

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
22 May 2008 (22.05.2008)

PCT

(10) International Publication Number  
WO 2008/060963 A2(51) International Patent Classification:  
A61K 9/24 (2006.01) A61K 31/00 (2006.01)(74) Agent: HART, Daniel; Knobbe Martens Olson & Bear  
Llp, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US)(21) International Application Number:  
PCT/US2007/084177(22) International Filing Date:  
8 November 2007 (08.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/865,157 9 November 2006 (09.11.2006) US(71) Applicant (for all designated States except US): OREX-  
IGEN THERAPEUTICS, INC. [US/US]; 12481 High  
Bluff Drive, Suite 160, San Diego, CA 92130 (US).

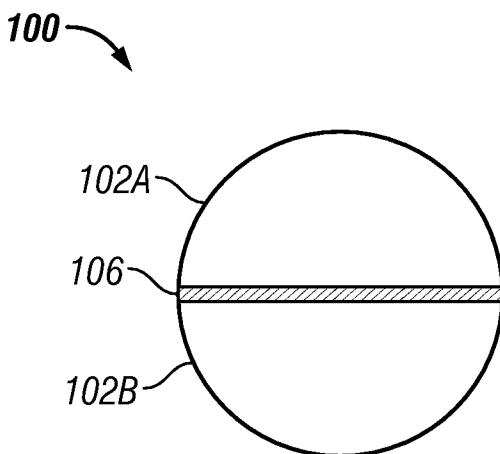
(72) Inventors; and

(75) Inventors/Applicants (for US only): MCKINNEY, An-  
thony, A. [US/US]; 5457 Harvest Run Drive, San Diego,  
CA 92130 (US). TOLLEFSON, Gary [US/US]; 9052 Di-  
amond Pointe Drive, Indianapolis, IN 46236 (US). WE-  
BER, Eckard [US/US]; 4040 Miller Street, San Diego, CA  
92103 (US). SOLTERO, Rick [US/US]; 5509 Solomon  
Seal Court, Holly Springs, NC 27540 (US).(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,  
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,  
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,  
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,  
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,  
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,  
ZM, ZW.(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,  
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Published:

— without international search report and to be republished  
upon receipt of that report

(54) Title: LAYERED PHARMACEUTICAL FORMULATIONS



(57) Abstract: In one embodiment a layered pharmaceutical formulation includes two or more pharmaceutical layers and an intermediate layer disposed between at least two of the two or more pharmaceutical layers, the intermediate layer configured to dissolve in vivo to thereby leave the two or more pharmaceutical layers substantially intact. In one embodiment, an active pharmaceutical ingredient in at least one of the pharmaceutical layers is selected from bupropion, zonisamide, naltrexone, topiramate, phentermine, metformin, olanzapine and fluoxetine.

## LAYERED PHARMACEUTICAL FORMULATIONS

### BACKGROUND

**[0001]** The present application claims priority from U.S. Provisional Patent Application Serial No. 60/865,157, filed November 9, 2006, which is hereby incorporated by reference in its entirety.

#### Field of the Invention

**[0002]** This invention relates to pharmaceutical formulations having two or more pharmaceutical layers interspersed with one or more intermediate layers, wherein the pharmaceutical layers include, but are not limited to, pharmaceutical compositions useful for affecting weight loss, suppressing appetite and/or treating obesity-related conditions in individuals.

#### Description of the Related Art

**[0003]** Certain types of layered tablets are known in pharmaceutical applications. Some pharmaceutical applications separate potentially interacting layers from one another within a tablet. For example, U.S. Patent No. 6,576,256 discloses separating potentially interacting compounds from each other using separate flat layers of a tablet, concentric layers, coated beads or granules, and/or using buffers. Thombre, A. G., L. E. Appel, et al. (2004), “Osmotic drug delivery using swellable-core technology” J. Control Release 94(1): 75-89 discloses a core tablet containing a drug and a water-swellable component, and one or more delivery ports in different core configurations including a tablet-in-tablet (TNT) bilayer and trilayer formation. U.S. Patent No. 6,706,283 discloses an osmotic delivery device fabricated in a bilayer geometry, wherein the core comprises a sweller layer “sandwiched” between two drug layers. The coating of a bilayer tablet may include a water permeable membrane, but is substantially impermeable to the drug and/or the excipients contained therein. U.S. Patent No. 6,630,165 discloses dosage forms and methods for providing sustained release reboxetine including a trilayered compressed core with a first component drug layer, a second component push layer and a third component barrier layer separating the drug layer from the push layer.

The barrier layer is inert with the respect to the composition of the drug layer and substantially impermeable, such that the drug and the components of the push layer are prevented from mixing.

**[0004]** Among multiple layer tablet forms, one type includes a first layer to provide immediate release of a drug and a second layer to provide controlled-release of the drug. U.S. Patent No. 6,514,531 discloses coated trilayer immediate/prolonged release tablets comprising zolpidem hemitartrate. U.S. Patent No. 6,087,386 discloses a trilayer tablet with an enalapril layer, a losartan potassium layer and a second enalapril maleate layer or an excipient layer. U.S. Patent No. 5,213,807 discloses an oral trilayer tablet with a core comprising a nonsteroidal anti-inflammatory drug (NSAID), ibuprofen and ibuprofen salts and an intermediate coating comprising a substantially impervious/impermeable material to the passage of ibuprofen. U.S. Patent No. 6,926,907 discloses a trilayer tablet that separates famotidine contained in a film coat from a core comprising controlled-release naproxen formulated using excipients which control the drug release. The film coat is an enteric coating configured to delay the release of naproxen until the dosage form reaches an environment where the pH is above four.

## SUMMARY

**[0005]** An embodiment provides a layered pharmaceutical formulation comprising two or more pharmaceutical layers and an intermediate layer disposed between at least two of the two or more pharmaceutical layers. In some embodiments the intermediate layer is configured to dissolve *in vivo* to thereby leave the two or more pharmaceutical layers substantially intact, but physically separated, essentially forming two distinct pills. In some embodiments the dissolution rate of one of the separated two or more pharmaceutical layers is substantially similar to that of a singly compressed tablet comprising the same pharmaceutical composition as that of the pharmaceutical layer.

**[0006]** Use of a first compound and a second compound in the preparation of a medicament for affecting weight loss, suppressing appetite and/or treating an obesity-related condition, wherein the medicament comprises layered pharmaceutical formulations of the present invention.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Other aspects of the disclosure will be readily apparent from the description below and the appended drawings, in which like reference numerals refer to similar parts throughout, which are meant to illustrate and not to limit the disclosure, and in which:

[0008] Figure 1A illustrates an embodiment of a layered pharmaceutical formulation.

[0009] Figures 1B & 1C illustrate the layered pharmaceutical formulation of Figure 1A in progressive stages as an intermediate layer dissolves.

[0010] Figure 2A illustrates a second embodiment of a layered pharmaceutical formulation.

[0011] Figure 2B illustrates the second embodiment of Figure 2A after an intermediate layer dissolves.

[0012] Figure 3 illustrates a third embodiment of a layered pharmaceutical formulation.

[0013] Figure 4 illustrates a fourth embodiment of a layered pharmaceutical formulation.

[0014] Figure 5 illustrates a fifth embodiment of a layered pharmaceutical formulation with multiple intermediate layers.

[0015] Figure 6 illustrates a sixth embodiment of a layered pharmaceutical formulation with lenticular shaped layers.

[0016] Figure 7 illustrates a seventh embodiment of a layered pharmaceutical formulation.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0017] Embodiments of the present disclosure provide significant improvements to multilayer tablet technology. In an embodiment, a layered pharmaceutical formulation comprises two or more pharmaceutical layers and at least one intermediate layer disposed between at least two of the two or more pharmaceutical layers. The at least one intermediate layer is configured to dissolve *in vivo* to thereby leave the two or more pharmaceutical layers

substantially intact. In some embodiments the dissolution rate of one or more of a separated pharmaceutical layer is substantially similar to that of a singly compressed tablet comprising the same pharmaceutical composition as that of the pharmaceutical layer. The separated pharmaceutical layer thus has an independent and predictable dissolution profile.

**[0018]** A dissolution profile for a drug comprises the known dissolution rate and particular dissolution characteristics of the drug. A predictable dissolution profile for a specific drug allows for more accurate treatment of a given symptom. Predictable dissolution profiles for different drugs within a multilayer tablet allow for coordinated treatment of multiple symptoms with a single pharmaceutical formulation.

**[0019]** In general, multilayer pharmaceutical formulations present challenges in maintaining predictable dissolution profiles. For example, *in vivo* conditions often disrupt an otherwise predictable multilayer pharmaceutical formulation dissolution profile. A multilayer tablet may be manufactured with drugs of known dissolution profiles. Once the multilayer tablet is ingested by a patient, however, there is no guarantee that each drug will dissolve as predicted by its individual dissolution profile. Drug configuration within a tablet, tablet shape, excipients or fillers in the tablet, tablet coatings and *in vivo* conditions may all affect the dissolution profiles. Additionally, interaction between different drugs within a multilayer tablet may cause a change in dissolution profile for one or more compositions within the multilayer tablet.

**[0020]** Further, in one possible *in vivo* condition, if the multilayer tablet becomes attached to the lining of the stomach, only a portion of the tablet would be exposed to the stomach fluids. The dissolution of the exposed portion of the tablet may occur at a more predictable rate while the unexposed portion of the multilayer tablet shielded from the stomach fluids would have a longer dissolution profile than would otherwise be expected from a singly compressed tablet of an identical composition. As mentioned above, having a multilayer tablet is desirable for ease of administration of multiple pharmaceutical compositions within a single tablet. Thus, it is desirable to configure a multilayer pharmaceutical formulation such that each pharmaceutical layer has a predictable dissolution profile.

**[0021]** Herein disclosed is a pharmaceutical formulation comprising two or more pharmaceutical layers and at least one intermediate layer configured to dissolve *in vivo* to thereby leave the two or more pharmaceutical layers substantially intact. In preferred embodiments the dissolution rate of one or more of the separated pharmaceutical layers is substantially similar to that of a singly compressed tablet comprising the same pharmaceutical composition as that of the pharmaceutical layer. In some embodiments, the pharmaceutical layer comprises a single pharmaceutically active compound or drug. In other embodiments the pharmaceutical layer comprises a pharmaceutical composition. The term “pharmaceutical composition” refers to a mixture of a chemical compound or compounds (e.g., a drug or drugs) with additional pharmaceutical components, such as diluents or carriers. Herein, the term “drug” is synonymous with the term “pharmaceutically active ingredient.” The pharmaceutical composition facilitates administration of the drug to an organism. Pharmaceutical compositions can also be obtained in the form of pharmaceutically acceptable salts by reacting drug compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

**[0022]** In some embodiments the two or more pharmaceutical layers comprise one or more immediate-release formulations. The term “immediate-release” is used herein to specify that the immediate release formulation is not configured to alter the dissolution profile of the pharmaceutical layer. For example, an immediate release pharmaceutical layer may be a pharmaceutical composition that does not contain ingredients included for the purpose of altering the dissolution profile. In some embodiments the two or more pharmaceutical layers comprise one or more controlled-release formulations. The term “controlled-release” is used herein in its ordinary sense and thus includes pharmaceutical compositions combined with ingredients to alter their dissolution profile. A “sustained-release” formulation is a type of controlled-release formulation, wherein ingredients have been added to a pharmaceutical composition such that the dissolution profile is extended over a longer period of time than that of an immediate release formulation comprising a similar pharmaceutical composition.

**[0023]** In some embodiments the at least one intermediate layer is a flat layer separating at least two pharmaceutical layers. In some embodiments the at least one

intermediate layer has exposed edges. Exposed edges allow for fluid to contact and dissolve the at least one intermediate layer. In some embodiments the pharmaceutical formulations comprises a coating covering the two or more pharmaceutical layers and the at least one intermediate layer. The coating is configured to dissolve *in vivo* more or less uniformly over the two or more pharmaceutical layers and the at least one intermediate layer such that the at least one intermediate layer is left exposed to the fluids that will dissolve the at least one intermediate layer *in vivo*.

**[0024]** In some embodiments the at least one intermediate layer is or comprises an impermeable membrane. In some embodiments the at least one intermediate layer has a substantially higher dissolution rate than at least one of the pharmaceutical layers. In some preferred embodiments the at least one intermediate layer dissolves in a nearly immediate fashion with respect to the dissolution of at least one of the pharmaceutical layers. In some embodiments the at least one intermediate layer comprises at least one of a monosaccharide or a disaccharide sugar, a starch (e.g., corn or potato starches), or any other suitable tablet ingredients known in the art. In some preferred embodiments the at least one intermediate layer comprises lactose. In some preferred embodiments, the intermediate layer dissolves in a nearly immediate fashion as compared to the dissolution rates of the respective pharmaceutical layers, e.g., such that upon dissolution of the intermediate layer, substantially all of the surface area of each of the two pharmaceutical layers is exposed. Thus, in one embodiment, under a standard dissolution test the immediate release layer is dissolved to the extent that at least two pharmaceutical layers present in the pharmaceutical formulation are separated in less than 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or 30 minutes.

**[0025]** Pharmaceutical formulations of drugs can be configured in various ways and in a variety of dosage forms to modify a dissolution rate of the drug. For example, one type of controlled-release pharmaceutical formulation is a sustained-release pharmaceutical formulation. Sustained-release pharmaceutical formulations can contain a variety of excipients, such as retardant excipients (also referred to as release modifiers) and/or fillers that are selected and incorporated into the formulation in such a way as to slow the dissolution rate of the formulation (and thereby slow the dissolution and/or release of the zonisamide) under in vivo conditions as compared to an otherwise comparable immediate-release formulation. Thus, a “comparable” immediate-release formulation is one that is substantially identical to the controlled-release formulation, except that that it is configured to provide immediate-release instead of controlled-release under substantially identical conditions.

**[0026]** The term “immediate-release” is used herein to specify a formulation that is not configured to alter the dissolution profile of the active ingredient (e.g., zonisamide, bupropion, naltrexone, olanzapine, phentermine, topiramate, metformin, fluoxetine). For example, an immediate-release pharmaceutical formulation may be a pharmaceutical formulation that does not contain ingredients that have been included for the purpose of altering the dissolution profile. An immediate-release formulation thus includes drug formulations that take less than 30 minutes for substantially complete dissolution of the drug in a standard dissolution test. A “standard dissolution test,” as that term is used herein, is a test conducted according to United States Pharmacopeia 24th edition (2000) (USP 24), pp. 1941-1943, using Apparatus 2 described therein at a spindle rotation speed of 100 rpm and a dissolution medium of water, at 37°C, or other test conditions substantially equivalent thereto. The term “controlled-release” is used herein in its ordinary sense and thus includes pharmaceutical formulations that are combined with ingredients to alter their dissolution profile. A “sustained-release” formulation is a type of controlled-release formulation, wherein ingredients have been added to a pharmaceutical formulation such that the dissolution profile of the active ingredient is extended over a longer period of time than that of an otherwise comparable immediate-release formulation. A controlled-release formulation thus includes drug formulations that take 30 minutes or longer for substantially complete dissolution of the

drug in a standard dissolution test, conditions which are representative of the *in vivo* release profile.

**[0027]** A pharmaceutical layer may be configured in various ways. For example, in some embodiments a layer comprises a flat portion of a pharmaceutical formulation. In some embodiments a layer comprises a rounded portion of a pharmaceutical formulation. In some embodiments a layer comprises a conical section of a pharmaceutical formulation. In some embodiments a layer comprises an elliptical section of a pharmaceutical formulation. In some embodiments a layer comprises a sideways section of a pharmaceutical formulation. In some embodiments a layer comprises a cubical section of a pharmaceutical formulation. In some embodiments a layer comprises a wedge of a pharmaceutical formulation. In some embodiments a layer comprises a substantial portion of a pharmaceutical formulation. A substantial portion is preferably at least about 25% of the pharmaceutical formulation and more preferably at least about 50% of the pharmaceutical formulation.

**[0028]** In some embodiments at least one pharmaceutical layer reacts when brought into contact with another of the pharmaceutical layers within the layered pharmaceutical formulation. In some embodiments at least one pharmaceutical layer does not react when brought into contact with another of the pharmaceutical layers.

**[0029]** In some embodiments an intermediate layer is configured to dissolve *in vivo*. Dissolving is the act of solvation wherein a solute is dissolved in a solvent to create a solution. Dissolving *in vivo* means that the dissolving takes place within an organism or within living tissue either taken from or part of an organism. An organism is any living animal, plant, bacteria or fungus. In preferred embodiments the organism is human.

**[0030]** In some embodiments a dissolving intermediate layer separates at least two of the pharmaceutical layers. In some embodiments the two pharmaceutical layers contain different pharmaceutical compositions. In some embodiments after the intermediate layer dissolves, the pharmaceutical layers are no longer held together within the pharmaceutical formulation. In some embodiments after the intermediate layer dissolves, the pharmaceutical layers remain substantially intact. A pharmaceutical layer remains substantially intact when it retains at least about 50% of its original mass in a single entity post-dissolution of the one or more intermediate layers. In preferred embodiments the pharmaceutical layer remains

substantially intact when it retains at least about 75% of its original mass post-dissolution of the one or more intermediate layers. In more preferred embodiments the pharmaceutical layer remains substantially intact when it retains at least about 85% of its original mass post-dissolution of the one or more intermediate layers. In some embodiments each pharmaceutical layer has a different dissolution rate. A dissolution rate is the solvation of a pharmaceutical layer volume per unit time. In some embodiments one or more pharmaceutical layers have similar dissolution rates. Preferably the one or more intermediate layers have a higher dissolution rate than the two or more pharmaceutical layers.

**[0031]** Figure 1A illustrates a preferred embodiment of a pharmaceutical formulation 100. The pharmaceutical formulation 100 comprises two pharmaceutical layers 102A and 102B. Pharmaceutical layer 102A comprises a pharmaceutical composition. In some embodiments of the pharmaceutical formulation 100, the pharmaceutical layer 102B comprises the same pharmaceutical composition as that of the pharmaceutical layer 102A. In the illustrated embodiment of pharmaceutical formulation 100, the pharmaceutical layer 102A comprises a different pharmaceutical composition than that of the pharmaceutical layer 102B. The pharmaceutical formulation 100 also comprises an intermediate layer 106. In the illustrated embodiment the intermediate layer 106 is configured to dissolve *in vivo*.

**[0032]** Each of the pharmaceutical layers 102A and 102B comprises one or more pharmaceutical compositions. As illustrated in the pharmaceutical formulation 100, the dosage amount of each pharmaceutical layer 102A and 102B is similar. The dosage strength of each pharmaceutical layer may also be similar. In other embodiments the dosage amount and/or strength of one pharmaceutical layer is much greater than that of another layer. This difference in dosage amount or strength allows for individualized treatment of symptoms that are addressed by increasing or decreasing a dosage of one or more pharmaceutical layers while maintaining a dosage of other layers. The amount or strength of dosage of a drug contained within a pharmaceutical formulation will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

**[0033]** The illustrated pharmaceutical formulation 100 includes, but is not limited to, drugs for affecting weight loss, suppressing appetite and/or treating an obesity-related

condition in a patient. Specifically, the illustrated pharmaceutical layer 102A comprises zonisamide and the pharmaceutical layer 102B comprises bupropion. The intermediate layer 106 comprises lactose or a suitable monosaccharide sugar, disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises naltrexone, one or more of the pharmaceutical layers comprises bupropion, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises naltrexone, one or more of the pharmaceutical layers comprises zonisamide, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises naltrexone, one or more of the pharmaceutical layers comprises fluoxetine, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises olanzapine, one or more of the pharmaceutical layers comprises zonisamide, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises metformin, one or more of the pharmaceutical layers comprises zonisamide, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch. In another embodiment, one or more of the pharmaceutical layers comprises phentermine, one or more of the pharmaceutical layers comprises topiramate, and at least one intermediate layer comprises a monosaccharide sugar, a disaccharide sugar or a starch.

**[0034]** In some embodiments the presence of one drug in a pharmaceutical formulation enhances the desired physiological effects and/or reduces undesired physiological effects of one or more other drugs in the pharmaceutical formulation. In some embodiments the presence of one or more drugs in a pharmaceutical formulation enhances the desired physiological effects of the drugs over the additive physiological effects of the one or more drugs in comparable, but separate pharmaceutical formulations when administered alone.

**[0035]** Figure 1B illustrates the pharmaceutical formulation 100 of Figure 1A as a fluid, as represented by the arrow 108, begins to dissolve the intermediate layer 106. In the illustrated embodiment, the fluid comprises at least one bodily fluid selected from saliva, sweat, chyme, mucus and bile. As the intermediate layer 106 dissolves the pharmaceutical

layers 102A and 102B begin to separate as shown. As noted above, in some embodiments each pharmaceutical layer comprises the same pharmaceutical composition. However, in the illustrated embodiment, the pharmaceutical layers 102A and 102B each comprise a different pharmaceutical composition. In some embodiments, one or more of the pharmaceutical layers comprises a controlled-release formulation. In some embodiments, one or more of the controlled-release formulations comprises a sustained-release formulation.

**[0036]** Figure 1C illustrates the layered pharmaceutical formulation 100 of Figure 1A after the intermediate layer 106 has completely dissolved. The pharmaceutical layers 102A and 102B have separated and remain substantially intact.

**[0037]** Figure 2A illustrates an embodiment of a second layered pharmaceutical formulation 200. The second pharmaceutical formulation 200 comprises second pharmaceutical layers 202A, 202B and 202C. In some embodiments two or more of the second pharmaceutical layers 202A, 202B and 202C comprise the same pharmaceutical composition. In the illustrated embodiment each of the pharmaceutical layers 202A, 202B and 202C comprises a different pharmaceutical composition. The second pharmaceutical formulation 200 also comprises an intermediate layer 106 configured to dissolve *in vivo*.

**[0038]** Figure 2B illustrates the second layered pharmaceutical formulation 200 of Figure 2A. The fluid, as represented by the arrow 108, has dissolved an intermediate layer 106 and the second pharmaceutical layers 202A, 202B and 202C are separated and left substantially intact.

**[0039]** Figure 3 illustrates an embodiment of a third layered pharmaceutical formulation 300. The third pharmaceutical formulation 300 comprises third pharmaceutical layers 302A, 302B and 302C separated by an intermediate layer 106. Each of the third pharmaceutical layers 302A, 302B and 302C comprises one or more pharmaceutical compositions. As illustrated in the third layered pharmaceutical formulation 300, the third pharmaceutical layer 302A comprises a similar dosage volume to the third pharmaceutical layer 302B. The third pharmaceutical layer 302C, however, comprises a larger dosage volume than third pharmaceutical layers 302A or 302B. As noted above with regard to Figure 1, varying dosage amounts or strengths of particular pharmaceutical layers within a pharmaceutical formulation allows for individualized treatment of particular symptoms.

**[0040]** Figure 4 illustrates an embodiment of a fourth layered pharmaceutical formulation 400. The fourth pharmaceutical formulation 400 includes, but is not limited to fourth pharmaceutical layers 402A and 402B and an intermediate layer 106. The fourth pharmaceutical layer 402A comprises a first drug 404A and a second drug 404B. The first drug 404A and the second drug 404B are positioned within the fourth pharmaceutical layer 402A so as to be in physical contact with the other; no intermediate layer 106 separates the first drug 404A from the second drug 404B within the layer 402A. Similarly, the fourth pharmaceutical layer 402B comprises a third drug 404C and a fourth drug 404D; no intermediate layer 106 separates the third drug 404C and the fourth drug 404D.

**[0041]** In the fourth pharmaceutical formulation 400 the intermediate layer 106 is disposed between fourth pharmaceutical layers 402C and 402B. In this embodiment, the edges of intermediate layer 106 are not aligned with the fourth pharmaceutical layers 402C and 402B. A space 408 allows for fluids to interact with and dissolve the intermediate layer 106. Thus, although the intermediate layer 106 is not flush with the outside edge of the fourth pharmaceutical formulation 400, the intermediate layer 106 is exposed for purposes of dissolution upon contact with bodily fluids.

**[0042]** Figure 5 illustrates an embodiment of a fifth layered pharmaceutical formulation 500 depicted after separation has occurred. The fifth pharmaceutical formulation 500 includes, but is not limited to fifth pharmaceutical layers 502A and 502B. The fifth pharmaceutical layers 502A and 502B each include, but are not limited to one or more pharmaceutical compositions.

**[0043]** The fifth pharmaceutical formulation 500 further comprises a first intermediate layer 506A and a second intermediate layer 506B. In some embodiments the first intermediate layer 506A is configured to physically and chemically separate the fifth pharmaceutical layers 502A and 502B. In some embodiments the second intermediate layer 506B is configured to physically and chemically separate the fifth pharmaceutical layers 502A and 502B. The first intermediate layer 506A and the second intermediate layer 506B each comprise one or more formulations configured to dissolve *in vivo*.

**[0044]** Figure 6 illustrates an embodiment of a sixth layered pharmaceutical formulation 600. The sixth pharmaceutical formulation 600 includes, but is not limited to

sixth pharmaceutical layers 602A and 602B and an intermediate layer 106. The sixth pharmaceutical formulation 600 is configured in a lenticular shape, wherein each pharmaceutical layer 602A and 602B comprises a single convex shape.

**[0045]** Pharmaceutical layers may be configured in various shapes. For example, pharmaceutical layers may be configured in elliptical shapes, spherical shapes, oblong shapes, square shapes or flat shapes. In some embodiments pharmaceutical formulations are combined with fillers or excipients and placed in tablets, granules or capsules for later administration. In some embodiments the tablets are configured in spherical, elliptical, lenticular or capsule shapes.

**[0046]** Figure 7 illustrates another embodiment of a seventh layered pharmaceutical formulation 700. The seventh pharmaceutical formulation 700 includes, but is not limited to seventh pharmaceutical layers 702A, 702B, 702C, 702D, 702E and 702F. Each seventh pharmaceutical layer 702A, 702B, 702C, 702D, 702E and 702F comprises one or more pharmaceutical compositions. Each seventh pharmaceutical layer 702A, 702B, 702C, 702D, 702E and 702F is in a wedge shape. The seventh pharmaceutical formulation 700 additionally comprises an intermediate layer 106 disposed between seventh pharmaceutical layers 702B, 702C and 702D and also between seventh pharmaceutical layers 702A, 702F and 702E. As described above the intermediate layer 106 is configured to dissolve *in vivo* upon contact with a certain type of bodily fluid. The seventh pharmaceutical formulation 700 additionally comprises a special intermediate layer 706 disposed between seventh pharmaceutical layers 702A and 702B and between seventh pharmaceutical layers 702D and 702E. The special intermediate layer 706 is configured to dissolve under bodily conditions different than those conditions that dissolve intermediate layer 106. Upon dissolution of the special intermediate layer 706, the seventh pharmaceutical layers 702A and 702B and the seventh pharmaceutical layers 702D and 702E are left substantially intact.

**[0047]** For example, if intermediate layer 106 were configured to dissolve under the acidic conditions of the stomach in a human patient, special intermediate layer 706 may be configured to dissolve only after the pharmaceutical formulation 700 reaches the duodenum. In some embodiments at least one of the pharmaceutical layers comprises an enteric coating.

### Manufacture of Pharmaceutical Formulations

**[0048]** As noted above, pharmaceutical formulations may be configured in various shapes and sizes for ease of administration to a patient. Manufacture of pharmaceutical formulations configured in tablets comprises steps known in the art. For example, tablets may be prepared through wet-granulation, dry-granulation or direct compression. Layered pharmaceutical formulations may be configured in tablet form in a similar manner. To manufacture each pharmaceutical layer, one or more drugs are obtained in, for example, a crystalline, amorphous or powdered form, and mixed with or without diluents and/or excipients into a solid with pressure. The solid pharmaceutical layer is added with other pharmaceutical layers and/or intermediate layers and configured in a desired tablet geometry with pressure.

**[0049]** In some embodiments pharmaceutical formulations include, but are not limited to, one or more of polyvinylpyrrolidine (polyvinylpyrrolidone), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers (Eudragit), maleic anhydride/methyl vinyl ether copolymers.

**[0050]** In some embodiments pharmaceutical formulations include, but are not limited to controlled-release formulations. In some embodiments the controlled-release formulations include, but are not limited to sustained-release formulations.

### Pharmaceutical Formulations to Treat Obesity

**[0051]** In some embodiments the layered pharmaceutical formulation may be used to treat obesity. Obesity is a disorder characterized by the accumulation of excess fat in the body. Obesity has been recognized as one of the leading causes of disease and is emerging as a global problem. Increased instances of complications from obesity, such as hypertension, non-insulin-dependent diabetes mellitus, arteriosclerosis, dyslipidemia, certain forms of cancer, sleep apnea and osteoarthritis, have been related to increased instances of obesity in the general population.

**[0052]** Prior to 1994, obesity was generally considered a psychological problem. The discovery of the adipostatic hormone leptin in 1994 brought forth the realization that in

certain cases, obesity may have a biochemical basis. The corollary to this realization was the idea that treatment of obesity may be achieved by chemical approaches. Since then, a number of such chemical treatments have entered the market.

**[0053]** Various methods of affecting weight loss, suppressing appetite and/or treating an obesity-related condition in a patient involve administering certain drugs or combinations thereof. For example, a number of references disclose the administration of certain weight loss formulations that include an anticonvulsant, an opioid antagonist and/or a norepinephrine reuptake inhibitor (NRI) to a patient in need thereof to affect weight loss. See, for example, U.S. Patent Application Publication Nos. 2004/0033965; 2004/0198668; 2004/0254208; 2005/0137144; 2005/0143322; 2005/0181070; 2005/0215552; 2005/0277579; 2006/0009514; 2006/0142290; 2006/0160750 and 2006/0079501, all of which are hereby incorporated by reference in their entireties. Weight gain has been a major concern with certain of the newer antidepressants, particularly, with paroxetine (PAXIL® PAXIL CR®) and mirtazapine (Fava, J. Clin. Psych. 61 (suppl. 11):37-41 (2000); Carpenter et al, J. Clin. Psych. 60:45-49 (1999); Aronne et al, J. Clin. Psych. 64 (suppl. 8):22-29 (2003), both of which are incorporated by reference herein in their entirety).

**[0054]** Other descriptions of bupropion, zonisamide, controlled-release zonisamide and combinations thereof are disclosed in U.S. Provisional Patent Application Nos. 60/740,034, filed on November 28, 2005; 60/832,110, filed on July 19, 2006; 60/835,564, filed on August 4, 2006; and U.S. Patent Application 11/194,201 entitled COMBINATION OF BUPROPION AND A SECOND COMPOUND FOR AFFECTING WEIGHT LOSS, filed on August 1, 2005; all of which are hereby incorporated by reference in their entireties.

**[0055]** For methods of administering pharmaceutical compositions useful for affecting weight loss, suppressing appetite and/or treating obesity-related conditions in individuals controlled-release formulations help to suppress some if not all of the negative side effects that may arise from administration of such medication. Even in controlled-release formulations, however, the administration of certain anticonvulsants or opioid receptor antagonists at a full dosage may initially incur severe adverse side effects. Thus, at least initially, patients may be unable to tolerate a full dosage of the prescribed drug, which may include, but is not limited to an anticonvulsant or an opioid receptor antagonist. This

intolerance may lead to more severe side effects and/or premature abandonment of the medication and/or the treatment program.

**[0056]** Administering combinations of drugs, for example, a combination including, but not limited to an anticonvulsant or an opioid receptor antagonist in combination with an antidepressant may enhance the ability of the anticonvulsant to affect weight loss, but does not necessarily eliminate the initial adverse side effects that may accompany the administration of the anticonvulsant or the opioid receptor antagonist. In some embodiments a system comprises a layered pharmaceutical for minimizing side effects during treatment of obesity. In some embodiments a method comprises administering a layered pharmaceutical formulation comprising an anticonvulsant or the opioid receptor antagonist to affect weight loss while minimizing or eliminating the initial adverse side effects on the patient.

**[0057]** Thus, some preferred embodiments, the layered pharmaceutical formulation is useful for the treatment of obesity and/or for affecting weight loss. Some preferred embodiments comprise at least one of an antidepressant and an anticonvulsant. Other preferred embodiments comprise at least one of an antidepressant and an opioid receptor antagonist. Other preferred embodiments comprise at least one of an anticonvulsant and an opioid receptor antagonist. Other preferred embodiments comprise at least one of an anticonvulsant and an antidiabetic.

#### Antidepressants and Psychotherapeutics

**[0058]** In some embodiments an antidepressant comprises a dopamine reuptake inhibitor or receptor antagonist. Examples of dopamine reuptake inhibitors include, but are not limited to phentermine and pharmaceutically acceptable salts or prodrugs thereof. Examples of dopamine receptor antagonists include, but are not limited to haloperidol, oclacitinib, risperidone, olanzapine, quetiapine, amisulpride, and pimozide and pharmaceutically acceptable salts or prodrugs thereof. In some embodiments the antidepressant comprises a norepinephrine reuptake inhibitor. Examples of norepinephrine reuptake inhibitors include, but are not limited to bupropion, thionisoxetine, atomoxetine and reboxetine and pharmaceutically acceptable salts or prodrugs thereof. Other embodiments include, but are not limited to those in which the antidepressant is a dopamine agonist.

Dopamine agonists available on the market include cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine. In some embodiments the antidepressant comprises a serotonin reuptake inhibitor. Examples of serotonin reuptake inhibitors include, but are not limited to fluoxetine and pharmaceutically acceptable salts or prodrugs thereof

**[0059]** Throughout the disclosure of the present specification the term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the disclosure with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the disclosure with a base to form a salt such as ammonium salt, an alkali metal salt such as a sodium or a potassium salt, an alkaline earth metal salt such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl) methylamine and salts thereof with amino acids such as arginine, lysine and the like.

**[0060]** The term “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They can, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug can also have improved solubility in pharmaceutical compositions over the parent drug or can demonstrate increased palatability or be easier to formulate.

**[0061]** An example, without limitation, of a prodrug would be a compound of the present disclosure which is administered as an ester (the “prodrug”) to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to provide the active moiety.

**[0062]** Bupropion, whose chemical name is  $(\pm)$ -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone, is the active ingredient in the drugs marketed as ZYBAN<sup>®</sup> and WELLBUTRIN<sup>®</sup>, and is usually administered as a hydrochloride salt. Throughout the present disclosure, whenever the term “bupropion” is used, it is understood that the term encompasses bupropion as a free base, or as a physiologically acceptable salt thereof, or as a bupropion metabolite or salt thereof.

**[0063]** The metabolites of bupropion suitable for inclusion in the methods and compositions described herein include the erythro- and threo-amino alcohols of bupropion, the erythro-amino diol of bupropion, and morpholinol metabolites of bupropion. In some embodiments, the metabolite of bupropion is  $(\pm)$ -(2R\*,3R\*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol. In some embodiments the metabolite is  $(-)$ -(2R\*,3R\*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, while in other embodiments, the metabolite is  $(+)$ -(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol. Preferably, the metabolite of bupropion is  $(+)$ -(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, which is known by its common name of radafaxine. The scope of the present disclosure includes the above-mentioned metabolites of bupropion as a free base or as a physiologically acceptable salt thereof. Controlled-release bupropion formulations of bupropion are known in the art. For example, U.S. Patent 6,905,708 discloses a once-daily dosage configured to deliver bupropion *in vivo* over a 6 to 12 hour period.

**[0064]** Olanzapine, whose chemical name is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is used as a psychotherapeutic agent primarily for the treatment of schizophrenia, acute manic episodes in bipolar disorder acute, maintenance treatment in bipolar disorder and agitation associated with both these disorders. Throughout the present disclosure, whenever the term “olanzapine” is used, it is understood that the term encompasses olanzapine as a free base, or as a physiologically acceptable salt thereof, or as a olanzapine metabolite or salt thereof.

**[0065]** Olanzapine displays linear kinetics. Its elimination half-life ranges from 21 to 54 hours. Steady state plasma concentrations are achieved in about a week. Olanzapine undergoes extensive first pass metabolism and bioavailability is not affected by food.

**[0066]** The psychotherapeutic agent may be selected from the group consisting of mirtazapine, setiptiline, paroxetine, venlafaxine, olanzapine, bupropion, risperidone, lamotrogine, risperidone, a lithium salt, valproic acid, and pharmaceutically acceptable salts or prodrugs thereof. In some embodiments the psychotherapeutic agent is an antidepressant, an antimigraine, an antipolar, an antimania drug, a mood stabilizer, or an antiepileptic. Examples of antidepressants include paroxetine, mirtazapine, and bupropion. Examples of antipolar drugs include lithium, valproate, carbamezepine, oxycarbamezepine, lamotrogine, tiagabine, olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone, and benzodiazepines. Also included are pharmaceutically acceptable salts or prodrugs of these drugs, extended release or controlled release formulations of the above drugs, as well as combinations of the above drugs.

**[0067]** Fluoxetine is a selective serotonin reuptake inhibitor (SSRI), whose chemical name is N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine, is used primarily for the treatment of depression (including pediatric depression), obsessive-compulsive disorder (in both adult and pediatric populations), bulimia nervosa, panic disorder, premenstrual dysphoric disorder, hypochondriasis and body dysmorphic disorder. Throughout the present disclosure, whenever the term “fluoxetine” is used, it is understood that the term encompasses fluoxetine as a free base, or as a physiologically acceptable salt thereof, or as a fluoxetine metabolite or salt thereof.

**[0068]** Fluoxetine has a bioavailability of approximately 72%, and peak plasma concentrations are reached in 6 to 8 hours. It is highly bound to plasma proteins, mostly albumin. Its elimination half-life ranges from 1 to 3 days—after a single dose—to 4 to 6 days (after long-term use) in healthy adults, and is prolonged in those with liver disease. The half-life of norfluoxetine is longer (16 days after long-term use). Complete excretion of the drug may take several weeks.

**[0069]** The SSRI can be selected from fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, sibutramine, duloxetine, and venlafaxine, and pharmaceutically acceptable salts or prodrugs thereof. In some embodiments, the SSRI is fluoxetine or a pharmaceutically acceptable salt or prodrug thereof.

**[0070]** Fluoxetine has a physiological half life of about 24 hours, whereas that of naltrexone is about 1.5 hours. However their metabolites may demonstrate half-lives in excess of 24 hours. Thus, in some cases, it may be beneficial to administer one dose of fluoxetine per day in conjunction with two or three or more doses of naltrexone throughout the day. Naltrexone may also be in a time-release formulation where the dose is administered once a day, but naltrexone gradually enters the blood stream throughout the day, or in the course of a 12 hour period.

**[0071]** Symptoms of the obsessive compulsive disorders are inhibited in individuals being administered fluoxetine and naltrexone. Adverse events associated with the obsessive compulsive disorders are reduced in individuals being administered fluoxetine and naltrexone. The effects of administration of both fluoxetine and naltrexone on obsessive compulsive disorder are synergistic compared to effects of those expected by administration of fluoxetine and naltrexone alone.

**[0072]** Newer generation antidepressants include selective serotonin reuptake inhibitors (e.g., fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram), venlafaxine, duloxetine, nefazodone, mianserin, setiptiline, viqualine, trazodone, cianopramine, and mirtazapine.

**[0073]** Phentermine is an example of a dopamine reuptake inhibitor with a chemical name 2-methyl-1-phenylpropan-2-amine and 2-methyl-amphetamine. Throughout the present disclosure, whenever the term "phentermine" is used, it is understood that the term encompasses phentermine as a free base, or as a physiologically acceptable salt thereof, or as a phentermine metabolite or salt thereof.

#### Antidiabetic

**[0074]** In some embodiments an antidiabetic includes, but is not limited to a biguanide, glucosidase inhibitor, insulin, meglitinide, sulfonylurea or a thiazolidinedione. In some embodiments a biguanide comprises metformin hydrochloride. In some embodiments a glucosidase inhibitor includes, but is not limited to acarbose and miglitol. Examples of insulin include, but are not limited to human insulin, pork insulin, beef insulin, beef-pork insulin, insulin from different sources such as recombinant DNA and animal sources, as well as

regular, NPH, and LENTE® types of insulin. Other examples of insulin include, but are not limited to mixtures of the various forms of insulin (e.g. NPH and regular human and pork insulin). Other examples of insulin include mixtures of Insulin Lispro Protamine and Insulin Injection (rDNA origin), a 50/50 (or a 70/30) mixture of Human Insulin Isophane Suspension and Human Insulin Injection, a 70/30 mixture of NPH Human Insulin Isophane Suspension and Human Insulin Injection (rDNA), insulin glargine, insulin lispro, insulin aspart, as well as insulin mixed with other ingredients such as zinc crystals or in a phosphate buffer. Insulin may be from *Saccharomyces cerevisiae* or other sources. Examples of meglitinides include, but are not limited to nateglinide and repaglinide. Examples of sulfonylureas include, but are not limited to glimepiride, glyburide, glibenclamide, gliquidone, gliclazide, chlorpropamide, tolbutamide, tolazamide and glipizide. Examples of thiazolidinediones include, but are not limited to rosiglitazone and pioglitazone. Also included are extended release formulations of the above drugs, as well as combinations of the above drugs and pharmaceutically acceptable salts or prodrugs thereof.

**[0075]** As mentioned above, in certain embodiments, the antidiabetic is metformin. Metformin, whose chemical name is 1-(diaminomethylidene)-3,3-dimethyl-guanidine, is often used in the treatment of diabetes mellitus type 2, especially when accompanied obesity and insulin resistance. Metformin has also been proven to reduce the cardiovascular complications of diabetes.

#### Anticonvulsants

**[0076]** In some embodiments, the anticonvulsant is selected from the group including, but not limited to zonisamide, topiramate, nembutal, lorazepam, clonazepam, clorazepate, tiagabine, gabapentin, fosphenytoin, phenytoin, carbamazepine, balproate, felbamate, levetiracetam, oxcarbazepine, lamotrigine, methsuximide and ethosuximide.

**[0077]** Zonisamide is a marketed anticonvulsant indicated as adjunctive therapy for adults with partial onset seizures. Without being bound by any particular theory, it is believed that the mechanism of antiepileptic activity appears to be: (1) sodium-channel blocking; and (2) reduction of inward T-type calcium occurrence. In addition, zonisamide binds to the GABA/benzodiazepine receptor complex without producing change in chloride flux. Further,

zonisamide facilitates serotonergic and dopaminergic neurotransmission and possesses a weak inhibitory effect on carbonic anhydrase.

**[0078]** Zonisamide has been shown to cause significant weight loss (comparable to marketed weight loss medications) in patients presenting primary obesity. It has been postulated that the affect of zonisamide on the CNS concentration of serotonin, dopamine and carbonic anhydrase is responsible for this effect. There is evidence that zonisamide increases serotonin and dopamine synthesis rates herein. There is further evidence suggesting that zonisamide stimulates dopamine D<sub>2</sub> receptors.

**[0079]** Zonisamide can be formulated in a controlled- or sustained-release tablet or gel form. This allows a patient newly prescribed zonisamide to ramp up the dosage level over a period of several days. This increase in dosage form allows the patient to avoid some of the negative side effects that have been exhibited during the initial administration of zonisamide to a patient. Some of these initial side effects include a shock to the body. Although patients who start with a full dose of zonisamide will become acclimated to the dosage over a period of time, the negative side effects accompanying the initial shock to the body can be avoided with a method wherein dosages are increased over a period of several days.

**[0080]** In a pharmaceutical composition with a drug such as bupropion, a method of administering sustained-release zonisamide in a layered tablet can reduce shock to the body while maximizing bioavailability, and thus have a maximum effect for prevention of weight gain and/or treatment of obesity.

**[0081]** Although the exact dosages will be determined on a drug-by-drug basis, in most cases some generalizations regarding the dosage can be made. Some descriptions of appropriate unit dosages of drugs including, but not limited to bupropion, zonisamide, controlled-release zonisamide and combinations thereof are disclosed in U.S. Provisional Patent Application No. 60/740034 entitled CONTROLLED RELEASE FORMULATION OF ZONISIMIDE, filed on November 28, 2005; and U.S. Patent Application 11/194202 entitled COMBINATION OF BUPROPION AND A SECOND COMPOUND FOR AFFECTING WEIGHT LOSS, filed on August 1, 2005; which are hereby incorporated by reference in their entireties, and U.S. Patent Publication Nos. 2005/0215552 and 2006/0079501 mentioned previously.

**[0082]** In some embodiments the anticonvulsant is a  $\gamma$ -amino butyric acid (GABA) inhibitor, a GABA receptor antagonist or a GABA channel modulator. By “GABA inhibitor” it is meant a compound that reduces the production of GABA in the cells, reduces the release of GABA from the cells, or reduces the activity of GABA on its receptors, either by preventing the binding of GABA to GABA receptors or by minimizing the effect of such binding. The GABA inhibitor may be a 5-HT1b agonist or another agent that inhibits the activity of NPY/AgRP/GABA neurons. In addition, the GABA inhibitor may suppress the expression of the AgRP gene, or the GABA inhibitor may suppress the production or release of AgRP. It is, however, understood that a 5-HT1b agonist may inhibit the NPY/AgRP/GABA neuron (and therefore activate pro-opiomelanocortin (POMC) neurons) without acting as an inhibitor of the GABA pathway.

**[0083]** In certain other embodiments the GABA inhibitor increases the expression of the POMC gene. In some of these embodiments, the GABA inhibitor increases the production or release of POMC protein. In certain other of these embodiments, the GABA inhibitor increases the activity on POMC expressing neurons.

**[0084]** In some embodiments, the GABA inhibitor is topiramate. Topiramate, whose chemical name is 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate, is often used to treat epilepsy, Lennox-Gastaut syndrome (a disorder causing seizures and developmental delays), neuropathic pain, bipolar disorder, obesity including reduction of binge eating, alcoholism, Post Traumatic Stress Disorder, infantile spasm, bulimia nervosa, or obsessive-compulsive disorder or to assist smoking cessation or prevent migraines. Generally, initial doses of topiramate are low and increased in slow steps. The usual initial dose is 25 to 50 mg daily in 2 single doses. Recommended increments vary, but are usually between 25 mg and 50 mg every 1 or 2 weeks. Common doses for maintenance treatment include, but are not limited to doses of approximately 100 to 200 mg daily.

#### Opioid Receptor Antagonists

**[0085]** In certain embodiments the opioid antagonist antagonizes a  $\mu$ -opioid receptor (MOP-R) in a mammal. The mammal may be selected from the group including, but

not limited to mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans.

**[0086]** In some embodiments the opioid antagonist is selected from the group including, but not limited to alvimopan, norbinaltorphimine, nalmefene, naloxone, naltrexone, methylnaltrexone, and nalorphine, and pharmaceutically acceptable salts or prodrugs thereof.

**[0087]** In other embodiments, the opioid antagonist is a partial opioid agonist. Compounds of this class have some agonist activity at opioid receptors. However, because they are weak agonists, they function as de-facto antagonists. Examples of partial opioid agonists include, but are not limited to pentacozine, buprenorphine, nalorphine, propiram, and lofexidine.

**[0088]** Naltrexone (17-(cyclopropylmethyl)-4, 5 $\alpha$ -epoxy- 3, 14-dihydroxymorphinan-6-one), shown below, is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.  $\mu$ -subtype selective opioid antagonists such as naltrexone are also of considerable current interest as agents for the treatment of obesity (Glass, M. J.; Billington, C. J.; Levine, A. S. *Neuropeptides* **1999**, *33*, 350) and CNS disorders (Reneric, J. P.; Bouvard, M. P. *CNS Drugs* **1998**, *10*, 365).

**[0089]** It is marketed as its hydrochloride salt, naltrexone hydrochloride, under the trade name REVIA<sup>TM</sup>. REVIA<sup>TM</sup> is an immediate release formulation of naltrexone, with 100 mg strength. The maximum serum concentration of immediate release naltrexone is reached very rapidly, typically a  $T_{max}$  of approximately 1 hour. Immediate release naltrexone can induce side effects such as nausea, which is attributable to the maximum blood plasma concentration levels ( $C_{max}$ ).

**[0090]** An oral dosage form of naltrexone that is able to effect naltrexone release at a rate sufficiently slow to ameliorate side effects, yet sufficiently fast to achieve good bioavailability would provide a significant improvement in dosing compliance and convenience. Likewise, an improved dosage form which lowered the incidence of gastrointestinal side-effects would also be of significant value.

**[0091]** In some embodiments, oral dosage forms of naltrexone are effective to provide an AUC between about 75% to about 125% of 50 mg immediate release naltrexone tablets. In some embodiments oral dosage forms of naltrexone provide an amount of a

retardant excipient that is effective to provide a  $C_{max}$  that is less than or equal to about 80% of the  $C_{max}$  of 50 mg immediate release naltrexone tablets.

**[0092]** Formulations of controlled- or sustained-release naltrexone have been disclosed in U.S. Provisional Patent Application Serial No. 60/811,251, filed June 5, 2006, which is hereby incorporated by reference in its entirety. In some embodiments, oral dosage forms of naltrexone are effective to provide an AUC between about 75% to about 125% of 50 mg immediate release naltrexone tablets. In some embodiments oral dosage forms of naltrexone comprise an amount of a retardant excipient that is effective to provide a  $C_{max}$  that is less than or equal to about 80% of the  $C_{max}$  of 50 mg immediate release naltrexone tablets.

**[0093]** Those skilled in the art informed by the guidance provided herein can formulate oral dosage forms described herein. For example, one skilled in the art could formulate an oral dosage form that includes, but is not limited to an amount of naltrexone effective to provide an AUC between about 75% to about 125% of 50 mg immediate release naltrexone tablets, and an amount of an appropriate retardant excipient effective to provide a  $C_{max}$  that is less than or equal to about 80% of the  $C_{max}$  of 50 mg immediate release naltrexone tablets. Further, given the guidance provided herein, the skilled artisan could formulate an oral dosage form having a pharmacodynamic profile characterized by coverage of greater than or equal to 80% of the opioid receptors in the hypothalamus.

### Examples

**[0094]** Below are found specific examples of pharmaceutical compositions that may be formed into layered pharmaceutical formulations of the present disclosure.

Table 1: Formulations for Sustained-Release (SR) Tablets Containing Bupropion

Ingredient	70 mg Bupropion SR Amount per Tablet	90 mg Bupropion SR Amount per Tablet
Bupropion HCL, USP	70.0 mg	90.0 mg
Microcrystalline Cellulose, NF (Avicel PH 101)	173.3 mg	153.3 mg
Hydroxypropyl Cellulose, NF (Klucel HXF)	56.7 mg	56.7 mg
Cysteine HCL, NF	12.5 mg	12.5 mg
Magnesium Stearate, NF	2.5 mg	2.5 mg
Tablet Weight	315.0 mg	315.0 mg

Table 2: Formulations for Sustained-Release (SR) Tablets Containing Zonisamide

Ingredient	30 mg Zonisamide SR Amount per Tablet	60 mg Zonisamide SR Amount per Tablet	90 mg Zonisamide SR Amount per Tablet
Zonisamide	30 mg	60 mg	90 mg
Klucel	110 mg	35 mg	35 mg
Lactose	55 mg	70 mg	60 mg
Colloidal Silicon Dioxide, NF	2 mg	2 mg	2 mg
Cross Povidone	20 mg	14 mg	14 mg
Magnesium Stearate, NF	6 mg	6 mg	6 mg
Microcrystalline Cellulose, NF	127 mg	163 mg	143 mg

Table 3: Formulations for Sustained -Release (SR) Tablets Containing Naltrexone

Ingredient	Percent per Tablet “12.5% HPMC” SR-Fast	Percent per Tablet “30% HPMC” SR-Medium	Percent per Tablet “44% HPMC” SR-Slow
Naltrexone (5 mg)	6.667	6.667	6.667
Hydroxypropylmethyl Cellulose (Methocel K15 Premium)	10.000	30.000	44.333
Common QBQ01 Placebo Granulation	81.733	61.833	47.500
Colloidal Silicon Dioxide, NF (Cab-O-Sil M5P)	1.000	0.500	1.000
Sodium Edetate	0.1	-	-
Magnesium Stearate, NF, Ph.Eur. (Vegetable Source) (Grade 905-G)	0.500	6.667	0.500
	100.000	100.000	100.000

**[0095]** Thus, as illustrated in Tables 1-3 above, embodiments of pharmaceutical formulations may comprise controlled-release (e.g., sustained release in the illustrated embodiments) formulations of bupropion, zonisamide and/or naltrexone. In one embodiment, a layered pharmaceutical formulation is a tablet comprising a first layer comprising a controlled-release zonisamide and a second layer comprising a bupropion. In another embodiment a layered pharmaceutical formulation is a tablet comprising a first layer comprising a controlled-release naltrexone and a second layer comprising a controlled-release bupropion. In some embodiments the first layer and the second layer are separated by an intermediate layer comprising lactose or other suitable fast-dissolving ingredient.

**[0096]** The oral dosage forms of pharmaceutical formulations can, if desired, be presented in a unit dosage package which may contain one or more unit dosage forms containing the active ingredient. The unit dosage package may for example comprise metal or plastic foil, such as a blister pack. The unit dosage package may be accompanied by

instructions for administration. The unit dosage package may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the disclosure formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

**[0097]** Novel methods and systems for administering weight loss medications are described in co-pending application entitled METHODS FOR ADMINISTERING WEIGHT LOSS MEDICATIONS filed on the same day as the present application, which is hereby incorporated by reference in its entirety.

**[0098]** In some embodiments, the weight loss medications are provided at least once, twice or three times a day for a set period, which can be at least, at least about, less than, less than about, equal to or between any range within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive days or at least, at least about, less than, less than about, equal to or between any range within of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive weeks or at least, at least about, less than, less than about, equal to or between any range within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive months. The amount of drug in any pharmaceutical formulation described herein includes, but is not limited to amounts of at least, at least about, less than, less than about, equal to or between any range within 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1500, 2000, 3000, 4000 or 5000 mg.

**[0099]** In one embodiment a layered pharmaceutical formulation for the administration of two or more active pharmaceutical ingredients comprises a first pharmaceutical layer comprising a first active pharmaceutical ingredient, a second

pharmaceutical layer comprising a second active pharmaceutical ingredient and at least one intermediate layer disposed between the first and the second pharmaceutical layers, wherein the at least one intermediate layer is configured to dissolve in vivo to thereby leave the first and the second pharmaceutical layers substantially intact.

**[0100]** In some embodiments each of the first and the second pharmaceutical layers comprises a dissolution profile substantially similar to a singularly compressed tablet of a similar composition. In some embodiments each of the first and the second pharmaceutical layers comprises a different pharmaceutical composition. In some embodiments at least one of the first and the second pharmaceutical layers comprises a controlled-release pharmaceutical composition. In some embodiments the controlled-release pharmaceutical composition comprises a sustained release pharmaceutical composition.

**[0101]** In some embodiments at least one of the first and the second pharmaceutical layers comprises zonisamide. In some embodiments the zonisamide comprises a controlled-release zonisamide. In some embodiments the controlled-release zonisamide comprises a sustained-release zonisamide. In some embodiments at least one of the first and the second pharmaceutical layers comprises bupropion. In some embodiments the bupropion comprises a controlled-release bupropion. In some embodiments the controlled-release bupropion comprises a sustained-release bupropion. In some embodiments at least one of the first and the second pharmaceutical layers comprises naltrexone. In some embodiments at least one of the first and the second pharmaceutical layers comprises fluoxetine.

**[0102]** In some embodiments at least one of the first and the second pharmaceutical layers comprises olanzapine. In some embodiments at least one of the first and the second pharmaceutical layers comprises an antidiabetic. In some embodiments the antidiabetic comprises metformin. In some embodiments at least one of the first and the second pharmaceutical layers comprises topiramate. In some embodiments at least one of the first and the second pharmaceutical layers comprises phentermine. In some embodiments the at least one intermediate layer comprises at least one of a monosaccharide sugar, a disaccharide sugar, or a starch. In some embodiments the at least one intermediate layer comprises lactose.

**[0103]** In one embodiment a method for affecting weight loss, suppressing appetite and/or treating an obesity-related condition in a patient comprises providing a first dosage of the layered pharmaceutical formulation to a patient in need thereof on a first day and providing a second dosage of the layered pharmaceutical formulation to the patient on a second day. In some embodiments the first dosage is greater than the second dosage. In some embodiments the second dosage is greater than the first dosage.

**[0104]** In one embodiment a method for treating an obesity related condition in a patient comprises identifying a patient with an obesity related condition or at risk of an obesity related condition comprises providing a first dosage of the layered pharmaceutical formulation of Claims 1 to the patient on a first day and providing a second dosage of the layered pharmaceutical formulation to the patient on a second day. In some embodiments the first dosage is different than the second dosage. In some embodiments the second dosage is greater than the first dosage.

**[0105]** In one embodiment use of a first compound and a second compound in the formulation of a medicament for affecting weight loss, suppressing appetite or treating an obesity-related condition, wherein the medicament comprises a layered pharmaceutical formulation of the present invention.

**[0106]** It will be appreciated by those skilled in the art that various modifications and changes can be made without departing from the scope of the disclosure. Such modifications and changes are intended to fall within the scope of the disclosure, as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A layered pharmaceutical formulation for the administration of two or more active pharmaceutical ingredients comprising:
  - a first pharmaceutical layer comprising a first active pharmaceutical ingredient;
  - a second pharmaceutical layer comprising a second active pharmaceutical ingredient; and
  - an intermediate layer disposed between said first and said second pharmaceutical layers,  
wherein said intermediate layer is configured to rapidly dissolve *in vivo*, and thereby leave said first and said second pharmaceutical layers substantially intact but physically separated.
2. The layered pharmaceutical formulation of Claim 1, wherein each of said first and said second pharmaceutical layers comprises a dissolution profile substantially similar to a singularly compressed tablet of a similar composition.
3. The layered pharmaceutical formulation of Claim 1 or Claim 2, wherein each of said first and said second pharmaceutical layers comprises a different pharmaceutical composition.
4. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said first and said second pharmaceutical layers comprises a controlled-release pharmaceutical composition.
5. The layered pharmaceutical formulation of Claim 4, wherein said controlled-release pharmaceutical composition comprises a sustained release pharmaceutical composition.
6. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said first and said second pharmaceutical layers comprises zonisamide.
7. The layered pharmaceutical formulation of Claim 6, wherein said zonisamide comprises a controlled-release zonisamide.
8. The layered pharmaceutical formulation of Claim 7, wherein said controlled-release zonisamide comprises a sustained-release zonisamide.

9. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said first and said second pharmaceutical layers comprises bupropion.

10. The layered pharmaceutical formulation of Claim 9, wherein said bupropion comprises a controlled-release bupropion.

11. The layered pharmaceutical formulation of Claim 10, wherein said controlled-release bupropion comprises a sustained-release bupropion.

12. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said first and said second pharmaceutical layers comprises naltrexone.

13. The layered pharmaceutical formulation of Claim 12, wherein said naltrexone comprises a controlled-release naltrexone.

14. The layered pharmaceutical formulation of Claim 13, wherein said controlled-release naltrexone comprises a sustained-release naltrexone.

15. The layered pharmaceutical formulation of any one of Claims 6 to 8, wherein said first pharmaceutical layer comprises zonisamide and said second pharmaceutical layer comprises bupropion.

16. The layered pharmaceutical formulation of any one of Claims 12 to 14, wherein said first pharmaceutical layer comprises naltrexone and said second pharmaceutical layer comprise bupropion.

17. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said two or more pharmaceutical layers comprises fluoxetine.

18. The layered pharmaceutical formulation of any one of Claims 12 to 14, wherein said first pharmaceutical layer comprises naltrexone and said second pharmaceutical layer comprises fluoxetine.

19. The layered pharmaceutical formulation of any one of Claims 17 or 18, wherein said fluoxetine comprises a controlled-release fluoxetine.

20. The layered pharmaceutical formulation of Claim 19, wherein said controlled-release fluoxetine comprises a sustained-release fluoxetine.

21. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said two or more pharmaceutical layers comprises olanzapine.

22. The layered pharmaceutical formulation of any one of Claims 6 to 8, wherein said first pharmaceutical layer comprises zonisamide and said second pharmaceutical layer comprises olanzapine.

23. The layered pharmaceutical formulation of any one of Claims 21 or 22, wherein said olanzapine comprises a controlled-release olanzapine.

24. The layered pharmaceutical formulation of Claim 23, wherein said controlled-release olanzapine comprises a sustained-release olanzapine.

25. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said two or more pharmaceutical layers comprises an antidiabetic.

26. The layered pharmaceutical formulation of any one of Claims 6 to 8, wherein said first pharmaceutical layer comprises zonisamide and said second pharmaceutical layer comprises an antidiabetic.

27. The layered pharmaceutical formulation of any one of Claims 25 or 26, wherein said antidiabetic comprises metformin.

28. The layered pharmaceutical formulation of Claim 27, wherein said metformin comprises a controlled-release metformin.

29. The layered pharmaceutical formulation of Claim 28, wherein said controlled-release metformin comprises a sustained-release metformin.

30. The layered pharmaceutical formulation of any one of Claims 1 to 3, wherein at least one of said two or more pharmaceutical layers comprises topiramate.

31. The layered pharmaceutical formulation of Claim 30, wherein said topiramate comprises a controlled release topiramate.

32. The layered pharmaceutical formulation of Claim 31, wherein said controlled release topiramate comprises a sustained release topiramate.

33. The layered pharmaceutical formulation of Claims 1 to 3, wherein at least one of said two or more pharmaceutical layers comprises phentermine.

34. The layered pharmaceutical formulation of Claims 30 to 32, wherein said first pharmaceutical layer comprises topiramate and said second pharmaceutical formulation comprise phentermine.

35. The layered pharmaceutical formulation of any one of Claims 33 to 34, wherein said phentermine comprises a controlled release phentermine.

36. The layered pharmaceutical formulation of Claim 35, wherein said controlled release phentermine comprises a sustained release phentermine.

37. The layered pharmaceutical formulation of any one of Claims 1 to 36, wherein said intermediate layer comprises at least one of a monosaccharide sugar, a disaccharide sugar, or a starch.

38. The layered pharmaceutical formulation of Claim 37, wherein said intermediate layer comprises lactose.

39. A method for affecting weight loss in a patient comprising:  
identifying a patient in need of weight loss;  
providing a first dosage of the layered pharmaceutical formulation of any one of Claims 15, 16, 18 or 22 to a patient in need thereof on a first day; and  
providing a second dosage of the layered pharmaceutical formulation to the patient on a second day.

40. The method of Claim 39, wherein said first dosage is greater than said second dosage.

41. The method of Claim 39, wherein said second dosage is greater than said first dosage.

42. A method for treating an obesity related condition in a patient comprising:  
identifying a patient suffering from or at risk of an obesity related condition;  
providing a first dosage of the layered pharmaceutical formulation of any one of Claims 15, 16, 18 or 22 to the patient on a first day; and  
providing a second dosage of the layered pharmaceutical formulation to the patient on a second day.

43. The method of Claim 42, wherein said first dosage is different than said second dosage.

44. The method of Claim 42, wherein said second dosage is greater than said first dosage.

45. Use of a first compound and a second compound in the preparation of a medicament for affecting weight loss, suppressing appetite or treating an obesity-related condition, wherein said medicament comprises the layered pharmaceutical formulations of any one of Claims 15, 16, 18 or 22.

1/5

100

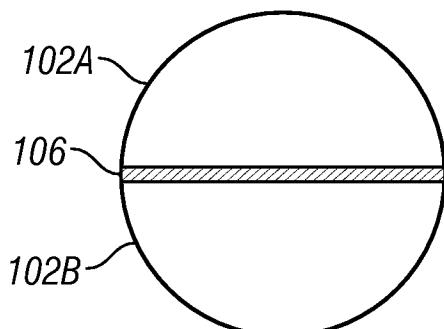


FIG. 1A

100

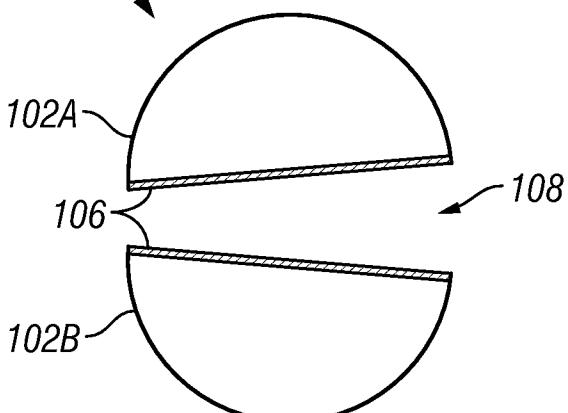


FIG. 1B

100

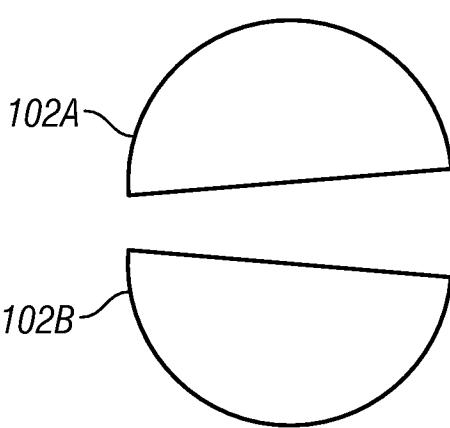


FIG. 1C

2/5

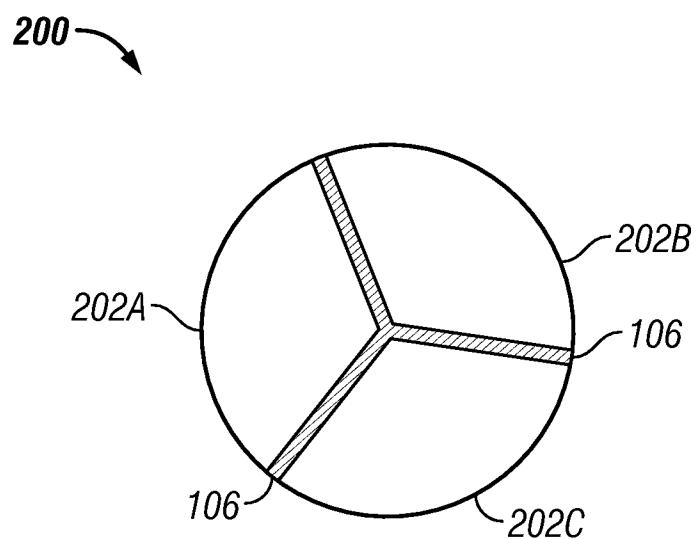


FIG. 2A

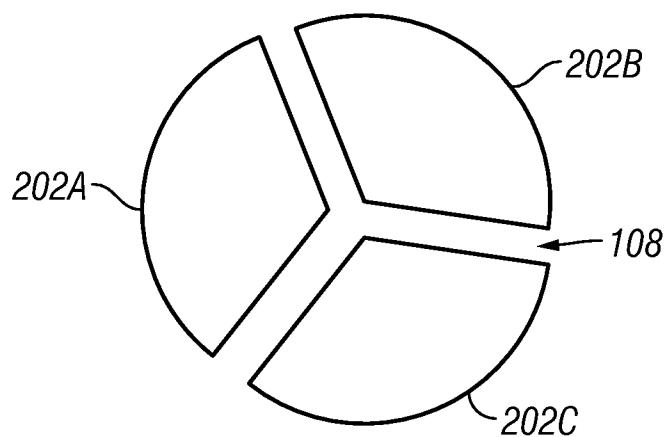


FIG. 2B

3/5

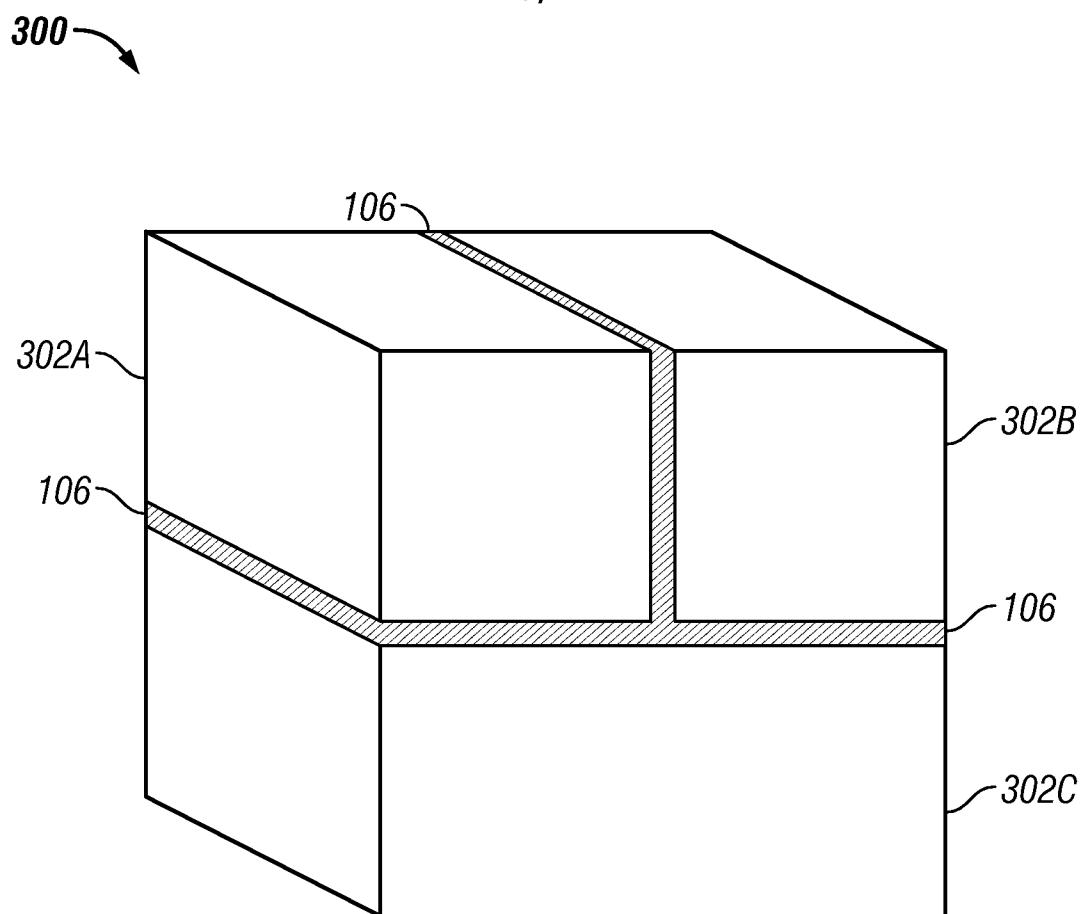


FIG. 3

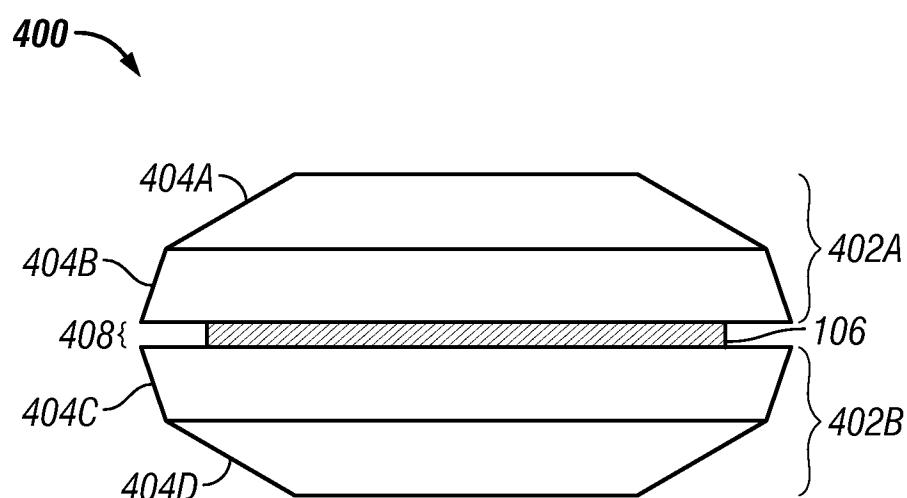


FIG. 4

4/5

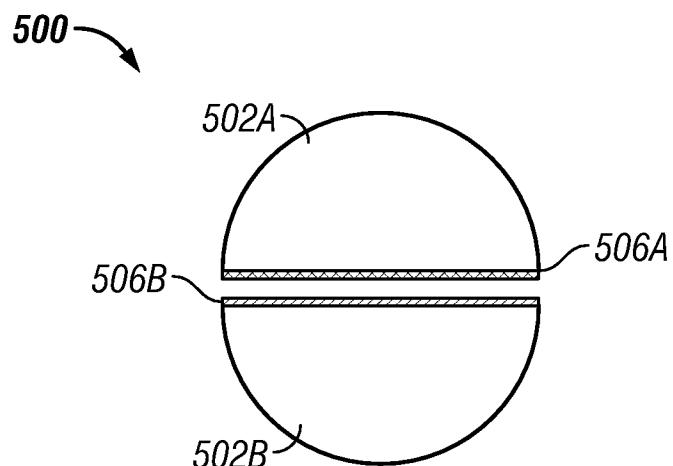


FIG. 5

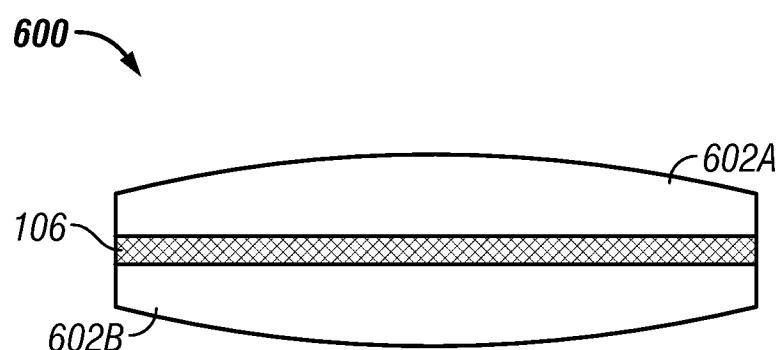


FIG. 6

5/5

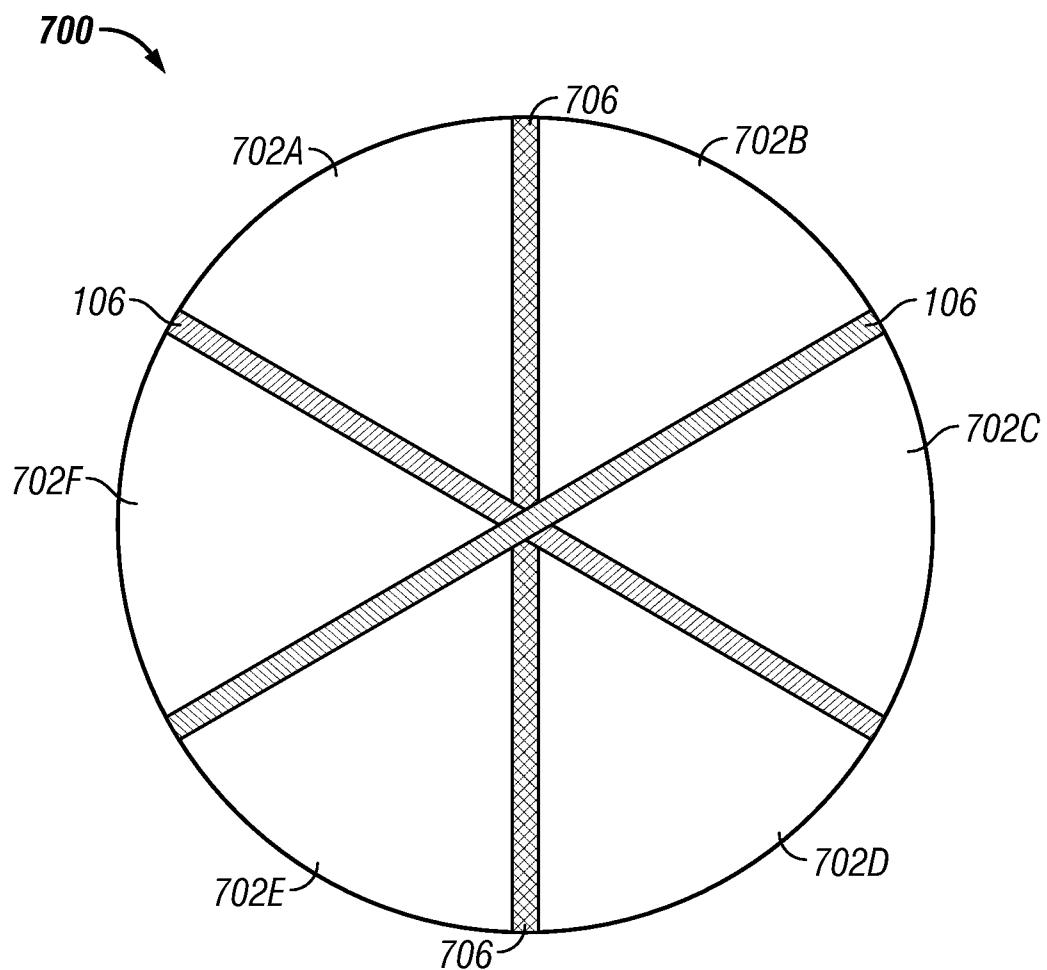


FIG. 7