine sulfate, epinephrine, epirubicin, epirubicin hydrochloride, epirubicin, eprodisate, eravacycline, erdafitinib, erdosteine, eribulin mesylate, erlotinib, eretapenem, ertugliflozin, ertylumycin, ertylumycin acistrate, ertylumycin stinoprate, escitalopram, esmolol, esomeprazole, esomeprazole magnesium, esomeprazole strontium, estetrol, estradiol, estradiol acetate, estradiol cypionate, estradiol valerate, estrogen, esuberaprost sodium, eszopiclone, etamicastat, ethambutol hydrochloride, ethaselen, ethinylestradiol, ethylhydrogenfumarate calcium, ethylhydrogenfumarate magnesium, ethylhydrogenfumara zinc, ethynylestradiol, etidronicacid, etimicin sulfate, etirinotecanpegol, etizolam, etodolac, etonogestrel, etoposide, etoposide phosphate, etoricoxib, etravirine, etripamil, eupatilin, evenamide hydrochloride, everolimus, evofosfamide, evogliptin, exemestane, exendin(9-39), exeporfinium chloride, ezatiostat, etazimine, ezutromid, fadolmidine, fadrozole, faldaprevir, falcicalcitriol, famciclovir, famitinib, famotidine, fampridine, faropenem, fasitibant chloride, fasoracetam, fasudil, fasudil hydrochloride, fasudil mesylate, favipiravir, febarbamate, febuxostat, fedovapagon, felbamate, felbinac trometamol, felodipine, femitra, fenfluramine hydrochloride, fenobam, fenofibrate, fenofibric acid, fenoldopam, fenoterol, fenretinide, fentanyl, fentanyl citrate, fenticonazole, fermanate, ferriccitrate, ferricmaltol, ferumoxytol, fesoterodine fumarate, fevipiprant, fexinidazole, fexofenadine, fibrinsealant, fibrinogen, fibrinogensealant, fidaxomicin, filanesib, filgotinib, filociclovir, fimaporfin, fimasartan, finafloxacin, finafloxacin hydrochloride, finasteride, finerenone, fingolimod, fipamezole, firtecanpegol, flecainide, fleroxacin, flibanserin, flomoxef,
floxuridine, fluazolepali, fluconazole, fludarabine, flumatinib, flumazenil, flunisolide, fluocinolone acetonide, fluocinonide, fluorapacin, fluorouracil, fluvastatin, folic acid, folinate, foliumginkgo, fomepizole, fonadelpar, fondaparinux sodium, foretinib, formentane, formoterol, formoterol fumarate, forodesine, fosamprenavir, fosaprepitant, fosbretabulin, fosbretabulin disodium, fosfomycin, fosfomycin, fosfomycinindium sodium, fosfomycintrometamol, fosinopril, fosinopril sodium, fosmidomycin, fosphenytoin, fospropofol, fosravuconazole, fostataminib, fostemsavir tromethamine, fotaglitiptin benzoate, fotemustine, frovatriptan, fruquintinib, fudosteine, fulvestrant, funapide, furosemide, gabapentin, gabapentinencarbil, gabexate mesylate, gacyclidine, gadobutrol, gadoversetamid, gadoxetate disodium, galantamine, galeterone, galidesivir, gallium nitrate, galunisertib, gambogic acid, ganaxolone, ganciclovir, ganetespib, ganirelix acetate, garenoxacin, gatifloxacin, gatifloxacin mesylate, gedatolisib, gefitinib, gemcabene, gemcitabine, gemcitabine hydrochloride, gemfibrozil, gemifloxacin, gemiglipitin, gemiglipintartaric acid, genistein, gentamicin, gentiopicrin, gepirone, gepotidacin, gestodene, gestrinone, timolol maleate, gilteritinib, gimeracil, ginsenoside C-K, ginsenoside Rg3, givinostat, glasdegib, glatiramer acetate, glecaprevir, glesatinib glycolate, glibenclamide, gliclazide, glimepiride, glipizide, glufofamide, glutamine, glutathionarsenoxide, glycerol phenylbutyrate, glycopyrronium, glycopyrronium bromide, glycopyrroton tosylate, glycyrhrizi cacid, ganglioside, golotimod, gosogliptin, granisetron, granisetron hydrochloride, grazoprevir, guaifenesin, guaimesal, guanfacine, gusperimus trihydrochloride, haemophilus influenzae, halobetasol propionate, halofantrine, halometasone, healon, hematoporphyrin, hemearginate, hemocoagulase, Herbiron, hetrombopag, hextend, higenaminehydrochloride, histamine dihydrochloride, HPPHphotosensitizer, humanapotransferrin, humanplasminogen, huperzineA, hyaluronate sodium, hydralazine, hydrochloride, hydrochloorothiazide, hydrocodone, hydrocodone bitartrate, hydrocodone polistirex, hydrocortisone, hydrogenperoxide, hydromorphone, hydromorphone hydrochloride, hydroxocobalamin, hydroxy carbamide,
hydroxychloroquine, hydroxyprogesterone caproate, hydroxysafflor yellow A, hylastan, hypericin, hypoestoxide, ibandronate, ibandronic acid, iberogast N, ibodutant, ibrutinib, ibudilast, ibuprofen, ibutilide, ibutilide fumarate, icaritin, iclaprim, icosabutate, icosapent, icosapentethyl, icosapentylester, icotinib hydrochloride, idalopirdine, idasanutlin, idebenone, idealalisib, idoxuridine, idronoxil, ifetroban, ifetrobansodium, iguratimod, ilaprazole, iloperidone, iloprost, iloprostbetadexclathrate, imatinib, imatinibmesylate, imeglimin, imidafenacin, imidapril, imidazole salicylate, imidol hydrochloride, imiglittin hydrochloride, imipenem, imiquimod, imisopasem manganese, imrecoxib, incadronic acid, incobotulinumtoxin, indacaterol, indacaterol maleate, indapamide, indeloxazine, Indimitecan, indinavir, indisetron, indometacin, indoramin, indotecan, indoximod, inecalcitol, infgratinib, Ingavirin, ingenolmebutate, inhaled sodium nitrite, ferric carboxymaltose, inosine, intepirdine, iodiconazole, ipatasertib dihydrochloride, ipragliflozin, ipratropium, ipratropium bromide, iptakalim, irbesartan, irinotecan, irinotecan hydrochloride, irinotecan sucrosafate, irofulven, iron isomaltoside 1OOO, iron protein succinylate, irosustat, isavuconazonium chloride/sulfate, isodibut, isoflurane, isoniazid, isopropylunoprostone, isosorbide mononitrate, isosteviol, isothiafludine, isradipine, istaroxime, istradefylline, itacitinib, itopride hydrochloride, itraconazole, ivabradine hemi sulfate, ivabradine hydrochloride, ivacaftor, ivermectin, ivosidenib, aflibercept, ixabepilone, ixazomib citrate, kallikrein, kagbeide, ketamine, ketanserin, ketoconazole, ketoprofen, ketorolac, ketorolac tromethamine, ketotifen, kevetrin, kukoamine Bmesylate, L-4-chlorokynurenine, lacidipine, lacosamide, lactitol, ladarixin, ladostigil, laflunimus, lafutidine, lamivudine, lamotrigine, landiolol, landiolol hydrochloride, laninamivir octanoate, lanoconazole, lansoprazole, lanthanum carbonate, lapatinib, laquinimod, laromustine, lasmiditan, lasofoxifene, latanoprost, latanoprostenebunod, lauflumide, ledipasvir, lefamulin, leflunomide, lemboexant, lenalidomide, lentinan, lentinansulfate, lentinanviral, lenvatinib mesylate, lercanidipine, lesinurad, leteprinim, letermovir, letrozole, leucine, leuprorelin acetate, levalbuterol, levalbuterol hydrochloride, levamlodipine, levamisole, levamlodipine besylate, levamlodipine
maleate, levetiracetam, levobupivacaine, levocabastine, levocabastine hydrochloride, levocarnitine, levocetirizine dihydrochloride, levodopa, levodoxazosin mesylate, levofloxacin, levoketoconazole, levomilnacipran, levonadifloxacin arginine salt, levonorgestrel, levonorgestrel butanoate, levo-phenycyononate hydrochloride, levornidazole, levorphanol, levosimendan, levotuss, L-glutamine, lidocaine, lifitegrast, ligustrazine hydrochloride, limaprost, linagliptin, linezolid, liothyronine, liothyronine sodium, lipobean, liposomal curcumin, lipoteichoic acid, liranaftate, lisdexamfetamine, lisinopril, lisofylline, lisuridehydrogen maleate, lithiumcitrate, lithiumsuccinate, lixivaptan, lobaglitazone, lodenafil carbonate, lomexifon, lomerizine, lomerizine dihydrochloride, lomitapide, lonafarnib, lonidamine, loperamide, loperamidoxide, lopinavir, loratadine, lorazepam, lorcaserin, lorediplon, lorlatinib, L-ornithine L-aspartate, lornoxicam, losartan, losartan potassium, losmapimod, loteprednoletabonate, lovastatin,loxapine,loxoprofen,L-praziquantel,lubiprostone,lucanthone,lucinactant,lucitanibhydrochloride,luliconazole, lumacaftor, lumateperone toluene sulfonate, lumefantrine, lumiracoxib, lunacalcipol, lurasidone, lurbinectedin, luseogliflozin hydrate, lusutrombopag, lysine acetylsalicylate, macimorelin, macitentan, mafenide, magnesium carbonate, magnesium isoglycyrrhizinate, mangafodipir, manidipine, manidipine dihydrochloride, mannitol, maraviroc, maribavir, marizomib, masilukast, masitinib, mavoglurant, maxacalcitol, mebendazole, mebiphon, mecamylamine, mecamylamine hydrochloride, mechlorethamine, mecobalamin, medroxyprogesterone, medroxyprogesteroneacetate, mefloquine, megestrol, megestrolacetate, meisuoshuli, melevodopa, meloxicam, melphalan, melphalanflu fenamide hydrochloride, memantine, memantine hydrochloride, menadione sodium bisulfite, menatetrenone, mepacrine, mequinol, mercaptamine, mercaptamine bitartrate, mercaptamine hydrochloride, mercaptopurine, mesterinib, meropenem, merotocin, mesalamine, mesalazine, metacavir, metadoxine, metamizolesodium, metaxalone, metergoline, metformin, metformin hydrochloride, methadone, methazolamide, metotrexate, methoxyflurane, methylaminolevulinate hydrochloride, methylaltrexone bromide, methylaltrexone, methylphenidate, methylphenidate hydrochloride, methylprednisolone, methylprednisolone aceponate,
methylthioninium chloride, metirosine, metoclopramide, metoprolol, metoprolol succinate, metrifonate, metronidazole, metyrapone, mexiletine, mibefradil, miconazole, miconazole nitrate, midazolam, midazolam hydrochloride, midodrine, midostaurin, mifamurtide, mifepristone, migalastat, miglitol, miglitol, milnacipran, milrinone, miltefosine, minaprine, minocycline, minocycline hydrochloride, minodronic acid, minoxidil, mirabegron, miriplatin hydrate, mirodenafil, mirodenafil hydrochloride, mirogabalin, mirtazapine, misoprostol, mitiglinide, mitomycin, mitoxantrone, mitoxantrone hydrochloride, mivoltate, mizolastine, mizoribine, mofezolac, moexipril, mofezoloc, molidustat, molindone hydrochloride, momelotinib, mometasone, monepantel, monoammonium glycyrrhizinate, monobenzone, monosodium alphanolinol, monoterpane perillyl alcohol, montelukast, montelukast sodium, montmorillonite, moracizine, morindazole, morphine, morphine glucuronide, morphine pitavastatin, morphine sulfate, morphothiadine mesilate, mosapride, motolimod, moxidectin, moxifloxacin, oxifloxacin hydrochloride, moxonidine, moxonidine hydrochloride, mozavaptan, muparfostat sodium, mupirocin, mycobactovir, mycophenolatemofetil, myristylnicotinate, nabilone, nabiximols, nabumetone, N-acetylcysteine, nacystelyn, nadifloxacin, nadolol, nadroparin calcium, naftizine hydrochloride, naftopidil, nalbuphine, nalbuphine sebacate, naldemidine, nalfurafine, naloxegol, naloxone, naloxone hydrochloride, naltrexone, naltrexone hydrochloride, naluzotan, nandrolone decanoate, napabucasin, naphazoline, naphthoquine, naproxen, naproxen sodium, naquotinib mesylate, naratriptan, narlaprevir, nasapaque, nasaruplase, nastorazepide calcium, nateglinide, navamepent, nazartinib, nebivolol, necuparanib, nedaplatin, nedocromil, nelarabine, nelfinavir, nelotanserin, nemonapride, nemonoxacin, neoandrographolide, neosaxitoxin, neostigmine methylsulfate, nepadutant, nepafenac, nepicastat, nepolong, neramexane, neratinib, neridronic acid, netarsudil, netilmicin, netupitant, nevirapine, niacin, nicardipine, nicergoline, nicorandil, nicotiflorin, nicotinicacid, nicotinicacid, nicousamide, nifedipine, nifevalactal, nifeviroc, Nifurtimox, nifuzide, nikkomycin, nilotinib, nilutamide, nilvadipine, nimesulide, nimodipine, nimorazole, ningetinib, nintedanib, niraparib, nisoldipine, nitazoxanide,
nitisinone, nitrendipine, nitric oxide, nitroglycerin, nitroglycerine, nizatidine, nokxaban, nolatrexed, nomegestrol acetate, norelgestromin, norepinephrine, norethindrone, norethindrone acetate, norethindrone enantate, norethisterone, norethisterone acetate, norfloxacin, norgestimate, noribogaine, norursodeoxycholic acid, obeticholic acid, octenidine, octahydroaminooacidine succinate, octreotide, octreotide hydrochloride, odalasvir, odanacatib, odiparcil, ofloxacin, olanzapine, olaparib, olesoxime, oliferidine, olmesartan, olmesartan cilexetil, olmesartan medoxomil, olodaterol, olodaterol hydrochloride, olopatadine, olprinone, olsalazine, olsalazine, oltopraz, omacetaxine mepesuccinate, omadacycline, omariplatin, omaveloxolone, ombitasvir, omeacamitivmecarbil, omega-3-carboxylic acids, omeprazole, omigapil, omoconazole, onalespib, onapristone, ondansetron, ondolopran, opicapone, opipramol, methylphenidate, orcinoside, orlotimod, oritavancin, orlistat, ornithine phenylacetate, ornoprostil, ortataxel, orteronel, orthovisc, orvediant, osetamivir, osilodrostat, osimertinib, Osiris Phleum pratense, ospemifene, oteracil potassium, oteseconazole, oxaliplatin, oxaloacetic acid, oxandrolone, oxazepam, oxcarbazepine, oxfendazole, oxidized glutathione sodium, oxiracetam, oxybutynin, oxybutynin hydrochloride, oxycodone, oxycodone hydrochloride, oxymetazoline, oxymetazoline hydrochloride, oxymorphine, oxytocin, ozagrel, ozagrel hydrochloride, ozagrel sodium, ozanimod, ozenoxacin, paclitaxel, paclitaxel poliglumex, pacritinib, palbociclib, paliperidone, paliperidone palmitate, palmidrol, palonosetron, palovarotene, pamidronate disodium, pancrelipase, panipenem, panobinostat, pantoprazole, paracetamol, parecoxib, paricalcitol, paritaprevir, parnpararin sodium, parogrelil, paromomycin, paroxetine, paroxetine hydrochloride hemihydrate, paroxetine mesylate, patriomer calcium, patupilone, pazopanib, pazufloxacin, pazufloxacin mesylate, pefcalcitol, peficitinib, pegylated daso-filgrastim, pelubiprofen, pemafibrate, pemetrexed disodium, pemirolast, pemirolast potassium, pemirolast sodium, p enciclovir, penhyclidine hydrochloride, pentamidine, pentetate calcium trisodium, pentetate zinc trisodium, pentetrazol, pentosan polysulfate sodium, pentostatin, pentoxifylline, peramivir, perampanel, perchlozone, peretinoin, perflunapent, perfluoronemulsion, perfluorooctyl bromide, pergolide, perhexiline maleate, perifosine, perindopril,
perindopril arginine, perospirone, pevonedistat, pexidartinib, PhagoBioDerm,
phenchlobenpyrrone, phenethyl isothiocyanate, phenoxybenzamine hydrochloride,
phentermine, phentermine hydrochloride, phenolamine mesylate, phenylbutyrate,
phenylephrine, phenylephrine hydrochloride, phentolamine, phencyclidine,
perindopril arginine, perospirone, pevonedistat, pexidartinib, PhagoBioDerm,
phenchlobenpyrrone, phenethyl isothiocyanate, phenoxybenzamine hydrochloride,
phentermine, phentermine hydrochloride, phenolamine mesylate, phenylbutyrate,
phenylephrine, phenylephrine hydrochloride, phentolamine, phencyclidine,
ranitidine, ranitidine bismuth citrate, ranolazine, rasagiline, ravidasvir hydrochloride, raxatrigine, rebamipide, rebastinib, reboxetine, reboxetine mesylate, recilisib sodium, recoflavone, redaporfin, ibuprofen, naproxen, glycopyrronium bromide, refametinib, regorafenib, rebectam, relenopride, relugolix, remeglurant, remifentanil, remifentanil hydrochloride, remimazolam, remimazolam tosylate, remogliplozin etabonate, repaglinide, repirinast, amlexanox, chlorcyclizine hydrochloride, bucillamine, guanabenz, mazindol, naltrexone, nitisinone, ondansetron, phacetoperane, retigabine, rosiglitazone, sodium phenylbutyrate, resiniferatoxin, resiquimod, resminostat, resveratrol, retaglipitin, retapamulin, retigabine, retinoic acid, retosiban, revaprazan, revafenacin, reviparin sodium, rhein, rhenium-186 etidronate, ribavirin, ribociclib, ricolinostat, ridinilazole, ridostin, rifabutin, rifampicin, rifamycin, rifapentine, rifaximin, rigosertib sodium, rilapladib, rilpivirine, rinpivirine hydrochloride, riluzole, rimantadine, rimeporide, rimexolone, riociguat, ripasudil hydrochloride hydrate, risedronate sodium, risperidone, ritonavir, rivaroxaban, rivastigmine, rivipansel sodium, rizatriptan, rizatriptan benzoate, rmulation, rociletinib, roflumilast, rokitamycin, rolapitant, romurtide, ronacaleret, roneparstat, ronopterin, ropinirole, ropinirole hydrochloride, ropivacaine, rosebengal sodium, rosiglitazone, rosiglitazone maleate, rosiglitazone sodium, rostafuroxin, rosuvastatin, rosuvastatin calcium, rotigotine, rovatrelin, roxadustat, roxithromycin, rubitecan, rucaparib phosphate, rufinamide, rufloxacin, rupatadine, ruxolitinib, S-(−)-ornidazole phosphate disodium, sabarubicin, sacubitril, safinamide, salbutamol, salbutamol sulfate, salicylic acid, salmeterol, salmeterol xinafoate, salubrinal, salvicine, samarium(153Sm) lexidronam, samidorphan, S-amlodipine nicotinate, sapacitabine, sapropterin, sapropterin dihydrochloride, saquinavir, saracatinib, sarecycline, saroglitazar, sarpogrelate hydrochloride, savolitinib, saxagliptin, scopolamine, scorpion venom, omega-3-polyunsaturated fatty acid, secnidazole, segesterone acetate, selegiline, selegiline hydrochloride, selepressin, selexipag, seliciclib, selinexor, selisistat, selumetinib, selurampanel, sepranolone, seratrodast, serlopitant, sertaconazole, sertaconazole nitrate, sertindole, sertraline, sertraline hydrochloride, setipiprant, sevelamer carbonate, sevelamer hydrochloride, seviteronel, sevoflurane, sevuparin
sodium, sibutramine maleate, sibutramine mesylate, sildenafil, sildenafil citrate,
silibinin dihydrogen succinate, simotide, simtubosin, silver sulfadiazine, simprevir,
simmithecan hydrochloride, simvastatin, sipoglitcin, sipiatorin, sipoperforin,
tenofoviralafenamide, tenofovir dipivoxil fumarate, tenofovir disoproxil aspartate, tenofovir disoproxil fumarate, tenoxicam, tepotinib, teprenone, terameprocol, terazosin, terbinafine, terbinafine hydrochloride, terguride, teriflunomide, tesevatinib, tesofensine, testosterone, testosterone undecanoate, tetrabenazine, tetracaine, tetracaine hydrochloride, tetrahydrocannabinol, tetrahydrocannabidiol, tetrathiomolybdate, tetryzoline, tezacaftor, thalidomide, theliatinib, theophylline, therapeutic, thiazide, thienophene hydrochloride, thiopeta, thrombin, thromboreductin, thyroxine, tiagabine, tibolone, ticagrelor, ticlopidine, tigecycline, tiludronate sodium, timolol, timolol maleate, tindamax, tinidazole, tinzaparin sodium, tiotropium bromide, tiotropium bromide monohydrate, tipelukast, tipepidine hibenzate, tipifarnib, tipiracil hydrochloride, tipranavir, tirapazamine, tirasemtiv, tirilazad, tirofiban, tirofiban hydrochloride, tivantinib, tivozanib, tobramycin, tocofersolan, tocetinate, tofacitinib, tofogliflozin, tolcapone, tolimidone, tolperisone, tolterodine, tolterodine tartrate, tolvaptan, topramarone, toproxostat, toprotecan, toprotecan hydrochloride, torasemide, toremifene, tosedostat, tosufloxacin, totomembopag, tozadenostat, tozadentan, trabectedin, trabodenoson, tradipitant, tramadol, tramadol hydrochloride, trametrexate, tranexamic acid, tranilast, trandolapril, tranilast, transcrocetine-sodium, transepithelial riboflavin, transtiberin hydrochloride, travoprost, trazodone, trehalose, trelagluptin succinate, treosulfan, treprostinil, treprostinil diolamine, tretinoin, triamcinolone acetonide, triapine, triazolam, tribendimidine, trichlormethiazide, triciribine, triclabendazole, triclocarban, trientine hydrochloride, trifarotene, trifluridine, triflusal, triheptanoin, trilostane, trimebutine3-thiocarbamoyl-benzenesulfonate, trimebutine tosylate, trimegestone, trimethoprim, trimetrexate, trinitrate, tripotassium dicitratobismuthate, trofinetide, tropicamide, tropisetron, trospiumchloride, trovafloxacin, troxipide, tucatinib, tulobuterol, tylerdipinehydrochloride, ubenimex, ubidecarenone, ubrogepant, udenafil, ulinastatin, ulipristal, ulixertinib, ulobetasol, umaclidinium, umaclidinium bromide, upamostat, uprosertib, uracil, urapidil, uridinetriacetate, uroactides, ursodeoxycholic acid, ursolicacid, vaborbactam, vadadustat, valaciclovir, valaciclovir hydrochloride, valbenazine, valdecoxib, valganciclovir, valomaciclovir stearate, valproic acid, valubicin, valsartan, valsartan
tri sodium hemipentahydrate, vancomycin, vancomycin hydrochloride, vandetanib, vaniprevir, vanoxerine, vapendavir, vardenafil hydrochloride, varenicline, varithena, varlitinib, vatiquinone, vavelta, veliparib, velpatasvir, velusetrag, vemurafenib, venetoclax, venlafaxine, venlafaxine hydrochloride, vepoloxamer, verapamil, verapamil hydrochloride, verdinexor, veregen, vericiguat, verinurad, variltnib, varipretib, varitena, varlitinib, vatiquinone, vavelta, veliparib, velpatasvir, velusetrag, vemurafenib, venetoclax, venlafaxine, venlafaxine hydrochloride, vepoloxamer, verapamil, verapamil hydrochloride, verdinexor, veregen, vericiguat, verinurad, vernakalant, 

Fructus, Apocyni Veneti Folium, Aquilariae Lignum Resinatum, Arcae Concha, Arctii Fructus, A

5


10

Calculus Sativus, Bovis Calculus, Breviscapine, Broussonetiae Fructus, Bruceae Fructus, Bubali Cornu, Buddlejae Flos, Bumgarus Parvus, Bupleuri Radix, Calamina, Callicarpae Caulis Et Folium, Callicarpae Formosanae Folium, Callicarpae Macrophyllae Folium, Calomelani, Campsis Flos, Canarii Fructus, Canavaliae Semen, Cannabis Fructus, Capsici Fructus, Carotae Fructus, Carpessi Fructus, Carthami Flos, Caryophylli Flos, Caryophylli Fructus, Cassiae Semen, Castor Oil, Catechu, Celosiae Cristatae Flos, Celosiae Semen, Centella Total Glucosides, Centellae Herba, Centipeda Herba, Cera Chinensis, Cera Flava, Cervi Cornu Degelatinatum, Cervi Cornu Pantotrichum, Cervi Cornu, Cervi Cornus Colla, Chaenomelis Fructus, Changii Radix, Chebulae Fructus Immaturus, Chebulae Fructus, Chelidoni Herba, Chinese Angelica Liquid Extract, Chloriti

20


25

Reticulatae Pericarpium Viride, Citri Reticulatae Pericarpium, Citri Reticulatae Semen, Citri Sarcodactylis Fructus, Clematidis Armandii Caulis, Clematidis Radix Et Rhizoma, Clinopodi Herba, Cnidii Fructus, Codonopsis Radix, Coicis Semen, Commelinae Herba, Conyzae Herba, Coptidis Rhizoma, Cordyceps, Corni Fructus, Corydalis Bungeanae Herba, Corydalis Decumbentis Rhizoma, Corydalis Rhizoma, Crataegi Folium, Crataegi Fructus, Cremastre

30
Perforati Herba, Ilicis Chinensis Folium, Ilicis Cornutae Folium, Ilicis Rotundae Cortex,
Ulicii Cortex, Impatientis Semen, Imperatae Rhizoma, Indigo Naturalis, Inulae Flos, Inulae
Herba, Inulae Radix, Iridis Tectori Rhizoma, Isatidis Folium, Isatidis Radix, Juglandis Semen,
Jujubae Fructus, Junci Medulla, Kadsurae Caulis, Kaempferiae Rhizoma, Kaki Calyx, Kansui
Radix, Knoxiae Radix, Kochiae Fructus, Lablab Semen Album, Laggerae Herba, Lagotidis
Herba, Laminariae Thallus Eckloniae Thallus, Lamiophlomis Herba, Lasiosphaera Calvatia,
Leonuri Fructus, Leonuri Herba, Leonurus Liquid Extract, Licorice Extract, Licorice Liquid
Extract, Ligustici Rhizoma Et Radix, Ligustri Lucidi Fructus, Lilii Bulbus, Limonitum,
Linderae Radix, Lini Semen, Liquidambaris Fructus, Liquidambaris Resina, Liriopes Radix,
Litchi Semen, Litseae Fructus, Lobeliae Chinensis Herba, Longan Arillus, Lonicerae Flos,
Lonicerae Japonicae Caulis, Lonicerae Japonicae Flos, Lophatheri Herba, Luffae Fructus
Retinervus, Lycii Cortex, Lycii Fructus, Lycoptis Herba, Lygodii Spora, Lysimachiae Herba,
Lysionoti Herba, */-Borneolum, */-Menthol, Magnetitum, Magnoliae Flos, Magnoliae Officinalis
Cortex, Magnoliae Officinalis Flos, Mahoniae Caulis, Malvae Fructus, 
Manis Squama, Mantidis OOTheca, Margarita, Margaritifera Concha, Marsdeniae
Tenacissimae Caulis, Mel, Melanteritum, Meliae Cortex, Melo Semen, Menispermii Rhizoma,
Menthae Haplocalycis Herba, Meretricis Concha, Cyclinae Concha, Micae Lapis Aureus,
Microctis Folium, Mirabilitum Praeparatum, Momordicae Semen, Mori Cortex, Mori Folium,
Mori Fructus, Mori Ramulus, Morindae Officinalis Radix, Moschus, Moslae Herba, Moutan
Cortex, Mume Flos, Mume Fructus, Murrayae Folium Et Cacumen, Mylabris, Myristicae
Semen, Myrrha, Nardostachyos Radix Et Rhizoma, Natrii Sulfas Exsiccatus, Natrii Sulfas,
Nelumbinis Folium, Nelumbinis Plumula, Nelumbinis Receptaculum, Nelumbinis
Rhizomatis Nodus, Nelumbinis Semen, Nelumbinis Stamen, Nigellae Semen, Notoginseng
Radix Et Rhizoma, Notoginseng Total Saponins, Notoginseng Triol Saponins, Notopterygii
Rhizoma Et Radix, Ocimum Gratissimum Oil, Olibanum, Omphalia, Ophicalcitum,
Ophiopogonis Radix, Orostachyis Fimbriatae Herba, Oroxyli Semen, Oryzae Fructus
Germinatus, Osmundae Rhizoma, Ostreae Concha, Paeonieae Radix Alba, Paeonieae Radix
Rubra, Panacis Japonici Rhizoma, Panacis Majoris Rhizoma, Panacis Quinquefolii Radix,
Papaveris Pericarpium SI, Paridis Rhizoma, Patchouli Oil, Pegaeophyti Radix Et Rhizoma,
Peppermint Oil, Perillae Caulis, Perillae Folium, Perillae Fructus, Periplocae Cortex, Persicae
Ramulus, Persicae Semen, Peucedani Decursivi Radix, Peucedani Radix, Pharbitidis Semen,
Phellodendri Amurensis Cortex, Phellodendri Chinensis Cortex, Pheretima, Phragmitis
Rhizoma, Phyllanthi Fructus, Physalis Calyx Seu Fructus, Physochlainae Radix, Phytoleaccae
Radix, Picrasme Ramulus Et Folium, Picriciae Herba, Picrorhizae Rhizoma, Pinelliae
Rhizoma Praeparatum Cum Alumine, Pinelliae Rhizoma Praeparatum Cum Zingibere Et
Alumine, Pinelliae Rhizoma Praeparatum, Pinelliae Rhizoma, Pini Lignum Nodi, Pini Pollen,
Piperis Fructus, Piperis Kadsurae Caulis, Piperis Longi Fructus, Plantaginis Herba,
Plantaginis Semen, Platycladi Cacumen, Platycladi Semen, Platycodonis Radix,
Pogostemonis Herba, Polygala Liquid Extract, Polygalae Japonicae Herba, Polygalae Radix,
Polygonati Odorati Rhizoma, Polygonati Rhizoma, Polygoni Avicularis Herba, Polygone
Cuspidati Rhizoma Et Radix, Polygoni Multiflori Caulis, Polygoni Multiflori Radix
Praeparata, Polygoni Multiflori Radix, Polygoni Orientalis Fructus, Polygone Perfoliati Herba,
Polygone Tinctoriı Folium, Polyporus, Poria, Poriae Cutis, Portulacaæ Herba, Potentillae
Chinensis Herba, Potentillae Discoloris Herba, Powerdered Buffalı Horn Extract, Prinsepiae
Nux, Propolis, Prunellae Spica, Pruni Semen, Psammosilenes Radix, Pseudolaricis Cortex,
Pseudostellariaæ Radix, Psoraleae Fructus, Pterocephali Herba, Puerariaæ Lobataæ Radix,
Puerariaæ Thomsonii Radix, Pulsatillae Radix, Pyritum, Pyrolæ Fructus, Pyrrosiae Folium,
Qisqualis Fructus, Rabdosiae Rubescentis Herba, Ranae Oviductus, Ranunculi Ternati
Radix, Raphani Semen, Realgar, Rehmanniae Radix Praeparata, Rehmanniae Radix,
Rhapontici Radix, Rhei Radix Et Rhizoma, Rhodiolae Crenulataæ Radix Et Rhizoma,
Rhododendri Daurici Folium, Rhododendri Mollis Flos, Rhubarb Extract, Rhubarb Liquid
Extract, Ricini Semen, Rosae Chinensis Flos, Rosae Laevigataæ Fructus, Rosae Rugosæ Flos,
Rubi Fructus, Rubiae Radix Et Rhizoma, Saigaæ Tataricaæ Cornu, Salvia Total Phenolic
Acids, Salviae Miltiorrhizae Radix Et Rhizoma, Sanguisorbaæ Radix, Santali Albi Lignum,
Saposhnikoviae Radix, Sappan Lignum, Sarctandraæ Herba, Sargassum, Sargentodoxæ Caulis,
Sauropi Folium, Saururi Herba, Saussureae Involutææ Herba, Schisandraæ Chinensis
Fructus, Schisandraæ Sphenantherææ Fructus, Schizonepetaæ Herba Carbonisata,
Schizonepetaæ Herba, Schizonepetaæ Spica Carbonisata, Schizonepetaæ Spica, Scolopendra,
Scorpio, Scrophulariae Radix, Scutellariaæ Extract, Scutellariaæ Barbatææ Herba, Scutellariaæ
Radix, Sediæ Herba, Selaginellææ Herba, Semiaquilegææ Radix, Seneconis Scandentis Hebra,
Sennæ Folium, Sepiae Endoconcha, Serpentis Periostracum, Sesameæ Oil, Sesamiæ Semen
Nigrum, Setariaæ Fructæ Germinatus, Siegesbeckiææ Herba, Silybiæ Fructus, Sinapisæ Semen,
Sinomenii Caulis, Sinopodophylliææ Fructus, Siphonostegoææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææææae
Radix, Stemonae Radix, Stephaniae Tetrandrae Radix, Sterculiae Lychnophorae Semen, Strychni Semen Pulveratum, Strychni Semen, Styrax, Suis Fellis Pulvis, Sulfur, Swertiae Herba, Swertiae Mileensis Herba, Syngnathus, Syringae Cortex, Talcus Pulvis, Talcum, Tamarici Camum, Tanshinones, Taraxaci Herba, Taxilli Herba, Tea-Seed Oil, Terminaliae

5 Belliricae Fructus, Testudinis Carapacis Et Plastri Colla, Testudinis Carapax Et Plastrum, Tetrapanacis Medulla, Thalaspi Herba, Thunberg Fritillary Liquid Extract, Tinosporae Radix, Tootal Ginsenoside Of Ginseng Stems And Leaves, Toosendan Fructus, Torreyae Semen, Total Ginsenoside Ginseng Root, Toxicodendri Resina, Trachelospermi Caulis Et Folium, Trachycarpi Petiolus, Tribuli Fructus, Trichosanthis Fructus, Trichosanthis Pericarpium,


[0093] In certain embodiments, the drug content further comprises medium. The medium can be associated with the API, i.e., the medium is in physical contact with the API.

20 In certain embodiments, the API is embedded in the medium. In certain embodiments, the API is dispersed within the medium. In certain embodiments, the medium is made of a thermoplastic material as disclosed herein.

[0094] In certain embodiments, the medium comprises a water-soluble excipient selected from the group consisting of cocoa butter, polyethylene glycol (PEG), sucrose, glucose, galactose, fructose, xyloseolactose, maltose, trehalose, sorbitol, manitol, maltodextrins, raffinose, stachyose, fructo-oligosaccharides and a combination thereof. In certain embodiments, the substrate further comprises a plasticizer.

[0095] The drug content can be of any suitable shape and size to be loaded into the compartment.

[0096] In certain embodiments, the drug content is operably linked to the compartment via covalent bond, non-covalent interactions or through a linker. Thus, the drug content and the substrate can be made separately and associate together through a covalent bond or non-covalent interactions. In certain embodiments, dosage form is made by producing the drug content and the substrate in a single process using 3D printing methods.
In certain embodiments, the drug content is formed in the shape of a compressed tablet, an oval tablet, a pill, or a capsulet. In certain embodiments, the shape of the drug content matches the shape of the compartment. For example, when the compartment is a pie-shape, the drug content is also of a pie-shape, e.g., to fill the compartment.

In certain embodiments, the drug content is in the form of nanoparticles as illustrated in FIG. 6. The drug content can be mixed with solution in which the API is either dissolved or suspended. The solution is then atomized/sprayed atop a printing layer during the course of the three-dimensional printing of the dosage form. Once the solution containing the drug content dries, the drug content is dispersed in the dosage form. Nanoparticles have large surface area and will have high dissolution rate.

The size of the nanoparticles ranges from 1 nm to 900 nm in size (preferable 100-800 nm, 100-700 nm, 100-600 nm, 100-500 nm, 100-400 nm, 100-300 nm, 100-200 nm, 1 nm, 2 nm, 3 nm, 4 nm, 5 nm, 6 nm, 7 nm, 8 nm, 9 nm, 10 nm, 11 nm, 12 nm, 13 nm, 14 nm, 15 nm, 16 nm, 17 nm, 18 nm, 19 nm, 20 nm, 100 nm, 200 nm, 300 nm, 400 nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm in size). The size of nanoparticles can be controlled by selecting appropriate synthesis methods and/or systems. To obtain nanoparticles within a desired size range, the synthesis conditions may be properly controlled or varied to provide for, e.g., a desired solution concentration or a desired cavity range (a detailed review can be found at, e.g., Vincenzo Liveri, Controlled synthesis of nanoparticles in microheterogeneous systems, Published by Springer, 2006).

In certain embodiments, the drug content is in the form of microneedles as illustrated in FIG. 7. The microneedle would be printed in conjunction with the dosage form or inserted into the dosage form during the three-dimensional printing of the dosage form. The microneedles can be composed of a saccharide, a PLGA polymer or an API or a combination thereof. The microneedle can assist in the penetration of an API into the circulatory system of a patient when administered either parenteral or enteric.

In certain embodiments, the drug content forms a network. As shown in FIG. 8A, a dosage form has a substrate forming a compartment loaded with a drug content. The drug content has a substrate forming a network. The frame structure of tablet is made of a material that dissolves between 1-10 minutes, and the substrate dissolves in 2-60 seconds, preferably in 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 seconds. As shown in FIG. 8B, the API can be released in seconds after the dosage form is administered.

The drug content can be made using an additive method such as fused deposition modeling (FDM). In certain embodiments, the drug content can be made by using
a three-dimensional printer (3D printer) configured to extruding a mixture of API and the excipient. The API can be melted and mixed homogenously with the melted substrate before being extruded. Alternatively, the API in a solid form (e.g., powder) can be mixed with and dispersed in the melted substrate before being extruded. In general, the extrusion process can be conducted at temperatures 10° to 40°C above the glass transition (Tg) of the substrate and a temperature close to the melting point of the API. Once at a suitable temperature for use in the three-dimensional printer, the substrate can be deposited to the three-dimensional printing surface. The shape and size of the drug content can be controlled by programing the three-dimensional printing process. In certain embodiments, the drug content is fabricated in the same process of the substrate. In certain embodiments, the drug content is fabricated before the making of the substrate and loaded into the compartment during or after the substrate is fabricated.

[00103] In certain embodiments, when the drug content is loaded into the compartment, it is associated with the substrate, e.g., embedded or fixed in the substrate. In certain embodiments, the drug content is detachable from the substrate when loaded into the compartment.

[00104] D. Controlled Release

[00105] The dosage form disclosed herein can offer various release profiles after oral administration. In certain embodiments, the dosage form provides a constant release profile, pulsatile or delayed delivery, or non-linear drug release. In certain embodiments, the dosage form provides a zero-order release kinetics.

[00106] A proper release profile may offer benefits to certain drug therapy regimes. For example, a pulsatile release profile offers controlled absorption with resultant reduction in peak through ratios, targeted release of the drug to specific areas within the gastro intestinal tract, and absorption independent of the feeding state, thus may be used to prevent tolerance, reduce the side-effects and improve patient compliance, which is desirable to treat diseases like ADHD. For another example, a release profile with a loading dose followed by a maintenance dose may be good for treating chronic conditions such as hypertension and diabetes.

[00107] Some of the mechanisms to control the release profile using the dosage from disclosed herein have been discussed above. For example, by manipulating the exposed surface area of the substrate that erodes constantly over time, the drug content embedded in the substrate is able to deliver a constant amount of drug over time. In addition, the release
profile can be controlled by the size of compartment opening and/or by the geometric shape of the compartment.

[00108] In certain embodiments, the release profile can be controlled by the design of a compartment having an aperture that is sealed or blocked by a plug. The plug is made of a water-soluble, porous, or erodible material or pH sensitive materials or hydrophobic material that will undergo attrition when the dosage form passing the GI tract. When the dosage form is administered to a subject, the plug is dissolved, permeated or eroded, thus releasing the drug content from the compartment. The release profile of the drug content can be controlled by choosing a plug of proper erosion/dissolution rate or permeation rate. Alternatively, the release profile of the drug content can be controlled by using the shape and/or the size of the plug (e.g., a rod shape of proper length). The release profile can also be controlled by the number of the compartment. FIG. 9 shows an exemplary dosage form having a substrate forming a plurality of column-shaped compartments residing on both sides of the dosage form. Each compartment is loaded with a drug content. Each compartment has an aperture that is blocked by a rod-shaped plug. The plugs have different dissolution rate. Depending on the size, shape and dissolution rate of the plug, the APIs can be released in a sustained, continuous, simultaneous, consecutive or pulsatile manner.

[00109] FIG. 10A shows an exemplary dosage form providing a consecutive release profile. Referring FIG. 10A, the dosage form 700 has a substrate 701 forming three column-shaped compartments 702-704. Each compartment is loaded with a drug content of the same API. Each compartment has an aperture that is blocked by a rod-shaped plug 705-707. The plugs are made of the same material but have different length. Consequently, it takes different amount of time to dissolve the plugs and to open the compartments to release the drug content. As illustrated in FIG. 10C, the shortest plug dissolves first, releasing the API from the first compartment. When the API in the first compartment is completely released, the plug of the median length dissolves, releasing the API from the second compartment. When the API in the second compartment is completely released, the third plug dissolves to release the API from the third compartment. As a result, the plasma drug level reaches the first peak when the drug content in the first compartment is released. When the API released from the first compartment starts to be eliminated, the plasma drug level starts to decrease (see FIG. 10D). Before the plasma drug level falls below the critical level (the horizontal line, below which the drug would be ineffective), the API from the second compartment is released, and the plasma drug level increases again. When the API released from the second compartment reaches the second peak and starts to be eliminated, the plug of the third
compartment dissolves to open the compartment. As a result, the plasma API level is maintained above the critical level for a long time, which benefits certain diseases.

[00110] The consecutive release manner can also be achieved through another exemplary dosage form having several drug contents packed in the form of layers as illustrated in FIG. 10B. The API can be released in a sustained manner by having each layer dissolving in synchrony to provide a continuous, sustained release of API as depicted in FIG. IOC. In certain embodiments, the outer layers of the dosage form dissolve immediately and release the embedded drug content when the dosage form is administered. But the layers sandwiched in the middle do not dissolve or dissolve much slower because the outer layers block their interface with the environment. The dissolution of the outer layers exposes the layers sandwiched in the middle and expedites their dissolution, thus providing a consecutive release profile as illustrated in FIG. IOC.

[00111] In certain embodiments, the dosage form comprises a gas-generating component loaded into the first compartment. In certain embodiments, the gas-generating component is selected from the group consisting of organic acid and carbonates, sulphites, bicarbonates, sodium carbonate, sodium bicarbonate, sodium metabisulphite, calcium carbonate, and combinations thereof, which on contact with gastric fluid releases carbon dioxide or sulphur dioxide gas. When the substrate is dissolved, permeated or eroded in stomach, the gas generating component is exposed to the acid environment or water penetrate into compartment to induce the reaction between acid and sodium bicarbonate and generates gas to release the drug content in an effervescent manner.

[00112] The dosage form disclosed herein may comprise one or more drug content at least partially in delayed-release form, wherein the delayed release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the API in a delayed-release substrate/substrate or by the application of one or more delayed-release coatings. Through delayed release, API release may be so controlled that twice or once daily administration of the dosage form is sufficient, which is advantageous in particular in the case of a need for a sustained level active compound, e.g., for combatting pain.

[00113] In certain embodiments, the dosage form intends to release the active ingredients in oral cavity instantly. One example is to be given to oral cavity or take sublingual region.

[00114] In certain embodiments, the drug form can further comprise conventional auxiliary substances known to the person skilled in the art, preferably selected from the group...
consisting of glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatin, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

Manufacture of the Dosage Form

[00115] The controlled release dosage forms disclosed herein can be manufactured using any appropriate process. In certain embodiments, the dosage forms are produced using three-dimensional printing (3D printing).

[00116] As used herein, 3D printing refers to a process that produce 3D objects layer-by-layer from digital designs. The basic process of 3D printing has been described in U.S. Pat. Nos. 5,204,055; 5,260,009; 5,340,656; 5,387,380; 5,503,785; and 5,633,021. Additional U.S. patents and applications related to 3D printing include: U.S. Pat. Nos. 5,490,962; 5,518,690; 5,869,170; 6,530,958; 6,280,771; 6,514,518; 6,471,992; 8,828,411; U.S. PGPub. Nos: 2002/0015728; 002/0106412; 2003/0143268; 2003/0198677; 2004/0005360. Reference can be made to the patents and applications listed above for a detailed description of 3D printing.

In certain embodiments, the dosage forms disclosed herein are manufactured using extrusion methods. In an extrusion process, material is extruded from robotically-actuated nozzles. Unlike binder deposition, which requires a powder bed, extrusion methods can print on any substrate. A variety of materials can be extruded for 3D printing, including thermoplastic materials disclosed herein, pastes and colloidal suspensions, silicones and other semisolids. One common type of extrusion printing is fused deposition modeling, which uses solid polymeric filaments for printing. In fused deposition modeling, a gear system drives the filament into a heated nozzle assembly for extrusion (see L Gibson et al. (2015) Additive Manufacturing Technologies: 3D Printing, Rapid Prototyping, and Direct Digital Manufacturing. 2 ed. Springer, New York).

The manufacturing instructions for a print job may be generated a variety of ways, including direct coding, derivation from a solid CAD model, or other means specific to the 3D printing machine's computer interface and application software. These instructions may include information on the number and spatial placement of droplets, and on general print parameters such as the drop spacing in each linear dimension (X, Y, Z), and volume or mass of fluid per droplet. For a given set of materials, these parameters may be adjusted in order to refine the quality of structure created. The overall resolution of the structure created is a function of the powder particle size, the fluid droplet size, the print parameters, and the material properties.

Because of its ability of handling a range of pharmaceutical materials and control both composition and architecture locally, 3D printing is well suited to the fabrication of dosage forms with complex geometry and composition in accordance with the present invention.

Manufacturing the dosage forms using 3D printing methods also facilitate personalized medicine. Personalized medicine refers to stratification of patient populations based on biomarkers to aid therapeutic decisions and personalized dosage form design. Modifying digital designs is easier than modifying physical equipment. Also, automated, small-scale 3D printing may have negligible operating cost. Hence, 3D printing can make multiple small, individualized batches economically feasible and enable personalized dosage forms designed to improve adherence.

Personalized dosage form allows for tailoring the amount of drug delivered based on a patient's mass and metabolism. 3D printed dosage forms could ensure accurate dosing in growing children and permit personalized dosing of highly potent drugs.
Personalized dosage forms can also combine all of patients’ medications into a single daily
dose, thus improve patients’ adherence to medication.

FIG. 11 illustrates a process of using 3D printing to manufacture personalized
dosage forms. For each patient, a variety of clinical testing results can be obtained, including
body weight, age, metabolism indicator and genomic biomarkers, etc. The clinical testing
results are input into computer software. The information is combined with the prescription
of physician and pharmaco-kinetic model to design a dosage form of specific dose and drug
combination. The instruction is then sent to a 3D printer to manufacture the dosage form
designed, which is administered to the patient.

Controlled Release of Multiple Drugs

The dosage form and methods disclosed herein can be used to control release
of two or more drugs in order to optimize the drug combinations in certain therapeutic
regimes. For example, a tablet to treat hypercholesterolemia can be designed to offer
immediate release of Atorvastatin calcium and extended release of nicotinic acid. In another
example, a non-steroidal anti-inflammatory drug (NSAID) for pain relief may be designed to
provide sustained release of NSAID and a rapid release of H2-receptor antagonist for
preventing NSAID-induced mucosal damage.

In certain embodiments, the substrate forms multiple compartments, each
loaded with a drug content. In certain embodiments, the multiple compartments are
connected. In certain embodiments, the multiple compartments are disconnected. In certain
embodiments, the drug contents loaded into different compartments are the same. In certain
embodiments, the drug contents loaded into different compartments are different. The dosage
form can be so designed to provide simultaneous or sequential release of multiple drug
content to exert synergistic therapeutic effects.

FIG. 12A shows an exemplary dosage form that can release APIs
simultaneously. Referring to FIG. 12A, the dosage form 800 includes three stacked layers
801–803, each of which is embedded with a different drug content. As illustrated in FIG.
12B, when the dosage form 800 is administered, the drug contents are released
simultaneously but at different rates as the layers dissolve.

FIG. 13A depicts another exemplary dosage form of simultaneous release
profile. Referring to FIG. 13A, the dosage form 900 includes three column shaped
compartment 901–903, in which three drug contents are loaded. Each drug content contains
an API embedded in a substrate of different dissolution rate. As illustrated in FIG. 13B,
when the dosage form 900 is administered, the three APIs are released simultaneously but at
different rates as the substrates of the drug contents dissolve. The release rate of the APIs can also be controlled by the shape of the compartments or the size of the opening of the compartments.

Fig. 14A and 14B depict additional exemplary dosage forms of simultaneous release profile of three APIs. Referring to FIG. 14A, the dosage form 1000 contains three pie-shaped segments 1001-1003 wherein drug contents are embedded. As illustrated in FIG. 14C, he drug contents release simultaneously as the segments dissolve, and the release rate of the drug contents can be controlled by the dissolution rate of the segments. Referring to FIG. 14B, the dosage form 1100 contains three pie-shaped segments 1101-1103, which are wrapped by a shell 1104 that dissolves slower than the segments. The release rates of the drug contents embedded in the segments are reduced as the shell 1104 blocks the interface of the segments 1101-1103 with the environment.

FIG. 15A shows an exemplary dosage form of sequential release profile of two APIs. Referring to FIG. 15A, the dosage form 1200 includes a substrate 1201 forming a compartment that is filled by a drug content 1202. The substrate 1201 contains a first API, and the drug content 1202 contains a second API. As illustrated in FIG. 15B, the first API releases as the substrate dissolves when the dosage form is administered. The second API does not release until the substrate dissolves to expose the drug content, providing a sequential release profiles of the APIs.

FIG. 16A shows another exemplary dosage form of sequential release profiles. Referring to FIG. 16A, the dosage form 1300 has a substrate 1301 forming three column-shaped compartments 1302-1304 loaded with three drug contents. The compartments 1302-1304 have an aperture that are blocked by rod-shaped plugs that have different length and/or dissolution rate. As illustrated in FIG. 16B, the APIs are released in a sequential manner as the plugs dissolve sequentially to open the compartments.

FIG. 17A shows an exemplary dosage form having a simultaneous release profile or sequential release profile. Referring to FIG. 17A, the dosage form 1400 has a substrate containing four segments 1701-1704 having different dissolution rate. In certain embodiments, as illustrated in FIG. 17B, the drug contents are embedded in the segments 1701-1704 and are released simultaneously when the substrate dissolves. In certain embodiments, each segment contains a compartment where a drug content is loaded. As illustrated in FIG. 17C, the drug contents are released in a sequential manner when the substrate dissolves.

EXAMPLE 1
This example illustrates a design of dosage form that has controlled release profile.

As shown in FIG. 18A, the dosage form comprised a flat tablet substrate forming a pie shaped compartment. The substrate was made of PEG8000. Benzoic acid was used as a module drug content.

The release profile of the benzoic acid from the dosage form was measured as the following method. $\text{Na}_2\text{HPO}_4$ solution of pH 8 was prepared as dissolver of benzoic acid. Benzoic acid solution of 120µg/mL was serially diluted to 30µg/mL, 15µg/mL, 7.5µg/mL, 3.75µg/mL, and 1.875µg/mL solutions, whose absorbance at 226 nm was measured using a UV spectrophotometer. The numbers obtained were treated with linear regression to generate a standard curve of benzoic acid concentration with the formula $y=0.0599x+0.0347$. To measure the released amount of benzoic acid, the dosage form was dissolved in degassed pH 8 $\text{Na}_2\text{HPO}_4$ solution at $37^\circ C \pm 0.5^\circ C$ and centrifuged at 100 rpm. 5 mL solution was collected from the solution at each time point to measure the concentration of benzoic acid with 5 mL dissolver added back to the solution. The collected solution was filtered through 0.45 µm membrane before transferred to an UV spectrophotometer for measuring the absorbance at 226 nm. The percentage of benzoic acid released was calculated using the following formula:

$$\text{Benzoic acid released (％)} = \frac{C_nV_n+\sum V_sC_{n-1}}{Q_{\text{benzoic acid}}} \times 100$$

Wherein

- $C_n$ means concentrate measured,
- $V_n$ means total solution volume,
- $\frac{1}{3}$ means sample volume,
- $Q_{\text{benzoic acid}}$ means amount of benzoic acid in the dosage form.

The release of PEG8000 is measured using the following method. To prepare a standard curve of PEG8000, 0.1275 g PEG8000 standard sample was dissolved in water in a 25 mL volumetric flask. Transferring 1 mL, 2 mL, 5 mL and 10 mL to 10 mL volumetric flask, respectively, and diluted in water to prepare the control solution. Injecting 50 ul control solutions to a liquid chromatography (three Waters Ultrahydrogelf™ 120/250/500 connected in series, flow speed at 0.5ml/min, temperature at 40°C, measured by a differential refraction detector). The areas of the volume were measured and used as y-axis. The log numbers of the control solution concentration were used as x-axis. A standard curve of PEG8000 was generated with the formula of $y=1.024x+8.918$. The percentage of PEG800 released was calculated using the following formula:

$$\text{PEG8000 released (％)} = \frac{C_nV_n+V_s\sum C_{n-1}}{Q_{\text{PEG8000}}} \times 100$$

wherein $C_n$ means concentration measured,
\[ V_i \] means volume of solution, \( \frac{1}{4} \) means sample volume,

[00137] \( Q_{\text{PEG8000}} \) means amount of PEG8000 in the dosage form

[00138] Results: as illustrated in FIG. 18C, the release profile of the benzoic acid matches a model profile according to D. Brooke and R. J. Washkuhn (Zero-Order Drug Delivery System: Theory and Preliminary Testing, J Pharm Sci., 1977, 66: 159-162) and was controlled by the interface. Therefore, a controlled release profile can be designed according to the dosage forms disclosed herein.

EXAMPLE 2

[00139] This example illustrates a design of dosage form that controls release of drug contents from different compartments.

[00140] Dosage design: two dosage forms were produced using fused deposition modeling methods. The substrate of the dosage forms was made of Copovidone (Kollidon® VA64) 72%, PEG1500 18% and Soluplus® 10%. The drug content was consisted of Moxifloxacin Hydrochloride 30%, PEG1000 70%. The schematic of the dosage forms are illustrated in FIG. 19A and 19B. Referring to FIG. 19A and 19B, the dosage form 1600 contained a substrate 1601 that forms two compartments 1602 and 1603. The compartments were enclosed by a wall 1604 and 1605, respectively. For the first dosage form, the two compartments were enclosed by walls having a thickness of 0.75mm and 1.5mm, respectively. For the second dosage form, the two compartments were enclosed by walls having a thickness of 0.75mm and 2.25mm, respectively.

[00141] To detect the release of the drug content, the dosage form was added to 900 ml phosphate buffer of pH6.8 at 100 rpm. The UV absorption of the buffer was assayed to determine the release of the drug content.

[00142] The results of the release assays were illustrated in FIG. 19C and 19D. As shown in FIG. 19C, when the first dosage form was added to the buffer for 20 min, the first compartment was open, and the drug content in the first compartment was released. The second compartment was not open till 40 min after the dosage form was added to the buffer. For the second dosage form, whose results were illustrated in FIG. 19D, the second compartment was not open till 60 min after the dosage form was added to the buffer. Therefore, the release profile of the dosage form can be controlled through the thickness of the wall that encloses a compartment.
While the principles of this invention have been described in connection with specific embodiments, it should be understood clearly that these descriptions are made only by way of example and are not intended to limit the scope of the invention. What has been disclosed herein has been provided for the purposes of illustration and description. It is not intended to be exhaustive or to limit what is disclosed to the precise forms described. Many modifications and variations will be apparent to the practitioner skilled in the art. What is disclosed was chosen and described in order to best explain the principles and practical application of the disclosed embodiments of the art described, thereby enabling others skilled in the art to understand the various embodiments and various modifications that are suited to the particular use contemplated. It is intended that the scope of what is disclosed be defined by the following claims and their equivalence.
<table>
<thead>
<tr>
<th>Water Solubility</th>
<th>25 w/w%</th>
<th>40 w/w% (freely soluble)</th>
<th>poorly soluble</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Structure</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Amphiphilic</td>
<td>n/a</td>
</tr>
<tr>
<td>Commercial Name</td>
<td>Soluplus</td>
<td>Soluplus + 10% Plasticizer</td>
<td>Kolliphor P 188</td>
</tr>
<tr>
<td>Vendor</td>
<td>BASF SE, Germany</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymer</td>
<td>Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Description</td>
<td>Supplier Information</td>
<td>Solubility</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone-co-vinyl-acetate (PVP-VA)</td>
<td>International Specialty Products Inc., Manchester, UK</td>
<td>Soluplus+ 10% Plasticizer PEG 1500</td>
<td>soluble</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVP/VA</td>
<td>40 w/w% (freely soluble)</td>
</tr>
<tr>
<td></td>
<td>International Specialty Products Inc., Wayne, NJ, USA</td>
<td>Plasdone S-630</td>
<td>40 w/w% (freely soluble)</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone--polyvinyl acetate copolymer (PVP-VA 60/40)</td>
<td>BASF SE, Germany</td>
<td>Kollidon VA 64</td>
<td>40 w/w% (freely soluble)</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone--polyvinyl acetate copolymer (PVP-VA 60/40)</td>
<td>BASF SE, Germany</td>
<td>Kollidon VA 64+ 10% Plasticizer Kolliphor P 188</td>
<td>40 w/w% (freely soluble)</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone--polyvinyl acetate copolymer (PVP-VA 60/40)</td>
<td>BASF SE, Germany</td>
<td>Kollidon VA 64+ 10% Plasticizer Kolliphor RH40</td>
<td>poorly soluble</td>
</tr>
<tr>
<td>Material</td>
<td>Solubility</td>
<td>Solubility</td>
<td>Solubility</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Kollidon VA 64+ 10% Plasticizer PEG 1500</td>
<td>soluble</td>
<td>soluble</td>
<td>soluble</td>
</tr>
<tr>
<td>BASF SE, Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Specialty Products Inc., Wayne, NJ, USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymethylacrylate-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polyvinyl acetate copolymer (PV-VA 60/40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymethylacrylate-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polyvinyl sebacate (PVP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVP K25+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasticizer dibutylyl sebacate (DBS)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure](image)
<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>Kollidon 12 PF</th>
<th>Kollidon 12 PF</th>
<th>Kolliphor P 188</th>
<th>Kolliphor RH40</th>
<th>Kolliphor P 188</th>
<th>Kolliphor P 188</th>
<th>Kollidon 17 PF</th>
<th>Kollidon 17 PF</th>
<th>Kolliphor RH40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triethyl citrate (TEC)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
<td>PVP</td>
</tr>
<tr>
<td>PVP</td>
<td>Kollidon 17 PF+ 10% Plasticizer PEG 1500</td>
<td>poorly soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray formulated mixture of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) 80/20</td>
<td>BASF SE, Germany</td>
<td>Kollidon SR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (Because PVAc is lipophilic and water insoluble?)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray formulated mixture of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) 80/20</td>
<td>BASF SE, Germany</td>
<td>Kollidon SR+ 10% Plasticizer Kolliphor P 188</td>
<td>40 w/w% (freely soluble)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray formulated mixture of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) 80/20</td>
<td>BASF SE, Germany</td>
<td></td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kollidon SR+ 10% Plasticizer Kolliphor RH40</td>
<td>poorly soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray formulated mixture of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) 80/20</td>
<td>BASF SE, Germany</td>
<td>Kollidon SR+ 10% Plasticizer PEG 1500</td>
<td>soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Description</td>
<td>Supplier</td>
<td>Composition</td>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol-polyvinyl alcohol graft copolymer 25/75</td>
<td>BASF SE, Germany</td>
<td>Kollicoat IR</td>
<td>40 w/w%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(freely soluble)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol-polyvinyl alcohol graft copolymer 25/75</td>
<td>BASF SE, Germany</td>
<td>Kollicoat IR+ 10% Plasticizer PEG 1500</td>
<td>soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollicoat IR-polyvinyl alcohol 60/40</td>
<td>BASF SE, Germany</td>
<td>Kollicoat Protect</td>
<td>25 w/w%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollicoat IR-polyvinyl alcohol 60/40</td>
<td>BASF SE, Germany</td>
<td>Kollicoat Protect+ 10% Plasticizer PEG 1500</td>
<td>soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvinyl Alcohol (PVA or PV-OH)</td>
<td>DuPont Company, Wilmington, Delaware USA</td>
<td>Elvanol®</td>
<td>soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Supplier</td>
<td>Formula</td>
<td>Solubility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl cellulose (HPC)</td>
<td>Ashland Aqualon Functional Ingredients, Wilmington, DE, USA</td>
<td>$R = \text{H or CH}_2\text{CH(OH)CH}_2$</td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl cellulose (EC)</td>
<td>Dow Chemical, Midland, MI, US</td>
<td>Ethocel*</td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethylene oxide) (PEO)</td>
<td>Sigma-Aldrich Ltd, Poole, Dorset, UK</td>
<td>Polyox* WSR</td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethylene glycol) (PEG)</td>
<td>Dow Chemical, Midland, MI, US</td>
<td>Carbowax*</td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Company</td>
<td>Product</td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>-----------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbranched Polyesteramide</td>
<td>Polymer Factory, Stockholm, Sweden</td>
<td>Hybrane S1200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose or Hypromellose (HMPC)</td>
<td>Dow Chemical, Midland, MI, US</td>
<td>Methocel® E4M, K4M, K15M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose or Hypromellose (HMPC)</td>
<td>Colorcon Inc., Shanghai, China</td>
<td>HPMC (2910 grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose or Hypermellose (HMPC)</td>
<td>Syntapharm GmbH, Mülheim-Ruhr, Germany</td>
<td>Pharmacoat® 603 and 615</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------</td>
<td>-----------------------------</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose or Hypermellose (HMPC)</td>
<td>Shin-Etsu Co., Ltd., Niigata, Japan</td>
<td>Pharmacoat® 603 (2910 grade)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbomer</td>
<td>Lubrizol Advanced Materials Inc., Cleveland, OH, US</td>
<td>Carbopol® 974P+ Eudragit L-100-55</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>Anhydride DT NF</td>
<td>soluble</td>
<td>Avicel® PH 101</td>
<td>soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>---------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quest International, Hoffman Estates, IL USA</td>
<td>FMC, Philadelphia, PA, USA</td>
<td>Penwest Pharmaceuticals, Patterson, NY</td>
<td>Emcompress®</td>
<td>CP Kelco U.S. Inc., Chicago, IL USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>Microcrystalline cellulose (MCC)</td>
<td>Dibasic calcium phosphate</td>
<td>Xanthan gum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Company</td>
<td>Eudragit + Plasticizer/PEG</td>
<td>Notes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1</td>
<td>Evonik Rhein Chemie GmbH, Darmstadt, Germany</td>
<td>Eudragit® 4135F + Plasticizer PEG8000</td>
<td>soluble at pH &gt; 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® 4155F (freeze dried)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EUDRAGIT® FS 30 D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methylmethacrylate) 1:2</td>
<td>Evonik Industries, Piscataway, New Jersey, USA</td>
<td>Eudragit® S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methylmethacrylate) 1:2</td>
<td>Evonik Industries, Piscataway, New Jersey, USA</td>
<td>Eudragit® S + Plasticizer Triethyl citrate (TEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methylmethacrylate) 1:2</td>
<td>Evonik Industries, Piscataway, New Jersey, USA</td>
<td>Eudragit® S + Plasticizer PEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Company/Location</td>
<td>Eudragit/Plasticizer/Paraben</td>
<td>Solubility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------</td>
<td>------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methylmethacrylate) 1:2</td>
<td>Evonik Industries, Piscataway, New Jersey, USA</td>
<td>Eudragit® S + Plasticizer methylparaben</td>
<td>soluble at pH &gt;7 [36]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-ethyl acrylate) 1:1</td>
<td>Evonik Degussa, Piscataway, NJ</td>
<td>Eudragit L-100-55</td>
<td>Soluble at pH &gt;5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methyl methacrylate) 1:1</td>
<td>Evonik Degussa, Piscataway, NJ</td>
<td>Eudragit L-100</td>
<td>Soluble at pH &gt;6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate or Hypromellose phthalate</td>
<td>Shin-Etsu Co., Ltd., Niigata, Japan</td>
<td>HP-55F</td>
<td>Soluble at pH &gt;5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Acetate Succinate or Hypromellose</td>
<td>Shin-Etsu Co., Ltd., Niigata, Japan</td>
<td>Shin-Etsu Aqoat</td>
<td>MF</td>
<td>Soluble at pH &gt; 6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetate Succinate (HPMCAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Acetate Succinate or Hypromellose</td>
<td>Shin-Etsu Co., Ltd., Niigata, Japan</td>
<td>Shin-Etsu Aqoat</td>
<td>LF</td>
<td>Soluble at pH &gt; 5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetate Succinate (HPMCAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(dimethylaminoethylmethacrylate-co-methacrylic esters)</td>
<td>Rohm GmbH &amp; Co., Darmstadt, Germany</td>
<td>Eudragit E</td>
<td></td>
<td>Soluble at pH &lt; 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Acetate Succinate or Hypromellose</td>
<td>Shin-Etsu Co., Ltd., Niigata, Japan</td>
<td>Shin-Etsu Aqoat</td>
<td>MF</td>
<td>Soluble at pH &gt; 6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image1.png" alt="Polymer Structure" /></td>
<td><img src="image2.png" alt="Polymer Structure" /></td>
<td><img src="image3.png" alt="Polymer Structure" /></td>
<td><img src="image4.png" alt="Polymer Structure" /></td>
<td><img src="image5.png" alt="Polymer Structure" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLGA</td>
<td>Evnax® 40W: EV28</td>
<td>Evnax® 40W: EV9</td>
<td>Evratane®</td>
<td>PE1400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birmingham Polymers, Inc., Birmingham, AL, USA</td>
<td></td>
<td></td>
<td>Scientific Polymer Products Inc., Ontario, NY</td>
<td>Polyethylene (PE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Supplier/Details</td>
<td>Compound Structure</td>
<td>Solubility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>--------------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycaprolactone (PCL)</td>
<td>Scientific Polymer Products Inc., Ontario, NY</td>
<td><img src="image" alt="Compound Structure" /></td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnauba Wax</td>
<td>Noda Wax Co., Japan</td>
<td><img src="image" alt="n/a" /></td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyceryl Palmitostearate</td>
<td>Gattemosse, Cedex, France</td>
<td>Precirol® ATO 5</td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogenated Castor &amp; Soybean Oil</td>
<td>Abitec Corporation, Janesville WI, USA</td>
<td>Sterotex® K</td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose acetate butyrate (CAB)</td>
<td>Eastman Chemical Company, Kingsport, Tennessee, USA</td>
<td>CAB 381-0.5</td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB</td>
<td>FMC, Newark, DE, USA</td>
<td>CAB 500-1</td>
<td>Insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Supplier/Information</td>
<td>Adhesive Type</td>
<td>Solubility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(vinyl acetate) (PVAc)</td>
<td>Scientific Polymer Products Inc., Ontario, NY</td>
<td>Sentry® plus</td>
<td>insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride)</td>
<td>Rohm GmbH &amp; Co., Darmstadt, Germany</td>
<td>Eudragit RS PO (1:2:0.1)</td>
<td>insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride)</td>
<td>Rohm GmbH &amp; Co., Darmstadt, Germany</td>
<td>Eudragit RL PO (1:2:0.2)</td>
<td>insoluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polybutyl methacrylate-co-</td>
<td>Evonik Industries, Essen, Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-dimethylaminomethyl methacrylate) 1:2:1</td>
<td>Evonik Industries, Piscataway, New Jersey, USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EUROMAT®® PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WHAT IS CLAIMED IS:

1. A dosage form comprising:
   a substrate that forms a compartment; and
   a drug content loaded into the compartment.

2. The dosage form of claim 1, wherein the drug content is operably linked to the substrate.

3. The dosage form of claim 1, wherein the drug content is detached from the substrate.

4. The dosage form of claim 1, wherein the substrate is made from at least one thermoplastic material.

5. The dosage form of claim 4, wherein 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.

6. The dosage form of claim 4, wherein the thermoplastic material is selected from the group consisting of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, 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), poly(vinyl 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-methylnethacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic 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 (HMPC), hydroxypropyl
methylcellulose acetate succinate or hypromellose acetate succinate (HPMCAS),
poly(lactide-co-glycolide) (PLGA), carberomer, 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), Poloxamer, 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.

7. The dosage form of claim 1, wherein the compartment has a shape selected from the group consisting of a pie shape, a cone shape, a pyramid shape, a cylindrical shape, a cubic or cuboidal shape, a triangular or polygonal prism shape, a tetrahedron and a combination thereof.

8. The dosage form of claim 1, wherein the drug content is in a form of nanoparticles.

9. The dosage form of claim 1, wherein the drug content in a form of microneedles.

10. The dosage form of claim 1, wherein the drug content forms a network structure or porous structure.

11. The dosage form of claim 1, wherein the drug content comprises an active pharmaceutical ingredient (API).

12. The dosage form of claim 11, wherein the API is selected from the groups consisting of local anesthetics, pain management drugs, sleeping disorder drugs, antiepileptic drugs and anticonvulsants, anti-Alzheimer’s disease drugs, analgesics, antipodagric, anti-hypertensive drugs, antiarrhythmic drugs, diuretic drugs, drugs for treating liver diseases, drugs for treating pancreatic diseases, drugs for treating GI diseases, drugs for treating CNS diseases, antihistamine drugs, anti-allergic drugs, glucocorticoid drugs, hormone drugs and contraceptive drugs, hypoglycemic drugs, anti-osteoporosis drugs, antibiotics, sulfonamides, quinolones, and other synthetic antibacterial drugs, antituberculous drugs, antiviral drugs, anti-neoplasm drugs, immunomodulators, veterinary drugs, cosmetically active agents, traditional Chinese medicine and extract of traditional Chinese medicine.
13. The dosage form of claim 11, wherein the drug content comprises a medium which has a higher erode/dissolution rate than the API.

14. The dosage form of claim 11, wherein the drug content further comprises at least one excipient.

15. The dosage form of claim 14, wherein the excipient is made from a water-soluble material selected from the group consisting of cocoa butter, polyethylene glycol (PEG), sucrose, glucose, galactose, fructose, xyloselactose, maltose, trehalose, sorbitol, mannitol, maltodextrins, raffinose, stachyose, fructo-oligosaccharides and a combination thereof.

16. The dosage form of claim 1, wherein the compartment has an aperture which is blocked by a plug.

17. The dosage form of claim 16, wherein the plug is made from a material selected from the group consisting of a water-soluble polymer, an erodible or dissolvable polymer, a wax-like material, saccharides or a combination thereof.

18. The dosage form of claim 1, further comprising a gas-generating component loaded into the compartment.

19. The dosage form of claim 17, wherein the gas-generating component is selected from the group consisting of water soluble carbonates, sulphites, bicarbonates, sodium carbonate, sodium bicarbonate, sodium metabisulphite, calcium carbonate, and combinations thereof, which on contact with gastric intestinal fluid releases carbon dioxide or sulphur dioxide gas.

20. A dosage form comprising:

   a substrate that forms at least a first compartment and a second compartment; and
   a first drug content loaded into the first compartment and a second drug content loaded into the second compartment.
21. The dosage form of claim 20, wherein the first compartment and the second compartment are connected.

22. The dosage form of claim 20, wherein the first compartment and the second compartment are disconnected.

23. The dosage form of claim 20, wherein the first drug content is the same as the second drug content.

24. The dosage form of claim 20, wherein the first drug content is different from the second drug content.

25. The dosage form of claim 20, wherein the first compartment has a first aperture which is covered by a first plug, and the second compartment has a second aperture which is covered by a second plug.

26. The dosage form of claim 25, wherein the first plug is longer than the second plug.

27. The dosage form of claim 25, wherein the first plug has a first permeation rate and the second plug has a second permeability rate.

28. The dosage form of claim 27, wherein the first permeation rate is the same as the second permeation rate.

29. The dosage form of claim 27, wherein the first permeation rate is larger than the second permeation rate.

30. The dosage form of claim 25, wherein the first plug has a first erosion/dissolution rate and the second plug has a second erosion/dissolution rate.

31. The dosage form of claim 30, wherein the first erosion/dissolution rate is the same as the second erosion/dissolution rate.
32. The dosage form of claim 30, wherein the first erosion/dissolution rate is larger than the second erosion/dissolution rate.

33. The dosage form of claim 20, wherein the first compartment is enclosed by a first wall, and the second compartment is enclosed by a second wall.

34. The dosage form of claim 33, wherein the first wall is thicker than the second wall.

35. The dosage form of claim 33, wherein the first wall is more permeable than the second wall.

36. The dosage form of claim 33, wherein the first wall erodes/dissolves faster than the second wall.

37. A dosage form comprising:
   two or more matrix layers stacked together, wherein at least one of the two or more matrix layers is loaded with at least one drug content, respectively.

38. The dosage form of claim 37, wherein the two or more matrix layers are detachable from each other.

39. The dosage form of claim 37, wherein the two or more matrix layers are made from at least one thermoplastic material.

40. The dosage form of claim 39, wherein the at least one 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.

41. The dosage form of claim 39, wherein the at least one thermoplastic material is selected from but not limited to the group consisting of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, 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-OD), 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(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic 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 (HMPC), hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate (HPMCAS), poly(lactide-co-glycolide) (PLGA), carbomer, 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), Poloxamer, Hydrogenated Castor & Soybean Oil, Glycerol 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.

42. The dosage form of claim 37, wherein the drug content is in a form of nanoparticles.

43. The dosage form of claim 37, wherein the drug content in a form of microneedles.

44. The dosage form of claim 37, wherein the drug content forms a network structure or porous structure.

45. The dosage form of claim 37, wherein the drug content comprises an active pharmaceutical ingredient (API).

46. The dosage form of claim 45, wherein the API is selected from the groups consisting of local anesthetics, pain management drugs, sleeping disorder drugs, antiepileptic drugs and anticonvulsants, anti-Alzheimer's disease drugs, analgesics, anti-podagric, anti-hypertensive drugs, anti-arrhythmic drugs, diuretic drugs, drugs for treating liver diseases, drugs for treating pancreatic diseases, drugs for treating GI diseases, drugs for treating CNS diseases,
antihistamine drugs, anti-allergic drugs, glucocorticoid drugs, hormone drugs and contraceptive drugs, hypoglycemic drugs, anti-osteoporosis drugs, antibiotics, sulfonamides, quinolones, and other synthetic antibacterial drugs, antituberculous drugs, antiviral drugs, anti-neoplasm drugs, immunomodulators, veterinary drugs, cosmetically active agents, traditional Chinese medicine and extract of traditional Chinese medicine.

47. The dosage form of claim 37, wherein each matrix layer further comprises at least one excipient.

48. The dosage form of claim 47, wherein the excipient is made from a water-soluble material selected from the group consisting of cocoa butter, polyethylene glycol (PEG), sucrose, glucose, galactose, fructose, xyloselactose, maltose, trehalose, sorbitol, mannitol, maltodextrins, raffinose, stachyose, fructo-oligosaccharides and a combination thereof.

49. The dosage form of claim 37, wherein the two or more matrix layers have different thickness.

50. The dosage form of claim 37, wherein the two or more matrix layers have different erosion/dissolution rates.

51. The dosage form of claim 37, wherein the two or more matrix layers are configured that the loaded each of the at least one drug content is released in an aqueous solution based on a predetermine release profile.

52. The dosage form of claim 37, wherein the two or more matrix layers comprise a first matrix layer loaded with a first drug content and a second matrix layer loaded with a second drug content and positioned outer than the first matrix layer, such that the second drug content is released prior to the first drug content.
FIG. 11

- Physician
- Computer
- Patient
- 3D Printer

Prescription with specific dose and drug combination

Clinical testing results: clearance, metabolism, body weight etc.

Pharmacokinetic model
FIG. 12A

FIG. 12B
FIG. 18A

FIG. 18B

Benzoic acid release percentage measured by UV-Vis

PEG8000 release percentage measured by Gel Permeation Chromatography

FIG. 18C
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   A61K 9/24(2006.01)i; A61K 9/20(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
   A61K9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data database consulted during the international search (name of database and, where practicable, search terms used)
   CNPAT, WPI, EPDOC, USTXT, CNKI, GOOGLE, TRIASTEK, three dimensional printing, 3DP, compartment, chamber, region, polymer, controlled release, sustained release, prolonged release, shape, aperture, hole, passageway, plug, layer, gas-generating, microneedle, erosion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2004005360 A1 (THERICS, INC.) 08 January 2004 (2004-01-08) paragraphs [0013], [0026], [0039], [0040], [0053], [0054], [0057], [0060] Figures 2, 5</td>
<td>1-36</td>
</tr>
<tr>
<td>X</td>
<td>US 2008220061 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 11 September 2008 (2008-09-11) claims 1-17, paragraph [0064], Figure 3</td>
<td>1-52</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search

| 15 August 2016 |

Date of mailing of the international search report

| 29 August 2016 |

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China

Facsimile No. (86-10)62019451

Authorized officer

YU Li

Telephone No. (86-10)62413692

Form PCT/ISA/210 (second sheet) (July 2009)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date (day/month/year)</th>
<th>Patent family member(s)</th>
<th>Publication date (day/month/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WO 03092633 A3</td>
<td>08 April 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60323482 D1</td>
<td>23 October 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03092633 A2</td>
<td>13 November 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5041663 B2</td>
<td>03 October 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 8088415 B2</td>
<td>03 January 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 8465777 B2</td>
<td>18 June 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005524702 A</td>
<td>18 August 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1503741 B1</td>
<td>10 September 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2483028 C</td>
<td>05 April 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2003232078 A1</td>
<td>17 November 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2316791 T3</td>
<td>16 April 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012177696 A1</td>
<td>12 July 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010053152 A</td>
<td>11 March 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03041690 A2</td>
<td>22 May 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03041690 A3</td>
<td>28 August 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1439824 A2</td>
<td>28 July 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004091516 A1</td>
<td>13 May 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003099708 A1</td>
<td>29 May 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2002228629 A1</td>
<td>26 May 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005509001 A</td>
<td>07 April 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002018816 A1</td>
<td>14 February 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1014950 A1</td>
<td>05 July 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1014950 B1</td>
<td>30 October 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9836739 A1</td>
<td>27 August 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2001515472 A</td>
<td>18 September 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 5783401 A</td>
<td>11 October 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 733676 B2</td>
<td>24 May 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 6177198 A</td>
<td>09 September 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 762258 B2</td>
<td>19 June 2003</td>
</tr>
<tr>
<td>US 2011187015 A1</td>
<td>04 August 2011</td>
<td>CA 2464478 C</td>
<td>20 March 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60210650 D1</td>
<td>24 May 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 7931914 B2</td>
<td>26 April 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010227590 A</td>
<td>14 October 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4845340 B2</td>
<td>28 December 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03037607 A1</td>
<td>08 May 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60210650 T2</td>
<td>25 January 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1439945 A1</td>
<td>28 July 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 8758658 B2</td>
<td>24 June 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005507723 A</td>
<td>24 March 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2262851 T3</td>
<td>01 December 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003143268 A1</td>
<td>31 July 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1439945 B1</td>
<td>12 April 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2763676 A1</td>
<td>08 May 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2763676 C</td>
<td>27 January 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2002342221 A1</td>
<td>12 May 2003</td>
</tr>
</tbody>
</table>