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(54) Title: RATE-CONTROLLED ORAL DOSAGE FORMULATIONS

(57) Abstract: The present invention relates to a drug delivery system, in which a drug containing core, either alone or coated with a rate controlling membrane system, is enveloped on its circumference by an optionally bioadhesive coating, thereby yielding a monolithic system that allows for drug release in a regulated manner.



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RATE-CONTROLLED ORAL DOSAGE FORMULATIONS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/779,372, filed March 2, 2006, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Controlled release systems for drug delivery are often designed to administer drugs in specific areas of the body. In the case of drug delivery to the gastrointestinal tract, it is important that the drug not be delivered substantially beyond the desired site of action or absorption, respectively, before it has had a chance to exert a topical effect or to pass into the bloodstream.

Important to the safety and effectiveness of any pharmaceutical formulation is its ability to maintain a target blood level of the active pharmaceutical agent within the agent's therapeutic concentration range. The window of absorption for certain drugs presents a serious challenge to the development of effective modified-release preparations of these compounds. The poor or decreased absorption of these drugs may be attributed to a variety of barriers, which may be biological or physico-chemical in nature, and can be, but are not limited to poor solubility, low permeability, and saturable active absorption or influx mechanisms such as carrier-mediated transport. Poor solubility over a broad pH range is another barrier that inhibits absorption and overall bioavailability for a number of compounds. Furthermore, when solubility is limited at the higher pH's found in the distal gastrointestinal (GI) tract, a limited window of absorption is effectively created.

Such windows of absorption can significantly curtail the bioavailability of a compound and the extent to which T_{max} , the time at which the rate of absorption of an active agent into the bloodstream is equal to its rate of elimination from the bloodstream, can be extended using conventional modified release dosage forms known in the art.

For example, there is a need for developing formulations for blood glucose lowering drugs that are suitable for administration to patients suffering from type-2

diabetes, also known as non-insulin-dependent diabetes mellitus. For example, the absorption of the anti-diabetic agent, metformin, in humans is incomplete and the drug is excreted mainly in urine with a half life of 4 to 6 h. Metformin is protonated under physiological pH conditions. Ionized metformin is absorbed to the negatively charged intestinal epithelium. The absorption window is predominantly in the small intestine, and colonic absorption in healthy human subjects is poor (Marathe et al., *Br J Clin Pharmacol* 2000; 50: 325-332). A conventional oral sustained-release formulation releases the drug throughout the small intestine and the colon. However, the drug release after the small intestine would be of no therapeutic value and the conventional strategy of prolonging the metformin release from the dosage form throughout the gastrointestinal (GI) tract will not be effective. Evaluation of five commercial brands of Metformin HCl sustained release tablets, each containing 500 mg of Metformin, revealed no gastroretentive or bioadhesion tendency of these brands (Patel et al., *Drug Delivery Technology* 2005; 5:38-46). Metformin therapy with immediate-release or modified-release formulations, on the other hand, is associated with a high incidence of side effects such as diarrhea, nausea, vomiting, flatulence, etc.

Another drug used in the treatment of type 2 diabetes is glipizide. Gastrointestinal absorption of glipizide is uniform, rapid, and essentially complete. It has a short half-life (2-4 h) with no plasma accumulation upon repeated oral administration. Due to the short elimination half-life, an effective glipizide therapy requires twice daily dosing in a large number of patients (Berelowitz et al., *Diabetes Care* 1994; 17:1460-1464; Foster and Plosker, *Pharmacoeconomics* 2000; 18:289-306), which often leads to non-compliance.

It would therefore be useful to have dosage formulations that can deliver, for example, one or more anti-diabetic agents, such as metformin, glipizide, and/or other anti-diabetic agents, such as rosiglitazone and/or pioglitazone at a controlled rate in a substantially constant dose per unit time in the stomach or duodenum for its beneficial therapeutic effects and for better patient compliance.

Separately or in addition to the need to control the location at which a drug is released, there is also a need to control the duration over which a drug is released from a pharmaceutical formulation. In particular, certain drugs, especially neuroactive drugs, have side effects and lower efficacy if blood serum concentrations vary considerably.

Standard immediate release formulations typically cause such fluctuations in blood serum concentrations, because they dump large quantities of drug at one time into the patient's gastrointestinal tract.

Thus, there is a need for methods for controlling or increasing the absorption of pharmaceutical agents from drug delivery systems such as tablets through mucosal membranes.

BRIEF SUMMARY OF THE INVENTION

The present invention provides drug delivery systems including a bioadhesive drug delivery formulation (BIOadhesive Rate-controlled Oral Dosage (BIOROD) formulation) and a non-bioadhesive drug delivery formulation (POLYmeric, Rate-controlled, Oral Dosage (POLYROD), in which an optionally bioadhesive coating is optionally disposed over all or a portion of the surface of a core containing an agent, which core may optionally be coated with a rate-controlling membrane system, thus yielding a monolithic system that releases the agent in a regulated manner.

Polymers with improved bioadhesive properties and methods for improving bioadhesion of polymers have been developed. For example, a compound containing an aromatic group which bears one or more hydroxyl groups may be grafted onto a polymer or coupled to individual monomers. The monomers may then be polymerized to form any type of polymer, including biodegradable and non-biodegradable polymers. In one embodiment, the polymer is a biodegradable polymer. In some embodiments, the polymer is a hydrophobic polymer. In one embodiment, the aromatic compound is a catechol or a derivative thereof and the polymer contains reactive functional groups. In a preferred embodiment, the polymer is a polyanhydride that includes moieties of DOPA, a catechol derivative. These materials display bioadhesive properties superior to conventional bioadhesives used in therapeutic and diagnostic applications. In certain embodiments, the bioadhesive coating swells slightly and adheres to the mucosa in the aqueous environment of the gastrointestinal tract. As a result, the bioavailability of therapeutic agents is enhanced through increased residence time at the target absorption site. In certain embodiments, the bioadhesive dosage formulations described herein maintain a constant surface area for release of therapeutic agents at the target site.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a longitudinal section of a longitudinally compressed tablet containing a drug and excipients, and optionally permeation and/or dissolution enhancers, combined in a single monolithic layer. The tablet is coated peripherally, optionally with a
5 bioadhesive such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 2 is a longitudinal section of a longitudinally compressed tablet containing two different drugs (or same drug in different amounts) and excipients, and optionally permeation and/or dissolution enhancers, composed in two monolithic layers. Each layer
10 contains one drug. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 3 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in
15 four monolithic layers. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 4 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in
20 two monolithic layers with a slow dissolving or insoluble plug at one end. The tablet is coated, optionally peripherally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 5 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and dissolution enhancers, disposed in
25 two monolithic layers, separated by one or more slow-dissolving passive matrices, with an insoluble plug at one end. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 6 is a longitudinal section of a longitudinally compressed tablet containing
30 drugs and excipients, and optionally permeation and dissolution enhancers, disposed in two monolithic layers, which are separated by a fast-dissolving passive matrix. The tablet

is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 7 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in two monolithic layers, which are separated by a fast-dissolving active matrix containing one or more active drugs. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers). The active matrix is left unsealed.

Figure 8 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, combined in a single matrix in which three pre-compressed reservoirs of drugs are embedded. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 9 is a longitudinal section of a longitudinally compressed tablet that functions as an osmotic delivery system. Drugs and excipients, optionally including permeation and/or dissolution enhancers, are combined in a single core matrix. The periphery of the tablet is coated first entirely coated with a semi-permeable membrane, and then partially or completely coated, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers). One side of the tablet has a micrometer-sized orifice or exit port for drug release.

Figure 10 is a longitudinal section of a longitudinally compressed tablet that functions as a “push-pull” osmotic delivery system. The core contains one layer of drugs and another layer of swelling polymer to push the drug out of the tablet at controlled rates. Permeation and/or dissolution enhancers are optionally added to the core. The periphery of the tablet is first entirely coated with a semi-permeable membrane, and then partially or completely coated, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 11 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, combined in one monolithic layer, plugged from the two ends by slow dissolving passive

matrices. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 12 is a longitudinal section of a longitudinally compressed tablet that functions as an osmotic delivery system. Drugs and excipients, optionally including permeation and/or dissolution enhancers, are combined in a single core matrix. The periphery of the tablet is first entirely coated with a semi-permeable membrane, and then partially or completely coated, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 13 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a single monolithic layer. Particulates are optionally coated with release rate controlling polymer(s). The matrix may be optionally a passive matrix. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 14 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in three monolithic layers. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers). Drug is released from one end of the tablet in this design.

Figure 15 is a longitudinal section of a longitudinally compressed tablet that functions as a “push-rod” osmotic delivery system. The core contains one layer of drugs and another layer of swelling polymer to push the drug out of the tablet at controlled rates. Permeation and/or dissolution enhancers are optionally added to the core. The periphery of the tablet is first partially coated with a semi-permeable membrane, and then partially coated, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 16 is a longitudinal section of a longitudinally compressed tablet containing drugs, excipients, and an optionally bioadhesive polymer, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a single monolithic layer. The matrix may be optionally a passive matrix. The tablet is

coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 17 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a single monolithic layer. Particulates are coated with an enteric coating or other rate-controlling polymer. The matrix may be optionally a passive matrix. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 18 is a longitudinal section of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a single monolithic layer. Particulates are coated with bioadhesive polymer, which is further coated with an enteric coating or other rate-controlling polymer. The matrix may be optionally a passive matrix. The tablet is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 19 is a longitudinal section of a bullet-shaped inner core containing drugs and excipients, and optionally permeation and/or dissolution enhancers. The inner core is coated peripherally, optionally with a bioadhesive polymer such as Spheromer™ II (anhydride oligomers blended with pharmaceutical polymers).

Figure 20 depicts a formulation having a slow-eroding drug-containing core **201**, a capsule body **202**, a capsule cap **203**, and an optionally bioadhesive coating **204**. The capsule cap and body may be made of any suitable material, such as gelatin.

Figure 21 portrays a formulation having a slow-eroding drug-containing core **301**, a fast dissolving (e.g., immediate release) core **302**, a capsule body **303**, a capsule cap **304**, and an optionally bioadhesive coating **305**. The capsule cap and body may be made of any suitable material, such as gelatin.

Figure 22 illustrates a formulation having a slow-eroding drug-containing core **401**, a capsule **402**, an orifice **404**, and an optionally bioadhesive coating **403**, which may be microporous. The capsule cap and body may be made of any suitable material, such as

gelatin. The capsule cap may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create the orifice 404 without damaging the capsule 402.

Figure 23 depicts a formulation having a slow-eroding drug-containing core 501, a capsule 503, a push plug 502, an plurality of orifices 505 extending circumferentially around the capsule, and an optionally bioadhesive coating 504, which may be microporous. The capsule may be made of any suitable material, such as gelatin. The capsule may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create the orifice 505 without damaging the capsule 503.

Figure 24 portrays a formulation having a liquid drug-containing core 601, a capsule 602, a barrier layer 603, an orifice 605, and an optionally bioadhesive coating 604, which may be microporous. The capsule may be made of any suitable material, such as gelatin. The barrier layer 603 may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create the orifice 605 without damaging the capsule 602.

Figure 25 illustrates a formulation having a slow-eroding core 702 containing a drug or prodrug in its salt form, a slow-eroding core 703 containing a drug or prodrug in its neutral form, and an optionally bioadhesive cylinder 701.

Figure 26 shows a formulation having a slow-eroding core 802 containing a drug or prodrug in its salt form, a core 804 (which may be a slow- or rapid- (e.g., immediate release) eroding composition) containing a drug or prodrug in its neutral form, enteric plugs 803, and an optionally bioadhesive cylinder 801.

Figure 27 depicts a formulation having a slow-eroding core 902 containing a drug or prodrug in its salt form, enteric-coated multiparticulate beads 903, which contain the drug or prodrug in its neutral form, dispersed in a matrix (which may be a slow- or rapid- (e.g., immediate release) eroding composition), and an optionally bioadhesive cylinder 901.

Figure 28 portrays a formulation having a slow-eroding core 1002 containing a drug or prodrug in its salt form, enteric-coated multiparticulate beads 1005, which contain the drug or prodrug in its neutral form, dispersed in a matrix (which may be a slow- or rapid- (e.g., immediate release) eroding composition), enteric plugs 1003, a non-bioadhesive cylinder 1004, and an optionally bioadhesive cylinder 1001.

Figure 29 portrays a formulation having a slow-eroding core **1103** containing a drug or prodrug in its salt form, enteric/rate controlling -coated multiparticulate beads **1105**, which contain the drug or prodrug in its neutral form, dispersed in a matrix (which may be a slow- or rapid- (e.g., immediate release) eroding composition), enteric plugs **1104**, a non-bioadhesive (impermeable or rate controlling cylinder) **1101**, enteric plug **1103**, containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a monolithic layer. Particulates are optionally coated with release rate controlling polymer(s). The matrix may optionally be a passive matrix, a fast dissolving core **1104** and a capsule cap **1102**. The capsule cap and body may be made of any suitable material, such as gelatin.

Figure 30 presents a longitudinal section **1200** of a longitudinally compressed tablet containing three layers, top one **1204** being the IR layer, center layer **1203** being the eroding polymer layer (e.g., hydroxypropyl cellulose) and a bottom XR layer **1201**. The tablet is coated peripherally **1205** with a rate controlling polymer, such as ethylcellulose. Drug is released from both ends **1206A-B** of the tablet in this design, as described in Example 35 and 36.

Figure 31 displays a longitudinal section **1300** of a longitudinally compressed tablet containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in three monolithic layers **1301-1303**. The tablet is coated peripherally with a rate controlling polymer **1304**, such as ethylcellulose. Drug is released from both ends **1305A-B** of the tablet in this design, as described in Examples 39, 42, 44 and 45.

Figure 32 shows the *in vitro* dissolution profile of POLYROD tablets, 600mg (lot#608-164) in purified water containing 1% SLS at 60 rpm.

Figure 33 shows the *in vitro* dissolution profile of POLYROD tablets, 600 mg (lot # 609-025) in purified water containing 1% SLS at 60 rpm.

Figure 34 shows the pharmacokinetic performance of IR/XR tablets, 600 mg (lot # 609-025) given once daily in fed beagles.

Figure 35 shows the *in vitro* dissolution profile of POLYROD tablets, 600 mg (lot # 609-070) in purified water containing 1% SLS at 60, 75 and 100 rpm.

Figure 36 shows the *in vitro* dissolution performance of XR tablets, 600 mg (lot # 609-136 – 609-139) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 37 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 610-024, 610-025 and 610-026) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 38 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 701-105) using USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 39 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 611-006) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 40 shows the pharmacokinetic performance of IR/XR 600mg tablets in fed beagles.

Figure 41 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 611-035) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 42 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 611-027) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 43 shows the *in vitro* dissolution performance of IR/XR tablets, 600 mg (lot # 609-107) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

Figure 44 shows the *in vitro* dissolution performance of IR/XR tablets, 500 mg (lot # 701-116) using a USP type II Apparatus, with purified water containing 1% SLS at 60 rpm.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are pharmaceutical formulations having advantageous release characteristics. These formulations are typically for oral dosage.

In certain embodiments, the pharmaceutical formulations are coated with bioadhesive materials. These bioadhesive materials may be used in a wide variety of drug delivery and diagnostic applications. In preferred embodiments, the bioadhesive material is applied as a coating to any longitudinally compressed core, which forms the inner core of a bioadhesive, rate-controlled oral dosage formulation.

The term "rate-controlled" refers to controlling the release of an agent to provide a pre-determined release profile of each agent. For example, a drug can be released over a period of 1 hour, 2 hours, or more than 3 hours and/or can be released after a period of 1 hour, 2 hours, or more than 3 hours. The inner core may comprise a therapeutic, prophylactic, or diagnostic agent and may further comprise excipients, permeation enhancers, and/or dissolution enhancers.

In one embodiment, the present invention is an oral dosage form, such as a tablet, for oral delivery of a drug, comprising a compressed core including a drug to be delivered gastrointestinally, and an optionally bioadhesive polymeric coating applied to at least one surface of the dosage form. The coating preferably provides the dosage form with a fracture strength of at least 100 N/m² as measured on rat intestine, and, in certain embodiments, the dosage form optimally has a gastrointestinal retention time of at least 4 hours in a fed beagle dog model during which the drug is released from the dosage form. In another embodiment, the dosage form optimally has a gastrointestinal retention time of at least 3 hours in a fasted beagle dog model during which the drug is released from the dosage form. In certain embodiments, the bioadhesive polymer coating further includes metal compounds, low molecular weight oligomers or a combination thereof that enhance the mucosal adhesion of the synthetic polymer coating.

In preferred embodiments, a dosage form is prepared by extrusion of an optionally bioadhesive cylinder followed by insertion of an inner core composition and fusing the two units together.

In another embodiment, the invention is a drug eluting device for oral delivery of a drug, which includes a reservoir having a drug-containing compressed core contained therein, one or more orifices or exit ports through which drug from the core can elute from the device, and an optionally bioadhesive polymeric coating, applied to at least one surface of the device. The coating preferably provides the device with a fracture strength

of at least 100 N/m² as measured on rat intestine, and, in certain embodiments, the device optimally has a gastrointestinal retention time of at least 4 hours in a fed beagle dog model during which the drug is released from the device. In another embodiment, the tablet optimally has a gastrointestinal retention time of at least 3 hours in a fasted beagle dog model during which the drug is released from the device. In certain embodiments, the coating further includes metal compounds, low molecular weight oligomers or a combination thereof that enhance the mucosal adhesion of the coating. In a preferred embodiment, a coating does not substantially swell upon hydration.

In another embodiment, the present invention is an orally administrable, multi-layer, pharmaceutical tablet having an inner and one or more outer layers, each comprising a drug (e.g., a drug including a valproic moiety such as sodium valproate, divalproex sodium, valproic acid, etc.) admixed with one or more excipients, and an optionally bioadhesive polymeric coating applied to at least one surface of the tablet. At least one of the excipients is hydrophobic, although such excipient is not required in each layer. Additional outer layers (i.e., layers other than the inner and outer layers specified above) are optionally free of the drug.

In certain embodiments, the invention relates to a formulation that is suitable for rectal or vaginal administration. In certain such embodiments, the formulation is encapsulated, e.g., in a gelatin capsule or any other suitable capsule that will break down to release drug in a vaginal or rectal environment such that the encapsulated formulation is released from the capsule after insertion into the vagina.

In certain embodiments, the present invention provides methods for improving the bioadhesive properties of drug delivery systems such as tablets and drug eluting devices. The invention also provides methods for improving the adhesion of drug delivery systems to mucosal membranes including membranes of the gastrointestinal tract. In such embodiments, the polymeric drug delivery systems of the invention have an improved ability to bind to mucosal membranes, which can be used to deliver a wide range of drugs or diagnostic agents in a wide variety of therapeutic applications, and have an improved ability for uptake across the intestinal mucosa.

Oral Drug Delivery Formulations

Bioadhesive materials described herein may be used in a wide variety of drug delivery and diagnostic applications. Bioadhesive materials may be formed into microparticles, such as microspheres or microcapsules, or may be a coating on such microparticles. In certain embodiments, the material is applied as a coating to any longitudinally compressed tablet.

The overall shape of the device is typically designed to be compatible with swallowing. For example, in one embodiment, the active agent core is longitudinally compressed to form a capsule-shaped tablet, which is encapsulated and sealed in an optionally bioadhesive polymeric cylinder. The compressed tablet may comprise one or more than one active agent and may further comprise excipients and absorption enhancers (e.g., permeation and/or dissolution enhancers).

The subject formulas are suitable for the delivery of any kind of therapeutic, prophylactic or diagnostic agent in a wide variety of immediate and controlled-release formulations. Also, the subject invention provides for the delivery of more than one drug in a single dosage formulation. For example, different drugs may be included in one heterogeneous layer of a solid dosage formulation. Alternatively, different drugs, for example, a highly aqueous-soluble drug and a poorly aqueous-soluble drug, may be included in discrete layers of a compressed, multilayer solid dosage formulation, such as a compressed, multilayer tablet. In some instances, a compressed, multilayer tablet, for example, may comprise a combination of homogeneous and heterogeneous drug layers, such as a bilayer tablet that comprises one drug in one layer and a blend of two different drugs in the second layer.

The formulations of the invention advantageously have one or more of the following features. In certain embodiments, the formulations have complete or nearly complete (greater than 90%, 95%, 97%, 98% or 99%) drug release. In certain embodiments, the formulations exhibit a drug loading in excess of 60%, 70% or 80%, typically up to about 90%. In certain embodiments, the formulations are useful in achieving different release profiles for all four classes of drugs described herein, including one or more of a zero order release profile, an ascending release profile, a two or multiple release profile and a delayed release.

The different drug formulations in each layer may be designed such that the drug release profiles are the same or differ to one another. For example, single dosage forms of the invention can comprise more than one drug (e.g., two), wherein each drug is formulated for release in a manner that differs to the other drug, such as dosage formulations that comprise a combination of immediate release (IR), controlled release (CR), and/or ascending or descending drug release formulations. In such embodiments, each individual drug may be segregated in its own layer, or two or more drugs may be present in the same layer. Even in the latter arrangement, different release rates may be possible, for example, if one drug is present as a soluble powder and the other is present in particles, which may be formulated to be slow releasing or coated with a rate-controlling membrane. Each layer may further be coated with one or more coatings or layers (e.g., polymers or other suitable materials), such as an impermeable layer that restricts release to certain defined ports, a permeable layer that controls the rate of release through the layer, an optionally bioadhesive coating that may slow passage of that layer independent of other layers in the dosage form, or any combination thereof.

In some embodiments, a drug or drugs may be formulated for release in a pulsatile fashion. For example, two or more immediate-release formulations of a drug may be embedded within a slow-dissolving matrix, such that drug is released (e.g., in bursts) at discrete intervals as the surrounding matrix dissolves over time.

In any layer, the active agent may be dispersed evenly throughout, e.g., mixed as a powder with any excipients and additives to form a uniform, monolithic layer, or may be present as particles or granules dispersed in an excipient or other matrix. In addition to the active agent, layers may contain standard pharmaceutically acceptable excipients, biocompatible polymers (e.g., for controlling the rate of release), dispersants, disintegrants, superdisintegrants, or other additives that modify the physical, chemical, or biological properties of the layer. A layer may further contain additives that enhance the effect of the agents in that layer, such as permeability enhancers, efflux pump inhibitors, solubilizing agents, and other such adjuvants.

The solid dosage formulations of the invention preferably comprise a compressed inner core, on which an optionally bioadhesive polymer is disposed on at least one surface. When present, it is expected that the bioadhesive polymer will promote retention

of the dosage formulation at a target site of absorption in the gastrointestinal tract. The optionally bioadhesive polymer can be applied in any suitable way. Preferably, a pre-compressed core of the invention is inserted into an optionally bioadhesive polymer tube. Various embodiments of the instant invention are described in greater detail below.

5 One of skill in the art will understand that, as the term is used in this application, that when a surface is "coated" with a layer, it is not necessary that the entire surface be covered, only that at least a portion of that surface bears the specified layer, unless the context indicates that entire surface must be covered to achieve the desired effect.

10 In a preferred embodiment, illustrated in Figure 1, the solid oral dosage form is a longitudinally compressed tablet 10 containing a single drug or more than one drug, excipients, and optionally permeation and/or dissolution enhancers, combined in a single monolithic layer 11. The tablet is sealed peripherally with a layer of optionally bioadhesive composition 12 leaving the upper and lower sides 13A and 13B of the tablet available for drug release. First-order and, more advantageously, zero-order release
15 profiles are achievable with this tablet design. It is feasible to create different drug release rates by changing the composition of the core matrix.

In another embodiment, illustrated in Figure 2, the solid oral dosage form is a longitudinally compressed tablet 20 containing a drug or two different drugs or two different compositions of the same drug (e.g., concentration gradient), excipients, and
20 optionally permeation and/or dissolution enhancers, disposed in two monolithic layers 21 and 22. The tablet is sealed peripherally with a layer of optionally bioadhesive composition 23 leaving the upper and lower sides 24A and 24B of the tablet available for drug release. First-order and, more advantageously, zero-order release profiles are achievable with this tablet design. In this embodiment, the tablet can be designed to
25 provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from one layer and extended release (ER) of one or more soluble drugs from the other layer. Various drug release rates can be achieved by changing the composition and/or configuration of IR and ER matrices.

30 In another embodiment, illustrated in Figure 3, the solid oral dosage form is a longitudinally compressed tablet 30A containing a single drug, two or more different drugs, or two different concentrations of a single drug, in combination with excipients,

and optionally permeation and/or dissolution enhancers, in a single monolithic layer (not shown) or multiple monolithic layers **31-34**. The tablet is sealed peripherally with a layer of optionally bioadhesive composition **35** leaving the upper and lower sides **36A** and **36B** of the tablet available for drug release. First-order and, more advantageously, zero-order release profiles are achievable with this tablet design. The tablet can be designed to provide various extended release (ER) rates for the drugs by changing the composition of the core matrix or by changing the configuration of their respective layers. In a related embodiment, illustrated in Figure 14, the tablet **140** is sealed peripherally with a layer of optionally bioadhesive composition **144** leaving only the upper side **145** of the tablet available for drug release.

In another embodiment, illustrated in Figure 4, the solid oral dosage form is a longitudinally compressed tablet **40** containing one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, disposed in two or more monolithic layers **41** and **42** blocked at one end by a slow-dissolving or non-dissolving passive matrix (also referred to herein as "plug") **43**. The tablet is coated peripherally with a layer of optionally bioadhesive composition **44** leaving the upper side **45** of the tablet available for drug release. First-order and, more advantageously, zero-order release profiles are achievable with this tablet design. The tablet can be designed to provide different immediate release or extended release rates for drugs by changing the composition of the drug layers, or by changing the formulation of the plug.

In another embodiment, illustrated in Figure 5, the solid oral dosage form is a longitudinally compressed tablet **50** containing two drugs, excipients, and optionally permeation and/or dissolution enhancers, disposed in two or three (not shown) **51** and **52** monolithic layers which are separated by one or more slow dissolving passive matrices **53a** and blocked from one end by one insoluble plug **54a**. Alternatively, two monolithic layers **51** and **52** containing different drugs can be separated by one insoluble plug **54b** and blocked from one end by one slow dissolving passive matrix **53b**. The tablet is coated peripherally with a layer of optionally bioadhesive composition **55** leaving the upper side **56** of the tablet available for drug release. First-order and, more advantageously, zero-order release profiles are achievable with this tablet design. The tablet can be configured to provide different immediate release or extended release rates for drugs in a two-pulse

or three-pulse fashion by changing the composition or configuration of the drug layers, or by changing the formulation or configuration of the slow dissolving matrices and the insoluble plug.

In the embodiment illustrated in Figure 6, the solid oral dosage form is a longitudinally compressed tablet **60** containing one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, disposed in two or three (not shown) monolithic layers **61** and **62** which are separated by one or more fast dissolving passive matrices **63**. The tablet is coated peripherally with optionally bioadhesive composition **64** sealing the drug layers while leaving the passive matrix(s) unsealed. The upper and lower sides of the tablet **65A** and **65B** are available for drug release. The tablet splits into two or more segments upon the complete dissolution of the fast dissolving passive matrix **63**, thereby creating new surfaces for dissolution, resulting in an increased rate of drug release from layers **61** and **62**.

In another embodiment, illustrated in Figure 7, the solid oral dosage form is a longitudinally compressed tablet **70** containing two or more different drugs, excipients, and optionally permeation and/or dissolution enhancers, composed in two or three (not shown) monolithic layers **71** and **72** which are separated by one or more drug-containing layers **73** the latter being capable of providing an immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs. The tablet is coated peripherally with an optionally bioadhesive composition **74** sealing the drug layers **71** and **72**, while leaving the IR layer **73** unsealed. The upper and lower sides of the tablet **75A** and **75B** are available for drug release. The tablet splits into two or more segments upon the complete dissolution of the middle IR layer **73**, thereby creating new surfaces for dissolution, resulting in an increased rate of drug release from layers **71** and **72**.

In yet another embodiment, illustrated in Figure 8, the delivery system is a longitudinally compressed tablet **80** containing pre-compressed inserts **81-83** of a drug or two drugs, excipients, and optionally permeation and/or dissolution enhancers embedded in a matrix **84** of drugs, excipients, and optionally permeation and/or dissolution enhancers. The matrix may optionally be a passive matrix. The tablet is coated peripherally with a layer of optionally bioadhesive composition **85** leaving the upper and lower edges **86A** and **86B** of the tablet available for drug release. The kinetics of drug

release are controlled by the geometry of the inserts. Zero- and first-order release profiles are achievable with this tablet design, and it is possible to have different release rates for permeation enhancer and drug by changing the configuration of their respective inserts.

In still yet another embodiment, the drugs are delivered from an elementary osmotic delivery system. Figure 9 illustrates the cross section of a longitudinally compressed tablet **90** based on osmotic controlled delivery containing drugs, excipients, and optionally permeation and/or dissolution enhancers, composed in a single core matrix **91**. The tablet is coated with a semipermeable membrane **92**. One or both sides of the tablet may be perforated, such as by using a micro-drill or a laser beam to make a micrometer-sized orifice **93**. The tablet is sealed peripherally with a matrix of optionally bioadhesive composition **94** leaving the orifice **93** and upper and/or lower sides **95A** and **95B** of the tablet available for water uptake. The semi-permeable membrane allows permeation of water into the matrix, leading to the dissolution of drug and creation of osmotic pressure. An increase of osmotic pressure will push the drug slurry out of the device through the one or more orifice(s) and membrane at controlled rates. Zero-order release profiles are achievable with this tablet design. The osmotic system may also be designed in such a manner that the drug release is from the entire surface **95A**, and this system is referred to herein as a "Push Rod" system.

A cross section of an osmotic delivery system is illustrated in Figure 10. The osmotic delivery system is of the "push-pull" design **100A** and contains drugs and osmotic agents **101** to draw water across a semi-permeable membrane **102** and a swelling polymer **103** to push the drug out of the device at controlled rates. Drug sides of the tablet may be perforated, such as by using a micro-drill or a laser beam to make a micrometer-sized orifice **104**. Optionally, the drug layer **101** is separated from the push layer **103** by an "insoluble plug" **105**. The purpose of this insoluble plug is to ensure that there is complete drug release from the system. In a traditional "push-pull system", the drug may get trapped within the swollen push layer resulting in high residual drug in the system. The device is peripherally coated with an optionally bioadhesive composition **106**, leaving the orifice **104**, the upper edge **107**, and lower edge of the tablet available for drug release. In a related embodiment, illustrated in Figure 15, the osmotic delivery

system is of a "push-rod" design **150**. In this embodiment, the upper edge **156** is not covered by the semi-permeable membrane **152**.

In another embodiment, illustrated in Figure 11, the solid oral dosage form is a longitudinally compressed tablet **110** containing one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, combined in one monolithic layer **111** which is plugged from the two ends by slow eroding passive matrices **112A** and **112B**. The tablet is coated peripherally with a layer of optionally bioadhesive composition **113** leaving the upper and lower sides **114A** and **114B** of the tablet available for dissolution. Upon dissolution of the slow eroding passive layers **112A** and **112B** the active layer **111** is exposed to the surrounding environment, releasing the drug in an immediate release or extended release mode. The tablet can be designed to release its contents in a time-controlled manner with different delayed periods by changing the composition of the passive layers.

In another embodiment, the one or more drugs are delivered from a microporous/macroporous based osmotic delivery system. Figure 12 illustrates the cross-section of a longitudinally compressed tablet **120** containing one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, composed in a single core matrix **121**. The tablet is coated with a semi-permeable membrane **122** comprising a hydrophobic polymer and one or more hydrophilic pore formers or wicking agents. The tablet is sealed peripherally with a matrix of optionally bioadhesive composition **123** leaving the upper and lower sides **124A** and **124B** of the tablet available for water uptake and drug release. The hydrophilic pore formers or wicking agents in the semi-permeable membrane **122** dissolve in an aqueous environment, creating micro- or macro-pores or channels on the semi-permeable membrane. The micro- or macro-porous membrane allows permeation of water into the matrix, leading to the dissolution of drug and creation of osmotic pressure. The increase of osmotic pressure will push the drug out of the device through the micro- or macrochannels at controlled rates. Zero-order release profiles are achievable with this tablet design.

In yet another embodiment, illustrated in Figure 13, the solid oral dosage form is a longitudinally compressed tablet **130A** that comprises one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, in a single monolithic matrix **131**.

The matrix contains a plurality of particles 132 of a drug in combination with excipients, and optionally permeation and/or dissolution enhancers. The said particles are optionally coated with one or more layers of release rate-controlling polymers 133 and 134. The matrix may be optionally a passive matrix containing a filler and “cushioning component”. A cushioning material would preferentially absorb the forces exerted during the compaction of the inner core, thereby providing protection to the coated particles. The tablet is sealed peripherally with a layer of optionally bioadhesive composition 135 leaving the upper and lower sides 136A and 136B of the tablet available for drug release. First-order and, more advantageously, zero-order release profiles are achievable with this tablet design. It is feasible to create different release rates for drugs by changing the composition of the core matrix, embedded core particles, or rate-controlling polymer-coated multiparticles. In a related embodiment, illustrated in Figure 16, the particles 162 are formulated with bioadhesive polymers. In some embodiments, illustrated in Figure 17, the particles further comprise an enteric coating or other rate-controlling polymer 173. In another embodiment, illustrated in Figure 18, the particles comprise one or more drugs and excipients 182 and are coated with a bioadhesive polymer 183, which is coated with an enteric or other rate-controlling polymer 184.

The particles can be micro- or nanoparticles. The term “microparticles” is art-recognized, and includes microspheres and microcapsules, as well as structures that may not be readily placed into either of the above two categories, all with dimensions on average of less than about 1000 microns. The term “microspheres” is art-recognized, and includes substantially spherical colloidal structures having a size ranging from about one or greater up to about 1000 microns. In general, “microcapsules”, also an art-recognized term, may be distinguished from microspheres, because microcapsules are generally covered by a substance of some type, such as a polymeric formulation, e.g., a bioadhesive coating or rate-controlling polymer layer. If the structures are less than about one micron in diameter, then the corresponding art-recognized terms “nanoparticle,” “nanosphere,” and “nanocapsule” may be utilized. In certain embodiments, the nanospheres, nanocapsules and nanoparticles have an average diameter of about 500, 200, 100, 50 or 10 nm.

Other release rates that can be achieved with the dosage formulations of the present invention include ascending as well as descending drug release profiles. For example, in some embodiments, the inner core comprises two or more layers (e.g., a layer comprising the drug to be released and a “push” layer), from which the therapeutic agent is released at an increasing rate through an orifice or exit pore in the optionally bioadhesive layer. In some embodiments, the optionally bioadhesive layer is further coated with a drug formulation that dissolves quickly for immediate release of the drug while the drug disposed in the inner core is released at an escalating rate. In some embodiments, the geometry of the dosage formulation contributes to the ascending or descending drug release profile, for example, dosage formulations in a semi-ellipsoid shape (e.g., bullet-shaped). Such a dosage formulation is illustrated in Figure 19.

In the embodiment illustrated in Figure 19, the dosage form **190** is suitable as a suppository and comprises a bullet-shaped inner core **192** composed of one or more drugs, excipients, and optionally permeation and/or dissolution enhancers, combined in a single monolithic layer. The dosage formulation is sealed peripherally with a layer of optionally bioadhesive composition **191**, leaving the wide, upper side **193** of the dosage form available for drug release. As drug is released, the surface area of the inner core decreases, thereby releasing less drug over time. Thus, descending drug release profiles are achievable with this solid dosage form design. Alternatively, in some embodiments, the dosage formulation is sealed peripherally with a layer of optionally bioadhesive composition, leaving the narrow, lower end available for drug release. In this embodiment, the surface area of the inner core increases as drug is released, thereby releasing increasing amounts of drug over time. Accordingly, ascending drug release profiles are achievable in this embodiment. In some embodiments, the inner core comprises more than one layer of drug, excipients and permeation and/or dissolution enhancers, e.g., a trilayer dosage form design.

The embodiment illustrated in Figure 20 is a formulation having a slow-eroding drug-containing core **201**, embedded in a capsule body **202**, which has an optionally bioadhesive coating **204**. A capsule cap **203** seals the open end of the capsule. The capsule cap and body may be made of any suitable material, such as gelatin, starch, HPMC, and pullulan. Optionally, the capsule body may be coated with a release rate

controlling layer before applying the optionally bioadhesive coating. Optionally the optionally bioadhesive coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability. In additional embodiments, the optionally bioadhesive body of the capsule may be prepared by conventional methods of manufacturing of capsules (pin dipping).

The embodiment portrayed in Figure 21 is a formulation having a slow-eroding drug-containing core 301, and a fast dissolving (e.g., immediate release) core 302, embedded from the slow-eroding core 301 in a capsule body 303, which is coated with an optionally bioadhesive coating 305. A capsule cap 304 seals the fast-dissolving core 302 as well as the open end of the capsule. The capsule cap and body may be made of any suitable material, such as gelatin, starch, HPMC, and pullulan. Optionally, the capsule body may be coated with a release rate controlling layer before applying the optionally bioadhesive coating. Optionally the optionally bioadhesive coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability. In additional embodiments, the optionally bioadhesive body of the capsule may be prepared by conventional methods of manufacturing of capsules (pin dipping).

The embodiment illustrated in Figure 22 is a formulation having a slow-eroding drug-containing core 401, embedded in a capsule body 402. The capsule is coated entirely with an optionally bioadhesive coating 403, which may be microporous. The capsule cap may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create the orifice 404 without damaging the cap. The capsule cap and body may be made of any suitable material, such as gelatin, starch, HPMC, and pullulan. Optionally, the capsule may be coated with a release rate controlling layer before applying the optionally bioadhesive coating (or the optionally bioadhesive coating may be absent when the release rate controlling layer is present). Optionally, the capsule may be coated with a barrier layer containing the laser-resistant material before applying the optionally bioadhesive coating and/or the release rate controlling layer. Optionally, the release rate controlling layer and/or optionally bioadhesive coating may have plasticizers, pore formers, and other polymer to regulate their rigidity and permeability.

The embodiment illustrated in Figure 23 is a formulation having a slow-eroding drug-containing core 501, embedded along with a push plug 502, in a capsule 503. The

capsule is sealed entirely with an optionally bioadhesive coating **504**, which may be microporous. The coated capsule has a plurality of orifices or slits **505** extending circumferentially around the capsule. The capsule may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create the orifice **505** without damaging the capsule **503**. The capsule cap and body may be made of any suitable material, such as gelatin, starch, HPMC, and pullulan. Optionally, the capsule may be coated with a release rate controlling layer before applying the optionally bioadhesive coating, in which case the optionally bioadhesive coating may be absent. Optionally, the optionally bioadhesive coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

The embodiment depicted in Figure 24 is a formulation having a liquid drug-containing core **601**, filled in a capsule **602**, entirely sub-coated with a barrier layer **603** and top-coated with an optionally bioadhesive coating **604**, which may be microporous. The barrier layer **603** may comprise a laser-resistant material, such as a metal salt, so that a laser can be used to create an orifice **605** without damaging the capsule **602**. The capsule cap and body may be made of any suitable material, such as gelatin, starch, HPMC, and pullulan. Optionally, the capsule may be coated with a release rate controlling layer before applying the optionally bioadhesive coating, in which case the optionally bioadhesive coating is absent. Optionally, the optionally bioadhesive coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

The embodiment illustrated in Figure 25 is a formulation having a slow-eroding core **702** containing a drug or prodrug in its salt form, and a slow-eroding core **703** containing a drug or prodrug in its neutral (base) form. The cores are sealed peripherally with an optionally bioadhesive cylinder **701**. Optionally, the core may be coated peripherally with a release rate controlling layer before sealing within the optionally bioadhesive cylinder. Optionally, the optionally bioadhesive cylinder may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

The embodiment shown in Figure 26 is a formulation having a slow-eroding core **802** containing a drug or prodrug in its salt form, and a core **804**, which may be a slow- or rapid- (e.g., immediate release) eroding composition, containing a drug or prodrug in its

neutral (base) form. The cores are separated from each other and from the outside on core 804 end by enteric plugs 803. An optionally bioadhesive cylinder 801 seals the cores peripherally. Optionally, the core may be coated peripherally with a release rate controlling layer before sealing within the optionally bioadhesive cylinder. Optionally, the optionally bioadhesive cylinder may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

The embodiment depicted in Figure 27 is a formulation having a slow-eroding core 902 containing a drug or prodrug in its salt form, and enteric-coated multiparticulate beads 903, which contain the drug or prodrug in its neutral (base) form, dispersed in a matrix, which may be a slow- or rapid- (e.g., immediate release) eroding composition. An optionally bioadhesive cylinder 901 seals the cores peripherally. Optionally, the core may be coated peripherally with a release rate controlling layer before sealing within the optionally bioadhesive cylinder. Optionally, the optionally bioadhesive cylinder may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

The embodiment portrayed in Figure 28 is a formulation having a slow-eroding core 1002 containing a drug or prodrug in its salt form, and enteric-coated multiparticulate beads 1005, which contain the drug or prodrug in its neutral (base) form, dispersed in a matrix (which may be a slow- or rapid- (e.g., immediate release) eroding composition). The cores are separated from each other and from the outside on core 1005 end by enteric plugs 1003. A non-bioadhesive cylinder 1004 seals the core 1005 and an optionally bioadhesive cylinder 1001 seals the core 1002. Optionally, the core 1002 may be coated peripherally with a release rate controlling layer before sealing within the optionally bioadhesive cylinder. Optionally, the optionally bioadhesive cylinder may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability.

Figure 29 portrays a formulation having a slow-eroding core 1103 containing a drug or prodrug in its salt form, enteric/rate controlling -coated multiparticulate beads 1105, which contain the drug or prodrug in its neutral form, dispersed in a matrix (which may be a slow- or rapid- (e.g., immediate release) eroding composition), enteric plugs 1104, a non-bioadhesive (impermeable or rate controlling cylinder) 1101, enteric plug 1103, containing drugs and excipients, and optionally permeation and/or dissolution enhancers, disposed in multiparticulates embedded in a monolithic layer. Particulates are

optionally coated with release rate controlling polymer(s). The matrix may optionally be a passive matrix, a fast dissolving core **1104** and a capsule cap **1102**. The capsule cap and body may be made of any suitable material, such as gelatin.

5 In another embodiment, as illustrated in Figure 30, a longitudinally compressed tablet **1200** contains three layers. The top layer **1204** is an IR layer, the center layer **1203** is an eroding polymer layer (e.g., hydroxypropyl cellulose) and the bottom layer **1201** is an XR layer. The tablet is coated peripherally **1205** with a rate controlling polymer, such as ethylcellulose. Optionally, the rate controlling polymer coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability. Drug is
10 released from both ends **1206A-B** of the tablet in this design, as described in Example 35 and 36.

In yet another embodiment, as depicted in Figure 31, a longitudinally compressed tablet **1300** contains drugs and excipients, and optionally permeation and/or dissolution enhancers, in three monolithic layers **1301-1303**. The tablet is coated peripherally with a
15 rate controlling polymer **1304**, such as ethylcellulose. Optionally, the rate controlling polymer coating may have plasticizers, pore formers, and other polymer(s) to regulate its rigidity and permeability. Drug is released from both ends **1305A-B** of the tablet in this design, as described in Examples 39, 42, 44 and 45.

In certain embodiments, the IR layers of the formulations described above include
20 a macrocrystalline active agent in combination with excipients (e.g., the excipients described in Example 44).

In certain embodiments, the XR layer of the formulations described above include a micronized active agent in combination with excipients. In certain such embodiments, the IR and XR layers are present together to provide a formulation having a rapid onset of
25 action (e.g., within one hour, 30 minutes, 20 minutes or even 10 minutes) and then a prolonged release. Suitable properties are described in U.S. Patent No. 4,772,473, the contents of which are incorporated herein by reference.

In certain of the embodiments described above, the "optionally bioadhesive" polymer, layer or coating is non-adhesive. In certain such embodiments, the polymer,
30 layer or coating is rate-controlling and/or impermeable.

In certain of the embodiments described above, the "optionally bioadhesive" polymer, layer or coating is rate-controlling and/or impermeable.

Drugs and Active Agents

5 A wide variety of drugs can be included in tablets and drug eluting devices of the invention. Such tablets and drug eluting devices typically contain at least 1 mg of a drug. These tablets and drug eluting devices can also contain at least 2 mg, at least 5 mg, at least 10 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg of a drug (e.g., 2 mg to 1000 mg).

10 Drugs suitable for use herein can be any kind of therapeutic, prophylactic or diagnostic agent, including inorganic compounds, small organic molecules (e.g., non-polymeric molecules having a molecular weight of 2000 Da or less, such as 1000 Da or less), peptides or polypeptides, polysaccharides, and nucleic acids. Active agents suitable for use herein also include flavorants, nutraceuticals, and dietary supplements.

15 Drugs may be classified using the Biopharmaceutical Classification System (BCS), which separates pharmaceuticals for oral administration into four classes depending on their solubility and their absorbability through the intestinal cell layer. According to the BCS, drug substances are classified as follows:

Class I - High Permeability, High Solubility

20 Class II - High Permeability, Low Solubility

Class III - Low Permeability, High Solubility

Class IV - Low Permeability, Low Solubility

The interest in this classification system stems largely from its application in early drug development and then in the management of product change through its life-cycle.

25 In the early stages of drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stop its development.

Class I drugs of the BCS system are highly soluble and highly permeable in the gastrointestinal (GI) tract.

30 Class II drugs are drugs that are particularly insoluble, or slow to dissolve, but that readily are absorbed from solution by the lining of the stomach and/or the intestine.

Therefore, prolonged exposure to the lining of the GI tract is required to achieve absorption. Sometimes BCS Class II drugs may be micronized to sizes less than 2 microns to increase the rate of dissolution.

Many of the known Class II drugs are hydrophobic, and have historically been difficult to administer. Moreover, because of their hydrophobicity, there tends to be a significant variation in absorption depending on whether the patient is fed or fasted at the time of taking the drug. This in turn can affect the peak level of serum concentration, making calculation of dosage and dosing regimens more complex.

Class III drugs include biologic agents that have good water solubility and poor GI permeability, such as proteins, peptides, polysaccharides, nucleic acids, nucleic acid oligomers and viruses.

Class IV drugs are lipophilic drugs with poor GI permeability. Both Class III and IV drugs are often problematic or unsuitable for sustained release or controlled release. Class III and Class IV drugs are characterized by poor biomembrane permeability and are commonly delivered parenterally. Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-physiological pH solutions. These formulations, however, can increase the systemic toxicity of the drug composition or damage body tissues at the site of administration.

In one embodiment, one or more Class I, II, III, or IV drugs are included in a compressed core of a solid oral dosage formulation, and the core is surrounded on all or part of its exterior by one or more optionally bioadhesive polymers.

In one example, the drug is selected from hormones, enzymes, antigens, digestive aids, ulcer treatments (e.g., bismuth subsalicylate optionally in combination with antibiotics effective against *H. pylori*), antihypertensives, enzyme inhibitors, antiparasitics (e.g., antimalarials such as atovaquone), spermicides, anti-hemorrhoidal treatments, and radiopaque compounds. In another example, the drug is an antifungal agent (e.g., itraconazole, fluconazole, terconazole, ketoconazole, saperconazole, griseofulvin, griseoverdin). In a further example, the drug is an antineoplastic agent. In yet another example, the drug is an antiviral agent (e.g., acyclovir). Other classes of drugs suitable for inclusion in tablets and drug eluting devices of the invention include

steroids (e.g., danazol), immunosuppressants (e.g., cyclosporine), CNS active agents, cardiovascular agents, anti-depressant agents, anti-psychotic agents, anti-epileptic agents (e.g., carbamazepine), agents for treating a movement disorder (e.g., valproic acid) and anti-migraine agents (e.g., triptans such as sumatriptan).

5 In certain preferred embodiments, the drug is selected from valproic acid or a salt thereof, acyclovir or a salt thereof, or any combination thereof. In certain such embodiments the drug is selected from valproic acid, sodium valproate, acyclovir, and sodium acyclovir, or any combination thereof.

10 In certain embodiments, the drug is a combination of valproic acid and a salt thereof, preferably sodium valproate. In certain embodiments, the drug is a combination of acyclovir and a salt thereof, preferably sodium acyclovir.

15 Preferred materials to be incorporated into the compressed tablets or drug eluting devices are drugs and imaging agents. Suitable drugs include antibiotics, antivirals (especially protease inhibitors alone or in combination with nucleosides for treatment of HIV or Hepatitis B or C), anti-parasitics (helminths, protozoans), anti-cancer agents (referred to herein as "chemotherapeutics", including cytotoxic drugs such as cisplatin and carboplatin, BCNU, 5FU, methotrexate, adriamycin, camptothecin, and taxol), anti-TNF (tumor necrosis factor) agents, antibodies and bioactive fragments thereof (including humanized, single chain, and chimeric antibodies), antigen and vaccine formulations, 20 peptide drugs, anti-inflammatories, and oligonucleotide drugs (including antisense, aptamers, ribozymes, external guide sequences for ribonuclease P, and triplex forming agents).

25 Other suitable drugs include valacyclovir, gabapentin, metformin, pioglitazone, glipizide, rosiglitazone, carbidopa, caffeine, fluvastatin, ketoprofen, metoprolol, naproxen, propranolol, theophylline, verapamil, diltiazem, levodopa CR, divalproex sodium, digoxin, spironolactone, ibuprofen, neomycin B, captopril, atenolol, caspofungin, clorothiazide, tobramycin, cyclosporin, tacrolimus, and paclitaxel.

30 Examples of other useful drugs include ulcer treatments such as CarafateTM from Marion Pharmaceuticals, neurotransmitters such as L-DOPA, antihypertensives or saluretics such as Metolazone from Searle Pharmaceuticals, carbonic anhydrase inhibitors such as Acetazolamide from Lederle Pharmaceuticals, insulin like drugs such as

glyburide, a blood glucose lowering drug of the sulfonylurea class, synthetic hormones such as Android F from Brown Pharmaceuticals and Testred (methyltestosterone) from ICN Pharmaceuticals, and antiparasitics such as mebendazole (VermoxTM, Jansen Pharmaceutical).

5 Examples of useful proteins include hormones such as insulin, growth hormones including somatomedins, transforming growth factors and other growth factors, antigens for oral vaccines, enzymes such as lactase or lipases, and digestive aids such as pancreatin.

10 Antigens can be microencapsulated in one or more types of optionally bioadhesive polymer, and subsequently compressed into a tablet or filled into the reservoir of a drug eluting device, to provide a vaccine. The vaccines can be produced to have different retention times in the gastrointestinal tract. The different retention times, among other factors, can stimulate production of more than one type (IgG, IgM, IgA, IgE, etc.) of antibody.

15 In a preferred method for imaging, a radio-opaque material such as barium sulphate is coated with polymer. Radioactive materials or magnetic materials could be used in place of, or in addition to, radio-opaque materials. Examples of other materials include gases or gas-emitting compounds, which are radioopaque.

20 Optionally bioadhesive tablets and drug-eluting devices of the invention are especially useful for treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. In ulcerative colitis, inflammation is restricted to the colon, whereas in Crohn's disease, inflammatory lesions may be found throughout the gastrointestinal tract, from the mouth to the rectum. Sulfasalazine is one of the drugs that is used for treatment of the above diseases. Sulfasalazine is cleaved by bacteria within the colon to
25 sulfapyridine, an antibiotic, and to 5-amino salicylic acid, an anti-inflammatory agent. The 5-amino salicylic acid is the active drug and it is needed locally. Direct administration of the degradation product (5-amino salicylic acid) may be more beneficial. An optionally bioadhesive drug delivery system could improve the therapy by retaining the drug for a prolonged time in the intestinal tract. For Crohn's disease,
30 retention of 5-aminosalicylic acid in the upper intestine is of great importance since

bacteria cleave the sulfasalazin in the colon, the only way to treat inflammations in the upper intestine is by local administration of 5-aminosalicylic acid.

The oral dosage formulations described herein can also be used to treat type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM). The subject formulations have improved bioavailability over formulations that do not contain the optionally bioadhesive polymers. The formulations of the instant invention are designed to facilitate diffusion of drug into intestinal tissue. In some embodiments, the oral dosage formulations of the invention combine two glucose lowering drugs, such as glipizide and metformin, rosiglitazone and metformin, or pioglitazone and metformin. The combination of two drugs in one formulation functions to improve the different metabolic defects found in type 2 diabetes. For example, glipizide lowers blood glucose primarily by causing more of the body's own insulin to be released, and metformin lowers blood glucose, in part, by helping the body use its own insulin more effectively.

A class of drugs that is particularly suitable for use in the compressed tablets and drug-eluting devices of the invention, particularly the multi-layer tablets of the invention that include a hydrophobic excipient, are hygroscopic and/or deliquescent drugs. The term "hygroscopic" as used herein refers to substances that absorb significant amounts of atmospheric moisture when exposed to conditions of normal ambient relative humidity (RH), for example 10-50% RH. The term "deliquescent" refers to substances that tend to undergo gradual dissolution and/or liquefaction due to attraction and/or absorption of moisture from air when exposed to these conditions. Those skilled in the art will appreciate that over the usual range of ambient temperatures used in drug formulation, hygroscopicity and the state of deliquescence are largely temperature-independent, and that there are varying degrees of hygroscopicity and deliquescence.

Non-limiting examples of hygroscopic and/or deliquescent drugs suitable for use in the present invention include acetylcholine chloride, acetylcamitine, actinobolin, aluminum methionate, aminopentamide, aminopyrine hydrochloride, ammonium bromide, ammonium valerate, amobarbital sodium, anthiolimine, antimony sodium tartrate, antimony sodium thioglycollate, aprobarbital, arginine, aspirin, atropine N-oxide, avoparcin, azithromycin monohydrate, betahistine mesylate, betaine, bethanechol chloride, bismuth subnitrate, bupropion, butamirate, buthalital sodium, butoctamide,

cacodylic acid, calcium chloride, calcium glycerophosphate, calcium iodide, carbachol,
 carnitine, caspofungin, ceruletide, chlorophyllin sodium-copper salt, choline alfoscerate,
 choline salicylate, choline theophyllinate, cilastatin, citicoline, cobalt dichloride,
 cromolyn disodium, cupric sulfate pentahydrate, cyanocobalamin, cyclobutylol, cysteine
 5 hydrochloride, deaminooxytocin (L-isomer, anhydrous), deanol hemisuccinate,
 demecarium bromide, dexamethazone phosphate disodium salt, DL-dexpanthenol,
 dibucaine hydrochloride, dichlorophenarsine hydrochloride, diclofenac sodium,
 diethylcarbamazine citrate, dimethyl sulfoxidem, drotebanol, echinomycin, ephedrine
 (anhydrous), ergotamine, ethanolamine, fencamine hydrochloride, ferric chloride, ferrous
 10 iodide, ficin, gadobenate dimeglumine, gentamicin C complex sulfate, guanidine, heparin,
 hexadimethrine bromide, hexamethonium tartrate, hexobarbital sodium, histamine,
 hydrastine hydrochloride, hyoscyamine hydrobromide, S-[2-[(1-iminoethyl)amino]ethyl]-
 2-methyl-L-cysteine, imipramine N-oxide, isometheptene hydrochloride, isosorbide,
 levothyroxine sodium, lichenifonnins, lobeline sulfate, magnesium chloride hexahydrate,
 15 magnesium trisilicate, menadione, mercaptomerin sodium, mersalyl, metaraminol,
 methacholine chloride, methantheline bromide, methantheline chloride, methitural
 sodium, L-methyldopa sesquihydrate, methylmethioninesulfonium chloride, mildiomycin,
 minocycline hydrochloride, mitoxantrone dihydrochloride, morpholine, muscarine
 chloride, nafronyl acid oxalate, narceine, nicotine, nicotiny alcohol, nolatrexed
 20 dihydrochloride, omeprazole, oryzacin, oxalic acid, oxophenarsine hydrochloride,
 panthenol, pantothenic acid (sodium salt), papain, penicillamine hydrochloride, penicillin
 G (potassium salt), pentamethonium bromide, pentamidine isethionate, pepsin, perazine
 dihydrochloride, phenobarbital, sodium 5,5-diphenyl hydantoinate, phethenylate sodium,
 phosphocreatine (calcium salt tetrahydrate), physostigmine sulfate, pilocarpine
 25 hydrochloride, pipemidic acid, podophyllotoxin-beta-D-glucoside, potassium carbonate,
 potassium iodide, pralidoxime mesylate, prednisolone sodium phosphate, procainamide
 hydrochloride, procaine butyrate, L-proline, promazine hydrochloride, propamidine
 isethionate, prostacyclin sodium, pyridostigmine bromide, pyronaridine, quinacillin
 disodium, quinoline, radioactive sodium iodide, reserpilic acid dimethylaminoethyl ester
 30 dihydrochloride, secobarbital sodium, silver fluoride, sodium acetate, sodium bromide,
 sodium propionate, sodium dibunate, sodium dichromate(VI), sodium nitrite, sodium

pentosan polysulfate, sodium valproate, soluble sulfamerazine, stibocaptate, streptomycin, succinylcholine bromide, succinylcholine iodide, sulfaquinoxaline, sulisatin disodium, suramin sodium, tamoxifen citrate, taurocholic acid, terazosin hydrochloride, thiobutabarbital sodium, thiopental sodium, ticarcillin disodium, 2,2,2-trichloroethanol, trientine, triethanolamine, triflazin, tolazoline hydrochloride, vinbarbital sodium, viomycin, vitamin B12, zinc iodide, and combinations thereof, and pharmaceutically acceptable hygroscopic and/or deliquescent salts and variants thereof.

The subject formulations can be designed to release drug slowly, quickly or in a step-wise (pulsatile) manner. The formulations may release at least 80% of the drug in 30 minutes, 90 minutes, 4 hours, 8 hours, 12 hours, 16 hours, or up to 24 hours *in vitro*.

More than one type of drug can be present in a tablet or a drug eluting device of the invention. The drugs can be evenly distributed throughout a medicament or can be heterogeneously distributed in a medicament, such that one drug is fully or partially released before a second drug.

In some embodiments, the drug is incorporated into the optionally bioadhesive layer for delivery to a patient. In other embodiments, it is incorporated into the tablet or drug-eluting device, and an optionally bioadhesive layer is added to at least a part of the exterior of the tablet or drug-eluting device.

The subject dosage formulations will typically comprise an inner core, which comprises one or more drugs, excipients, and/or absorption enhancers that have been compressed to form a solid, such as a tablet. For example, powdered drug formulations of the invention can be compressed to form a solid, such as a longitudinally compressed tablet. In other embodiments, a drug can be used that in its pure form, under ambient conditions, is a liquid. In some embodiments, the liquid drug that is incorporated into a compressed inner core of the invention is present as a free base or free acid. In embodiments where the drug is a liquid drug (e.g., nicotine, valproic acid), the drug is preferably incorporated into a dosage form of the invention after it has been absorbed onto an absorbent material, such as kaolin clay or Cabosil (colloidal silicon dioxide).

In other embodiments, a solubilized form of an insoluble drug is incorporated into a dosage form of the invention. Solubilized forms of insoluble drugs may be aqueous-based or oil-based. For example, a water-insoluble drug may be dissolved in an organic

solvent and then absorbed onto an absorbent material, such as a synthetic aluminosilicate or silicate, which can absorb certain organic solvents while still retaining the properties of a solid.

5 Administration of Formulations of the Invention to Patients

The formulations disclosed herein can be administered in a suspension or in an ointment to the mucosal membranes, via the nose, mouth, rectum, or vagina.

Pharmaceutically acceptable carriers for oral or topical administration are known and determined based on compatibility with the polymeric material. Other carriers include
10 bulking agents such as METAMUCIL™.

The dosage formulations described herein are suitable for targeted delivery to the small intestine or colon. In embodiments where delivery to the small intestine is desired, the dosage formulations of the invention may be coated with an enteric polymer. In other
15 embodiments, the dosage formulations may be formulated for rectal administration as an optionally bioadhesive suppository.

In some embodiments, the dosage formulation is targeted for delivery to the colonic region of the gastrointestinal tract. In certain embodiments, it is expected that the extended residence time in the colon with such formulations will result in improved efficacy due to high local drug concentrations and minimum systemic absorption.
20 Targeted delivery to the colon can be achieved, for example, by coating the dosage formulation with a time-dependent and/or pH dependent polymer layer.

For drugs requiring absorption in buccal and sublingual regions of the GI tract, tablets and particularly multiparticulates and nanoparticles are desirable. Drugs absorbed in these sites avoid first-pass metabolism by liver and degradation by GI tract enzymes
25 and harsh pH conditions typically present in the stomach and small intestine. Drugs absorbed in the buccal and sublingual compartments benefit from rapid onset of absorption, typically within minutes of dosing. Particularly suitable are particulates in fast-dissolving dosage forms, e.g., OraSolv (Cima Labs) that disintegrate within 30 sec after dosing and release the particles. Target release profiles include immediate release
30 (IR) and combinations of zero-order controlled release (CR) kinetics and first-order CR kinetics. Preferably, pharmaceutical formulations targeting the buccal and sublingual

regions are constructed such that the formulation disintegrates before passing into the esophagus.

For drugs requiring absorption in the stomach and upper small intestine and/or topical delivery to these sites, particularly drugs with narrow absorption windows, optionally bioadhesive, gastroretentive drug delivery systems are the option of choice. In certain embodiments, tablets and multiparticulates are formulated to reside for durations greater than 3 hours and optimally greater than 4, 5, or 6 hours in the fed state. Drug release profiles from these systems are tailored to match the gastric residence times, so that greater than 85% of the encapsulated drug is released during the gastric residence time. Target release profiles include zero-order CR kinetics, first-order CR kinetics and combinations of IR and CR kinetics.

For drugs requiring absorption or topical delivery only in the small intestine, enteric-coated, optionally bioadhesive drug delivery systems are a preferred method. Such systems are particularly well suited for topical delivery of therapeutics to Crohn's disease patients. Enteric-coated, optionally bioadhesive tablets and multiparticulates are formulated to reside in the stomach for durations less than 3 hrs in the fed state and less than 1 hr in the fasted state, during which time less than 10% of the encapsulated drug is released, due to the enteric coating. Following gastric emptying, the enteric coating is "triggered" to dissipate, revealing the underlying optionally bioadhesive coating. Suitable triggers include pH and time duration. Typical of enteric polymers utilizing pH as a trigger are Eudragit polymers manufactured by Rohm America: Eudragit L100-55 dissolves at pH values less than 5.5, typically found in duodenum; Eudragit L100 dissolves at pH values exceeding 6.0, typically found in jejunum; Eudragit S100 dissolves at pH values exceeding 7.0, typically found in ileum and the ileocecal junction.

Time may be used as a trigger to unmask the optionally bioadhesive coating. Coatings that dissolve after 3 hrs when the dosage form is administered in the fed state and after 1-2 hrs when the dosage form is administered in the fasted state are suitable for optionally bioadhesive delivery systems to the small intestine. Erosion of soluble polymer layers is one means to achieve a time-triggered, enteric dissolution. Polymers such as HPMC, HPC, PVP, PVA or combinations of the above may be used as time-

delayed, enteric coatings and timing of the dissolution of the coating can be increased by applying thicker coating weights.

Alternately, non-permeable coatings of insoluble polymers, e.g., cellulose acetate, ethylcellulose, can be used as enteric coatings for delayed/modified release (DR/MR) by inclusion of soluble pore formers in the coating, e.g., PEG, PVA, sugars, salts, detergents, triethyl citrate, triacetin, etc., at levels ranging from 0.5 to 50% w/w of the coating and most preferably from 5 to 25% w/w of the coating.

Also suitable are rupturable coating systems, e.g., Pulsincap, that use osmotic forces of swelling from hydrophilic polymers to rupture enteric membranes to reveal underlying bioadhesive coatings.

Target release profiles for the small intestine include: no more than 10% drug release during the first 3 hours post-dosing followed by either IR kinetics, zero-order CR kinetics, first-order CR kinetics and combinations of IR and CR kinetics.

For gastrointestinal imaging, a barium sulphate suspension is the universal contrast medium used for examination of the upper gastrointestinal tract, as described by D. Sutton, Ed., *A Textbook of Radiology and Imaging*, Vol. 2, Churchill Livingstone, London (1980), even though it has undesirable properties, such as unpalatability and a tendency to precipitate out of solution. Several properties are critical: (a) Particle size: the rate of sedimentation is proportional to particle size (i.e., the finer the particle, the more stable the suspension; (b) Non-ionic medium: charges on the barium sulphate particles influence the rate of aggregation of the particles, aggregation is enhanced in the presence of the gastric contents; (c) Solution pH: suspension stability is best at pH 5.3. However, as the suspension passes through the stomach, it is inevitably acidified and tends to precipitate. The encapsulation of barium sulfate in microspheres of appropriate size provides a good separation of individual contrast elements and may, if the polymer displays bioadhesive properties, help in coating, preferentially, the gastric mucosa in the presence of excessive gastric fluid. In certain embodiments, with bioadhesiveness targeted to more distal segments of the gastrointestinal tract, it may also provide a kind of wall imaging not easily obtained otherwise.

The double contrast technique, which utilizes both gas and barium sulphate to enhance the imaging process, especially requires a proper coating of the mucosal surface.

Air or carbon dioxide must be introduced to achieve a double contrast. This is typically achieved via a nasogastric tube to provoke a controlled degree of gastric distension. Studies indicate that comparable results may be obtained by the release of individual gas bubbles in a large number of individual adhesive microspheres and that this imaging process may be used to image intestinal segments beyond the stomach.

Methods of Making Rate-Controlled Oral Dosages

As described above, one method of making dosage formulations according to the invention comprises inserting a core into an extruded optionally bioadhesive polymer tube. In certain embodiments, a extruded bioadhesive polymer tube comprises Spheromer™ I (p(FASA), as described in U.S. Patent No. 5,955,096 to Mathiowitz et al.), Spheromer™ II (oligomers and metal oxides, as described in U.S. Patent No. 5,985,312 to Jacob et al.), Spheromer™ III (DOPA side chains grafted onto a non-biodegradable polymeric backbone, see U.S. Application No. 11/009,327, filed December 9, 2004, and WO 2005/056708), or other bioadhesive polymers available commercially, along with suitable plasticizers, pore-forming agents, and solvents. In certain embodiments, the extruded non-bioadhesive polymer tube comprises cellulose acetate, ethyl cellulose, polyacrylic acids (e.g., Eudragit™) or other non-bioadhesive polymers available commercially, along with suitable plasticizers, pore-forming agents, and solvents. Other thermoplastic polymers can be added to modify the moldability and mechanical strength of the polymer tube.

In a preferred embodiment of the invention, the extruded polymer tube is prepared via a hot-melt extrusion process, where the desired optionally bioadhesive polymer is fed into the extruder as a pellet, flake, powder, etc. along with plasticizer. In certain such embodiments, the materials are blended as they are propelled continuously along a screw through regions of high temperature and pressure to form the polymer extrudate. The extrudate may then be pushed from the extruder through a die having the desired shape and dimension to form a tube, e.g., a cylindrical tube. The tube may be cooled after extrusion. The dimensions of the tube can be varied to accommodate the inner core system. The inner diameter of the tube can be configured to conform to the desired circumferential dimension of the preformed, pre-pressed inner system containing the

therapeutic agent(s). The thickness of the tube is determined in part by the polymer/plasticizer type as well its behavior with respect to the external fluid.

The optionally bioadhesive nature of the polymer tube may also be controlled by utilizing different types of polymers and excipients. Inorganic metal oxides may be added to improve adhesion. Pore formers may also be added to control porosity. Enterosoluble polymers may be added to promote disintegration of the optionally bioadhesive layer. For example, after drug release, the optionally bioadhesive layer may become weak and disintegrate upon release of entero-soluble polymers from the layer. Drugs may also be added into the polymer layer either as a plasticizer or pore-forming agent. Once formed, the inner system, preferably in the form of a longitudinally compressed tablet, is inserted into the tube, and the two components are fused together to get a finished dosage form.

Methods for Production of the Hollow Cylinder

Prior to hot-melt extrusion of the hollow cylinder, a suitable polymer, such as a polyanhydride polymer, e.g., poly(fumaric-co-sebacic) acid or polyadipic acid, and 20% triethyl citrate (based on polymer weight) are mixed in a planetary mixer. Extrusion can be performed using either a MP 19 TC25 laboratory scale co-rotating twin screw extruder of APV Baker (Newcastle-under-Lyme, UK) or a Killian extruder (Killian extruder Inc., Cedar Grove, NJ). Both machines are equipped with a standard screw profile with two mixing sections, an annular die with metal insert for the production of the cylinder and twin screw powder feeder. Typical extrusion conditions are: a screw speed of 5 rpm, a powder feed rate of 0.14 kg/hr and a temperature profile of 125-115-105-80-65°C from the powder feeder towards the die. The cylinders (internal diameter of 7mm and wall thickness of 1mm) are cut into 1cm long cylinders.

Methods for Production of the Inner Core System

Longitudinally compressed core tablets containing the therapeutic agent and other components may be compressed onto a single or multilayer tableting machine equipped with deep fill or regular tooling. For example, the therapeutic agent either alone or in combination with a rate controlling polymer and other excipients is mixed by stirring, ball

milling, roll milling or calendaring and pressed into a solid having dimensions conforming to an internal compartment defined by the extruded polymer cylinder. The inner core system may be a pre-fabricated osmotic system that is inserted into the optionally bioadhesive cylinder with orifices aligned along the open ends of the cylinder.

5 In certain embodiments, the rate-controlling polymer may be any polymer, such as a non-bioadhesive (PolyROD – polymeric, rate-controlling, oral dosage). In certain preferred such embodiments, the rate-controlling polymer is selected from cellulose acetate, ethyl cellulose, and polyacrylic acids (e.g., EudragitTM), either in their extruded or coated form.

10 In certain embodiments, the invention relates to a drug-eluting device, comprising a reservoir having a compressed core comprising a therapeutic, diagnostic, or prophylactic agent, an outer polymeric layer, and one or more openings that allow the agent to elute from the core.

15 **Method of Production of a Capsule**

Another method of making the dosage formulation according to the invention comprises inserting a core into an optionally bioadhesive capsule body followed by addition of a gelatin cap. The optionally bioadhesive capsule body may comprise a gelatin body coated with Spheromer I, II or III or other bioadhesive or non-bioadhesive
20 polymer, optionally along with a suitable plasticizer, one or more pore forming agents, and one or more solvents. Other thermoplastic polymers can be added to the coating to modify the mechanical strength of the optionally bioadhesive capsule. An inner rate-controlling coating can be added to modify the mechanical strength of the optionally bioadhesive capsule.

25 One or more layers containing different therapeutic agents can be included in a multilayer tablet. For example, in certain embodiments, the invention relates to multilayer tablets comprising a first, a second and a third layer, where each layer includes one or more drugs and one or more excipients, where the first layer forms the core of the tablet, the second layer is adjacent to one side of the first layer, and the third layer is
30 adjacent to the opposite side of the first layer. At least one layer of the tablet includes a hydrophobic excipient and at least one drug in the tablet is hygroscopic, deliquescent or

both. Preferably, at least one hygroscopic and/or deliquescent drug and at least one hydrophobic excipient are present (e.g., blended together) in at least one layer of a tablet.

Exemplary hydrophobic excipients include celluloses, particularly methylcellulose and ethylcellulose.

Such tablets optionally include one excipient present in an amount sufficient to be at least partially rate-controlling with respect to release of the drug from the tablet. Typically, tablets that include a rate-controlling excipient (e.g., a rate-controlling polymer) contain about 30% to about 60% by weight of the rate-controlling excipient. Alternatively, the amount of rate-controlling excipient is selected relative to the amount of drug in the tablet. In such cases, the weight of the rate-controlling excipient is about two times to about five times, such as about two times to about three times greater than the weight of the drug.

Typically, the inner and outer layers contain different proportions of each component (including the drug(s)), thereby establishing a gradient-type composition. In an exemplary embodiment, the first (inner) layer contains the greatest weight percentage of the drug(s). Accordingly, the second and third layers and any additional layers present contain lesser amounts of drug. In multi-layer tablets having more than three layers (e.g., those having a fourth and optionally a fifth layer), the additional layers can, for example, contain no drug or contain successively lesser amounts of drug. In general, layers the same distance away from the first or inner layer will contain approximately equal amount of drug, such that the tablet is essentially symmetrical about the inner layer. For tablets containing two or more drugs, the drugs can both be present in one or more layers or the different drugs are present in separate layers (i.e., the drugs are not mixed together in one layer).

In certain aspects, multi-layer compressed tablets of the invention exhibit an approximately zero-order release of drug in in vitro testing and/or in vivo administration. For formulations where delivery to the stomach is desired, zero-order release advantageously occurs over about 6-12 hours, particularly 8-10 hours. For formulations where delivery to the stomach and small intestine are desired, zero-order release advantageously occurs over about 8-16 hours, particularly 10-14 hours. For formulations

where delivery to the small intestine and colon are desired, zero-order release advantageously occurs over about 16-30 hours, particularly 22-26 hours.

Multi-layer or gradient tablets can be assembled in several different ways. In one embodiment, the tablet comprises at least one solid inner layer and two solid outer layers, each comprising one or more drugs and one or more pharmaceutical polymers and/or pharmaceutical excipients. In order to produce a gradient effect, the amount of drug and/or excipient differs among the inner and outer layers. For example, the one or more inner layers can comprise at least 34% of the total amount of the drug in the tablet and one or more polymer(s) and/or excipients(s), and each of the two outer layers can comprise not more than 33% of the total amount of drug in the tablet and one or more polymer(s) and/or excipients(s). Such tablets can also be used to commence release of different drugs at different times, by inclusion of different drugs in separate layers.

The core may contain, in any desired order, discrete layers of different composition. For example, different layers may contain the same or different drugs with varying release profiles. For example, one layer may comprise a drug formulated for extended release, and in a second layer, the same or different drug may be formulated for immediate release (or two layers may have different profiles of controlled release of the same or different drugs). Similarly, different drugs may be present in different layers, with the formulation of each layer adjusted to account for characteristics of the particular drug in that layer. For example, multi-layer tablets can be designed to incorporate an insoluble drug in one layer, optionally with permeation and/or dissolution enhancers, and a highly soluble drug in another layer. The subject multi-layer formulations may also have two or more layers of the same or different drugs for release at the same or varying target sites of absorption. For example, one layer may comprise a drug for release in the stomach and another layer (e.g., coated with a further enteric coating) may comprise a drug targeted for release in the small intestine.

In certain embodiments that comprise a drug formulated for extended release and a drug formulated for immediate release, the drug formulated for extended release is a charge-neutral form of the drug (such as a carboxylic acid or amine free base, e.g. valproic acid or acyclovir), and the drug formulated for immediate release is a salt form of the drug (such as a carboxylate salt or amine salt, e.g., sodium valproate or sodium

acyclovir). Similarly, other variant forms of a drug with different dissolution properties may be used to effect a combination of immediate release and extended release. For example, a high solubility drug form may be paired with a low solubility prodrug of that drug, thereby achieving immediate release of the high solubility form and extended release of the low solubility prodrug.

In another embodiment, the multi-layer tablet consists of a solid inner layer and two solid outer layers, each comprising a drug and one or more pharmaceutical polymers or pharmaceutical excipients, wherein at least one polymer or excipient is hydrophobic. Tablets of this embodiment preferably provide approximately zero-order or linear release kinetics. In still another embodiment, the multi-layer tablet is enteric coated.

One or more layers of the tablet can contain permeation enhancers and/or dissolution enhancers to provide permeability enhancement of drugs through mucosal lining of the gastrointestinal tract (GIT). An absorption enhancer facilitates the uptake of a drug across the gastrointestinal epithelium. Absorption enhancers include compounds that improve the ability of a drug to be solubilized in the aqueous environment in which it is originally released and/or in the lipophilic environment of the mucous layer lining of the intestinal walls. Absorption enhancers further include compounds that increase disorder of the hydrophobic region of the membrane exterior of intestinal cells, promote leaching of membrane proteins that results in increased transcellular transport, or widen the pore radius between cells for increased paracellular transport. Examples of absorption enhancers include sodium caprate, ethylenediamine tetra(acetic acid) (EDTA), citric acid, lauroylcarnitine, palmitoylcarnitine, tartaric acid and other agents known to increase GI permeability. Other suitable absorption enhancers include sodium salicylate, sodium 5-methoxysalicylate, indomethacin, diclofenac, polyoxyethylene ethers, sodium laurylsulfate, quaternary ammonium compounds, sodium deoxycholate, sodium cholate, octanoic acid, decanoic acid, glyceryl-1-monooctanoate, glyceryl-1-monodecanoate, DL-phenylalanine ethylacetoacetate enamine, chlorpromazine, D-myristoyl-L-propyl-L-prolyl-glycinate, concanavaline A, DL- α -glycerophosphate, and 3-amino-1-hydroxypropylidene-1,1-diphosphonate.

Alternatively, or in addition, the tablet is coated to provide additional control over diffusion of the drug or exposure of the tablet to the gastrointestinal tract (e.g., with an

enteric coating). The diffusion-limiting coating can be a pharmaceutically-accepted polymeric coating material, such as methacrylates (Eudragits™, Rohm and Hass; Kollicoat™, BASF), zein, cellulose acetate, cellulose phthalate and hydroxypropylmethylcellulose. The coatings can be applied using a variety of techniques including fluidized-bed coating, pan-coating and dip-coating.

Separately or in combination with the optionally bioadhesive coating, a bioadhesive (such as those described above) can be included in one or more layers of a compressed inner core of the invention.

Multi-layer tablets of the invention are readily prepared. In one example, the drug(s) is/are mixed with a compressible sugar and granulated with a binder solution of compressible sugar in purified water. Subsequent to drying, the granules are mixed with different amounts of colloidal silicon dioxide (Cabosil™) and magnesium stearate. The granules are mixed in different proportions with stearic acid or monostearate (30, 50, 70%, for example) and then fed into a multilayer tableting machine (such as a Korsch or Fette tableting machine) to yield a trilayer tablet. Additional layers, often with varying amount of drug granules (e.g., greater drug concentration in the center layer and decreasing in each subsequent outer layer), can readily be added. In certain embodiments, the outermost layers do not include a drug.

In some embodiments, the compressed inner core is a tablet that is coated, either entirely or partially, with a gelatin, which is further coated with an optionally bioadhesive polymer on at least one of its surfaces. In some embodiments, the gelatin layer itself may comprise an optionally bioadhesive polymer.

Gelatin layers can be applied to a subject compressed inner core by an enrobing technique. For example, in some embodiments, a pre-compressed tablet is fully enrobed in a soft elastic film material, such as a gelatin film, in a relatively dry state and at a relatively low temperature. It is fully enrobed between two layers of the applied elastic film material of selected thickness and composition, which layers substantially conform to the contours of the pre-compressed tablet and which are sealed to each other along a single line encircling the pre-compressed tablet and lying substantially in a common plane. The film layers, when applied to the pre-compressed tablet, exhibit substantially low water activity and have an elastic plastic character. Typically, the film material

applied in tablet-enrobing manner to the tablet is a gelatin-base film so formulated that, as applied to and sealed around the tablet, it conforms tightly to the tablet contours and bonds securely to the tablet surfaces and dries to a hard state. Various enrobing methods are described in U.S. Patent No. 6,482,516 and U.S. Patent Publication Nos.

5 2004/0161527, 2003/0215563, and 2003/0059614, each of which is incorporated herein by reference.

Capsules may incorporate drug in either solid or liquid form. In embodiments that comprise liquid formulations, the system may be modified to include an exit port for drug to diffuse from the capsule while the drug slurry remains intact without leaking. This can be accomplished, for example, by using a capsule wherein at least a portion of the capsule includes metal salt. The entirety of the capsule may then be coated with a microporous polymer (e.g., a bioadhesive or non-bioadhesive polymer) and portions of the coating covering the metal salts can then be removed using a laser, e.g., the metal salt is present in sufficient quantity to protect the metal-containing layer from the energy of the laser.

10 Processes and apparatus for forming such ports using a laser beam have been described in U.S. Patent Nos. 4,063,064 and 5,783,793, which is incorporated herein in its entirety. When the capsule containing metal salts is exposed to a biological fluid, the metal ions may dissolve into the coating layer, thereby augmenting its bioadhesive properties.

20 The microporous polymer wall is typically formed by dissolving the polymeric wall material and pore former in an appropriate solvent, such as acetone, methanol, or methylene chloride, and this solution then applied to the capsule cell. The inner capsule acts as a reservoir containing a liquid therapeutic agent. The inner capsule is composed of a water-soluble natural or synthetic polymer.

25 The dosage form may further comprise an inner barrier layer. The inner barrier layer may include a laser-reflective or laser -transmitting material dispersed in a water-soluble polymer, such as gelatin. This laser-reflective material acts as a barrier to the laser, either reflecting or transmitting the laser energy thereby preventing damage to the barrier layer. Suitable materials include metal oxides and silicates such as aluminum oxide, magnesium oxide, and iron oxides. These metal oxides may offer the additional
30 advantage that, if leached into the outer optionally bioadhesive layer, they further

improve the bioadhesiveness of the outer optionally bioadhesive coating (as discussed herein in the section pertaining to metal-containing bioadhesive polymers).

Many drugs, depending on their ionization state, are absorbed in different segments of the gastro-intestinal tract. For example, typically a soluble salt form of a drug, due to its high aqueous solubility, is better absorbed from the upper part of the GIT (such as the stomach) while its corresponding neutral form (e.g., amine free base, or free carboxylic acid) of the drug, perhaps due to its high permeability, is better absorbed from the distal part of the GIT, such as the colon. A dosage form that incorporates drug(s) or prodrug(s) both in salt and neutral forms will allow these different forms of the drug to be released at the corresponding site. This phenomenon can be used not only to allow complete drug release but also to maintain a substantially constant level of drug in the circulation for optimum performance, simply by using an appropriate balance of salt and neutral forms of the drug. By incorporating an optionally bioadhesive component in different segments of the system, it is possible to enhance drug absorption in the different regions of the GIT. This embodiment in its simplest form may contain drug in appropriate amounts of both salt and neutral forms at the outset, or may be configured to take advantage of the different pH levels in different portions of the digestive tract, for example by configuring the device to allow, for example, a portion of the salt form of a basic (e.g., amine-containing) drug to be converted to its corresponding free base form when it reached the higher pH regions of the distal part of the GI tract.

Such a system can be configured to allow drug release in a sequential manner, e.g., allowing the salt form of the drug to be released first in the upper part of the GI tract (e.g., where it will get absorbed rapidly) followed by subsequent release of the neutral form of drug as it moves downstream in the distal part of the GI tract.

Pharmaceutically acceptable salts or "salt form" of a basic (e.g., amine-containing) drug or prodrug mean any salt that is formed by reacting the base form of the drug with an appropriate pharmaceutically acceptable acid. The representative pharmaceutical salts include, but not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium acetate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edentate, edisylate, estolate, esylate, fumarate, gluconate, glutamate, hexylresorcinate, hydrobromide, hydrochloride, iodide, isothionate,

lactate, laurate, maleate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulphate, napsylate, N-methylglucamine ammonium salt, oleate, pamoate, palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, tosylate and valerate.

5 Typically, the hardness of a compressed tablet of the invention is between 2 kp and 30 kp. In some embodiments, it is between 2 kp and 5 kp, 2 kp and 10 kp, 2 kp and 15 kp, 2 kp and 20 kp, or 2 kp and 25 kp. In yet other embodiments, it is between 5 kp and 15 kp, 10 kp and 20 kp, or 15 kp and 30 kp.

Tablets and drug eluting devices of the invention typically weigh at least 5 mg.
10 Tablets and drug eluting devices can also weigh at least 10 mg, at least 15 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg. Typically, such objects weigh 10 mg to 500 mg.

Tablets and drug eluting devices of the invention typically measure at least 2 mm in one dimension. For example, tablets and drug eluting devices can measure at least 5 mm, at least 10 mm, at least 15 mm or at least 20 mm in one dimension. Typically, the
15 diameter of the tablets and drug eluting devices is 2 to 40 mm, preferably 10 to 30 mm such as 20 to 26 mm. Mini-tablets have a diameter of 2 mm to about 5 mm. Such tablets and devices can measure at least 2 mm, at least 5 mm, at least 10 mm, at least 15 mm or least 20 mm in a second dimension and, optionally, a third dimension. Preferably, the
20 tablet or drug eluting device is of a size that facilitates swallowing by a subject.

The volume of a typical tablet or drug eluting device of the invention is at least 0.008 mL, at least 0.01 mL, at least 0.05 mL, at least 0.1 mL, at least 0.125 mL, at least 0.2 mL, at least 0.3 mL, at least 0.4 mL or at least 0.5 mL, such as from 0.008 mL to 0.5 mL.

25

Methods of Insertion of the Inner Core System into the Cylinder

The preformed inner core with a diameter slightly smaller than the inner diameter of the tube may be either manually or mechanically inserted into the tube and heated to fuse the two units. Alternately, the core may be inserted into the tube by a positive
30 placement core insertion mechanism on the tableting machine. Initially, the extruded tube may be placed into the die of the machine followed by insertion of the compressed core

into the internal compartment of the tube, and the two components compressed to get the finished dosage form. Alternatively, the dosage form may be prepared via simultaneous extrusion of the optionally bioadhesive tube and expandable inner composition using an extruder capable of such an operation.

5 In certain embodiments, the optionally bioadhesive polymer is applied to the tablet by compression coating. In some embodiments, compression coating comprises adding one-half of the optionally bioadhesive polymeric layer to a die, positioning the compressed tablet in a flat position in the die, adding the remaining half of the optionally bioadhesive polymeric layer to the die, and compressing the optionally bioadhesive
10 polymeric layers and tablet together.

In other embodiments, compression coating comprises adding the optionally bioadhesive polymeric layer to a die, loosely compressing the optionally bioadhesive polymeric layer (e.g., with an upper shaped punch that creates room for insertion of the longitudinally compressed die), and inserting the tablet. Preferably, the upper punch has
15 a telescopic core rod within it. The telescopic rod will displace the coating material and will compact it at the bottom and sides of the die. Once a space has been created, the pre-compressed inner core is inserted. Creating room for the inner core and insertion of the inner core can be done sequentially or in the same process. In certain embodiments, the pre-compressed inner core is itself used as a telescopic core rod.

20 In other embodiments, the pre-compressed inner core is fully coated with a optionally bioadhesive coating. One or both ends of the coated tablet are then circumferentially perforated by a laser. In such embodiments, it is expected that when the dosage formulation takes up water, the perforated part of the dosage form will open up as a flap, thereby enabling release of the drug.

25 **Bioadhesives**

An orally ingested product can adhere to either the epithelial surface or the mucus lining of the gastrointestinal tract. For the delivery of bioactive substances, it can be advantageous to have a polymeric drug delivery device adhere to the epithelium or to the
30 mucous layer. Bioadhesion in the gastrointestinal tract proceeds in two stages: (1) viscoelastic deformation at the point of contact of the synthetic material into the mucus

substrate, and (2) formation of bonds between the adhesive synthetic material and the mucus or the epithelial cells. In general, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds, and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive interactions (i.e., Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups primarily responsible for forming hydrogen bonds are the hydroxyl and the carboxylic acid groups.

Duchene et al., in *Drug Dev. Ind. Pharm.*, 14:283-318 (1988), review the pharmaceutical and medical aspects of bioadhesive systems for drug delivery. Polycarbophils and acrylic acid polymers were noted as having the best adhesive properties. "Bioadhesion" is defined as the ability of a material to adhere to a biological surface for an extended period of time. Bioadhesion is one solution to the problem of inadequate residence time resulting from the stomach emptying and intestinal peristalsis, and from displacement by ciliary movement. Bioadhesion results from a confluence of factors, including an intimate contact between the bioadhesive and the receptor tissue, penetration of the bioadhesive into the crevice of the tissue surface and/or mucus, and formation of mechanical, electrostatic, or chemical bonds. Bioadhesive properties of polymers are affected by both the nature of the polymer and by the nature of the surrounding media.

Others have explored the use of bioadhesive polymers; however, the extent of bioadhesion achieved in these studies has been limited. In addition, these studies do not demonstrate how to prepare larger bioadhesive drug delivery devices, such as tablets. WO 93/21906 discloses methods for fabricating bioadhesive microspheres and for measuring bioadhesive forces between microspheres and selected segments of the gastrointestinal tract in vitro. Smart et al., *J. Pharm. Pharmacol.*, 36:295-299 (1984), report a method to test adhesion to mucosa using a polymer-coated glass plate contacting a dish of mucosa. A variety of polymeric materials were tested, including sodium alginate, sodium carboxymethyl-cellulose, gelatin, pectin and polyvinylpyrrolidone. Gurney et al., *Biomaterials*, 5:336-340 (1984) report that adhesion may be affected by physical or

mechanical bonds; secondary chemical bonds; and/or primary, ionic or covalent bonds. Park et al., "Alternative Approaches to Oral Controlled Drug Delivery: Bioadhesives and In-Situ Systems," in J. M. Anderson and S. W. Kim, Eds., "Recent Advances in Drug Delivery," Plenum Press, New York, 1984, pp. 163-183, report a study of the use of fluorescent probes in cells to determine adhesiveness of polymers to mucin/epithelial surface, which indicated that anionic polymers with high charge density appear to be preferred as adhesive polymers. Mikos et al., in J. Colloid Interface Sci., 143:366-373 (1991) and Lehr et al., J. Controlled Rel. Soc., 13:51-62 (1990) report a study of the bioadhesive properties of polyanhydrides and polyacrylic acid, respectively, in drug delivery. Lehr et al. screened microparticles formed of copolymers of acrylic acid using an in vitro system and determined that the copolymer "Polycarbophil" has increased adhesion.

As generally used herein "bioadhesives" or "bioadhesive materials" refer to polymers which have or are modified to have improved bioadhesion.

As used herein "bioadhesion" generally refers to the ability of a material to adhere to a biological surface for an extended period of time. Bioadhesion requires a contact between the bioadhesive material and the receptor surface, the bioadhesive material penetrates into the crevice of the surface (e.g., tissue and/or mucus) and chemical bonds form. Thus the amount of bioadhesive force is affected by both the nature of the bioadhesive material, such as a polymer, and the nature of the surrounding medium. Bioadhesive forces are measured in units of N/m^2 , by methods defined in U.S. Patent No. 6,197,346, which is herein incorporated by reference.

Bioadhesive Polymers

Suitable bioadhesive polymeric coatings are disclosed in U.S. Patent Nos. 6,197,346, 6,217,908 and 6,365,187, the contents of which are incorporated herein by reference, and include soluble and insoluble, biodegradable and nonbiodegradable polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, and/or natural or synthetic polymers. The preferred polymers are synthetic polymers, with controlled synthesis and degradation characteristics. Particularly preferred polymers are anhydride copolymers of fumaric acid and sebacic acid (P(FA:SA)), which

have exceptionally good bioadhesive properties when administered to the gastrointestinal tract. Examples of P(FA:SA) copolymers include those having a 1:99 to 99:1 ratio of fumaric acid to sebacic acid, such as 5:95 to 75:25, for example, 10:90 to 60:40 or at least 15:85 to 25:75. Specific examples of such copolymers have a 20:80 or a 50:50 ratio of fumaric acid to sebacic acid.

Mucoadhesive polymers are included in the formulation to improve gastrointestinal retention via adherence of the formulation to the walls of the GI tract. As used herein "mucoadhesive" generally refers to the ability of a material to adhere to a biological surface or mucous for an extended period of time. Mucoadhesion requires contact between a mucoadhesive material and a surface (e.g., tissue and/or cells such as epithelial cells) or mucous. Thus, the amount of mucoadhesive force is affected by both the nature of the mucoadhesive material, such as a polymer and the nature of the surrounding medium. "Mucoadhesive polymers", a subset of bioadhesive polymers, are polymers that have an adherence to mucosal tissue or mucous, e.g., of at least about 10, 25, 50, 75, 100 or even about 110 N/m² (11 mN/cm²) of contact area as measured on rat intestine, e.g., such that the dosage form optimally has a gastrointestinal retention time of at least four hours in a fed beagle dog model during which the drug is released from the dosage form. In certain embodiments, the dosage form optimally has a gastrointestinal retention time of at least 3 hours in a fasted beagle dog model during which the drug is released from the dosage form. The fracture strength of the tablets and drug eluting devices is advantageously at least 250 N/m², at least 500 N/m² or at least 1000 N/m². For example, the fracture strength of a polymer-containing tablet or drug eluting device can be from 100 to 500 N/m². The forces described herein refer to measurements made upon rat intestinal mucosa, unless otherwise stated. The same adhesive measurements made on a different species of animal will differ from those obtained using rats. This difference is attributed to both compositional and geometrical variations in the mucous layers of different animal species as well as cellular variations in the mucosal epithelium. However, the data shows that the same general trends prevail no matter what animal is studied (i.e., p(FA:SA) produces stronger adhesions than polylactic acid (PLA) in rats, sheep, pigs, etc.). For example, the fracture strength of tablets and drug eluting devices of the invention on rat intestine is generally at least 125 N/m², such as at least 150 N/m², at

least 250 N/m², at least 500 N/m² or at least 1000 N/m². For example, the fracture strength of tablets and drug eluting devices of the invention on pig intestine is generally at least 125 N/m², such as at least 150 N/m², at least 250 N/m², at least 500 N/m² or at least 1000 N/m².

The fracture strength of a tablet or drug eluting device can be measured according to the methods disclosed by Duchene et al. in *Drug Dev. Ind. Pharm.*, 14:283-318 (1988). Briefly, the tablet is attached on one side to a tensile tester and is contacted with a testing surface (e.g., a mucosal membrane) on the opposite surface. The tensile tester measures the force required to displace the tablet or drug eluting device from the testing surface.

Common tensile testers include a Texture Analyzer and the Instron tensile tester.

In the preferred method for mucoadhesive testing, tablets are pressed using flat-faced tooling, 0.3750" (9.525 mm) in diameter. Tablet weight will depend on composition; in most cases, the tablets have a final weight of 200 mg. These tablets are then glued to a plastic 10 mm diameter probe using a common, fast-drying cyanoacrylate adhesive. Once the tablets are firmly adhered to the probe, the probe is attached to the Texture Analyzer. The Texture Analyzer is fitted with a 1 kg load cell for maximum sensitivity. The following settings are used:

Pre-Test Speed	0.4 mm / sec	Stop Plot At	Final Position
Test Speed	0.1 mm / sec	Tare Mode	Auto
Post-Test Speed	0.1 mm / sec	Delay Acquisition	Off
Applied Force	20.0 g	Advanced Options	On
Return Distance	0 mm	Proportional Gain	0
Contact Time	420 s	Integral Gain	0
Trigger Type	Auto	Differential Gain	0
Trigger Force	0.5 g	Max Tracking Speed	0 mm / sec

The Test and Post-Test Speeds are as low as the instrument will allow, to ensure a maximum number of data points captured. The Pre-Test speed is used only until the probe encounters the Trigger Force; i.e., prior to contacting the tissue.

The Proportional, Integral, and Differential Gain are set to 0. These settings, when optimized, maintain the system at the Applied Force for the duration of the Contact Time.

With soft tissue as a substrate, however, the probe and tablet are constantly driven into the deformable surface. This results in visible damage to the tissue. Thus, the probe and tablet are allowed to relax gradually from the Applied Force by setting these parameters

to 0. The tracking speed, which is a measure of how rapidly the feedback is adjusted, is also set to 0.

The tissue on which the tablets are tested is secured in the Mucoadhesive Rig; the rig is then completely immersed in a 600 mL Pyrex beaker containing 375 mL of PBS.

5 The tissue is maintained at approximately 37 °C for the duration of the test; no stirring is used as the machine can detect the oscillations from the stir bar.

In the past, two classes of polymers have shown useful bioadhesive properties, hydrophilic polymers and hydrogels. In the large class of hydrophilic polymers, those containing carboxylic groups (e.g., poly[acrylic acid]) exhibit the best bioadhesive
10 properties. It is thus expected that polymers with the highest concentrations of carboxylic groups are preferred materials for bioadhesion on soft tissues. In other studies, the most promising polymers were sodium alginate, carboxymethylcellulose, hydroxymethylcellulose and methylcellulose. Some of these materials are water-soluble, while others are hydrogels.

15 Rapidly bioerodible polymers such as poly[lactide-co-glycolide], polyanhydrides, and polyorthoesters, whose carboxylic groups are exposed on the external surface as their smooth surface erodes, are particularly suitable for bioadhesive drug delivery systems. In addition, polymers containing labile bonds, such as polyanhydrides and polyesters, are well known for their hydrolytic reactivity. Their hydrolytic degradation rates can
20 generally be altered by simple changes in the polymer backbone.

Representative natural polymers suitable for the present invention include proteins (e.g., hydrophilic proteins), such as zein, modified zein, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as cellulose, dextrans, polyhyaluronic acid, polymers of acrylic and methacrylic esters and alginic acid. These are generally less
25 suitable for use in bioadhesive coatings due to higher levels of variability in the characteristics of the final products, as well as in degradation following administration. Synthetically modified natural polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses.

Representative synthetic polymers for use in bioadhesive coatings include
30 polyphosphazines, poly(vinyl alcohols), polyamides, polycarbonates, polyalkylenes,

polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof. Other polymers suitable for use in the invention include, but are not limited to, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, and polyvinylphenol. Representative bioerodible polymers for use in bioadhesive coatings include polylactides, polyglycolides and copolymers thereof, poly(ethylene terephthalate), poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), poly[lactide-co-glycolide], polyanhydrides (e.g., poly(adipic anhydride)), polyorthoesters, blends and copolymers thereof.

Polyanhydrides are particularly suitable for use in bioadhesive delivery systems because, as hydrolysis proceeds, causing surface erosion, more and more carboxylic groups are exposed to the external surface. However, polylactides erode more slowly by bulk erosion, which is advantageous in applications where it is desirable to retain the bioadhesive coating for longer durations. In designing bioadhesive polymeric systems based on polylactides, polymers that have high concentrations of carboxylic acid are preferred. The high concentrations of carboxylic acids can be attained by using low molecular weight polymers (MW of 2000 or less), because low molecular weight polymers contain a high concentration of carboxylic acids at the end groups.

The polymers listed above can be obtained from sources such as Sigma Chemical Co., St. Louis, Mo., Polysciences, Warrenton, Pa., Aldrich, Milwaukee, Wis., Fluka, Ronkonkoma, N.Y., and BioRad, Richmond, Calif., or can alternatively be synthesized from monomers obtained from these suppliers using standard techniques.

When the bioadhesive polymeric coating is a synthetic polymer coating, the synthetic polymer is typically selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric acid), poly(maleic acid), and blends and copolymers of thereof. In an exemplary embodiment, the synthetic polymer is poly(fumaric-co-sebacic) anhydride.

Another group of polymers suitable for use as bioadhesive polymeric coatings are polymers having a hydrophobic backbone with at least one hydrophobic group pendant from the backbone. Suitable hydrophobic groups are groups that are generally non-polar. Examples of such hydrophobic groups include alkyl, alkenyl and alkynyl groups. Preferably, the hydrophobic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers.

A further group of polymers suitable for use as bioadhesive polymeric coatings are polymers having a hydrophobic backbone with at least one hydrophilic group pendant from the backbone. Suitable hydrophilic groups include groups that are capable of hydrogen bonding or electrostatically bonding to another functional group. Example of such hydrophilic groups include negatively charged groups such as carboxylic acids, sulfonic acids and phosphonic acids, positively charged groups such as (protonated) amines and neutral, polar groups such as amides and imines. Preferably, the hydrophilic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers. The hydrophilic groups can be either directly attached to a hydrophobic polymer backbone or attached through a spacer group. Typically, a spacer group is an alkylene group, particularly a C₁-C₈ alkyl group such as a C₂-C₆ alkyl group. Preferred compounds containing one or more hydrophilic groups include amino acids (e.g., phenylalanine, tyrosine and derivatives thereof) and amine-containing carbohydrates (sugars) such as glucosamine.

Polymers can be modified by increasing the number of carboxylic groups accessible during biodegradation, or on the polymer surface. The polymers can also be

modified by binding amino groups to the polymer. The polymers can be modified using any of a number of different coupling chemistries available in the art to covalently attach ligand molecules with bioadhesive properties to the surface-exposed molecules of the polymeric microspheres.

5 The attachment of any positively charged ligand, such as polyethyleneimine or polylysine, to a polymer may improve bioadhesion due to the electrostatic attraction of the cationic groups coating the beads to the net negative charge of the mucus. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negative charge coating. Any ligand with a high binding
10 affinity for mucin could also be covalently linked to most polymers with the appropriate chemistry, such as with carbodiimidazole (CDI), and be expected to influence the binding to the gut. For example, polyclonal antibodies raised against components of mucin or else intact mucin, when covalently coupled to a polymer, would provide for increased bioadhesion. Similarly, antibodies directed against specific cell surface receptors exposed
15 on the luminal surface of the intestinal tract would increase the residence time when coupled to polymers using the appropriate chemistry. The ligand affinity need not be based only on electrostatic charge, but other useful physical parameters such as solubility in mucin or specific affinity to carbohydrate groups.

 The covalent attachment of any of the natural components of mucin in either pure
20 or partially purified form to the polymers generally increases the solubility of the polymer in the mucin layer. The list of useful ligands include but are not limited to the following: sialic acid, neuraminic acid, n-acetyl-neuraminic acid, n-glycolylneuraminic acid, 4-acetyl-n-acetylneuraminic acid, diacetyl-n-acetylneuraminic acid, glucuronic acid, iduronic acid, galactose, glucose, mannose, fucose, any of the partially purified fractions
25 prepared by chemical treatment of naturally occurring mucin, e.g., mucoproteins, mucopolysaccharides and mucopolysaccharide-protein complexes, and antibodies immunoreactive against proteins or sugar structure on the mucosal surface.

 The attachment of polyamino acids containing extra pendant carboxylic acid side groups, such as polyaspartic acid and polyglutamic acid, may also increase
30 bioadhesiveness. The polyamino chains would increase bioadhesion by means of chain entanglement in mucin strands as well as by increased carboxylic charge.

Polymer-Metal Complexes

As disclosed in U.S. Patent Nos. 5,985,312, 6,123,965 and 6,368,586, the contents of which are incorporated herein by reference, polymers, such as those named above, having a metal compound incorporated therein have a further improved ability to adhere to tissue surfaces, such as mucosal membranes, and are suitable for use in the invention. The metal compound incorporated into the polymer can be, for example, a water-insoluble metal oxide. The incorporation of metal compounds into a wide range of different polymers, even those that are not normally bioadhesive, often improves their ability to adhere to tissue surfaces such as mucosal membranes.

Metal compounds that can be incorporated into polymers to improve their bioadhesive properties preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming incorporated into and associated with a polymer to improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt (I) oxide (CoO), cobalt (III) oxide (Co₂O₃), selenium oxide (SeO₂), chromium (IV) oxide (CrO₂), manganese oxide (MnO₂), titanium oxide (TiO₂), lanthanum oxide (La₂O₃), zirconium oxide (ZrO₂), silicon oxide (SiO₂), scandium oxide (Sc₂O₃), beryllium oxide (BeO), tantalum oxide (Ta₂O₅), cerium oxide (CeO₂), neodymium oxide (Nd₂O₃), vanadium oxide (V₂O₅), molybdenum oxide (Mo₂O₃), tungsten oxide (WO), tungsten trioxide (WO₃), samarium oxide (Sm₂O₃), europium oxide (Eu₂O₃), gadolinium oxide (Gd₂O₃), terbium oxide (Tb₄O₇), dysprosium oxide (Dy₂O₃), holmium oxide (Ho₂O₃), erbium oxide (Er₂O₃), thulium oxide (Tm₂O₃), ytterbium oxide (Yb₂O₃), lutetium oxide (Lu₂O₃),

aluminum oxide (Al_2O_3), indium oxide (In_2O_3), germanium oxide (GeO_2), antimony oxide (Sb_2O_3), tellurium oxide (TeO_2), nickel oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel (III) oxide (Ni_2O_3), magnesium oxide (MgO), iron (II) oxide (FeO), iron (III) oxide (Fe_2O_3), copper (II) oxide (CuO),
5 cadmium oxide (CdO), and zirconium oxide (ZrO_2).

Preferred characteristics of the metal compound include: (a) substantial insolubility in aqueous environments, such as acidic or basic aqueous environments (such as those present in the gastric lumen); and (b) ionizable surface charge at the pH of the aqueous environment.

10 The water-insoluble metal compounds can be incorporated into the polymer by one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar
15 methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In one embodiment, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer.

In one embodiment, the metal compound is provided as a fine particulate dispersion of a water-insoluble metal oxide which is incorporated throughout the polymer
20 or at least on the surface of the polymer which is to be adhered to a tissue surface. The metal compound also can be incorporated in an inner layer of the polymer and exposed only after degradation or else dissolution of a "protective" outer layer. For example, a tablet core containing a polymer and metal may be covered with an enteric coating
designed to dissolve when exposed to gastric fluid. The metal compound-enriched core
25 then is exposed and become available for binding to GI mucosa.

Fine metal oxide particles can be produced for example by micronizing a metal oxide by mortar and pestle treatment to produce particles ranging in size, for example, from 10.0 to 300 nm. The metal oxide particles can be incorporated into the polymer, for example, by dissolving or dispersing the particles into a solution or dispersion of the
30 polymer.

Advantageously, metal compounds which are incorporated into polymers to improve their bioadhesive properties can be metal compounds which are already approved by the FDA as either food or pharmaceutical additives, such as zinc oxide.

Suitable polymers which can be used and into which the metal compounds can be incorporated include soluble and water-insoluble, and biodegradable and nonbiodegradable polymers, including hydrogels, thermoplastics, and homopolymers, copolymers and blends of natural and synthetic polymers, provided that they have the requisite fracture strength when mixed with a metal compound. In addition to those listed above, representative polymers which can be used in conjunction with a metal compound include hydrophilic polymers, such as those containing carboxylic groups, including polyacrylic acid. Bioerodible polymers including polyanhydrides, poly(hydroxy acids) and polyesters, as well as blends and copolymers thereof also can be used. Representative bioerodible poly(hydroxy acids) and copolymers thereof which can be used include poly(lactic acid), poly(glycolic acid), poly(hydroxy-butyrac acid), poly(hydroxyvaleric acid), poly(caprolactone), poly(lactide-co-caprolactone), and poly(lactide-co-glycolide). Polymers containing labile bonds, such as polyanhydrides and polyorthoesters, can be used optionally in a modified form with reduced hydrolytic reactivity. Positively charged hydrogels, such as chitosan, and thermoplastic polymers, such as polystyrene also can be used.

Representative natural polymers which also can be used include proteins, such as zein, modified zein, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as dextrans, polyhyaluronic acid and alginic acid. Representative synthetic polymers include polyphosphazenes, polyamides, polycarbonates, polyacrylamides, polysiloxanes, polyurethanes and copolymers thereof. Celluloses also can be used. As defined herein the term "celluloses" includes naturally occurring and synthetic celluloses, such as alkyl celluloses, cellulose ethers, cellulose esters, hydroxyalkyl celluloses and nitrocelluloses. Exemplary celluloses include ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate and cellulose sulfate sodium salt.

Polymers of acrylic and methacrylic acids or esters and copolymers thereof can be used. Representative polymers which can be used include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Other polymers which can be used include polyalkylenes such as polyethylene and polypropylene; polyarylalkylenes such as polystyrene; poly(alkylene glycols), such as poly(ethylene glycol); poly(alkylene oxides), such as poly(ethylene oxide); and poly(alkylene terephthalates), such as poly(ethylene terephthalate). Additionally, polyvinyl polymers can be used, which, as defined herein includes polyvinyl alcohols, polyvinyl ethers, polyvinyl esters and polyvinyl halides. Exemplary polyvinyl polymers include poly(vinyl acetate), polyvinyl phenol and polyvinylpyrrolidone.

Water soluble polymers can also be used. Representative examples of suitable water soluble polymers include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyethylene glycol, copolymers of acrylic and methacrylic acid esters, and mixtures thereof. Water insoluble polymers also can be used. Representative examples of suitable water insoluble polymers include ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or -higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethanes, and mixtures thereof. In one embodiment, a water insoluble polymer and a water soluble polymer are used together, such as in a mixture. Such mixtures are useful in controlled drug release formulations, wherein the release rate can be controlled by varying the ratio of water soluble polymer to water insoluble polymer.

Polymers varying in viscosity as a function of temperature or shear or other physical forces also may be used. Poly(oxyalkylene) polymers and copolymers such as poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) or poly(ethylene oxide)-poly(butylene oxide) (PEO-PBO) copolymers, and copolymers and blends of these polymers with polymers such as poly(alpha-hydroxy acids), including but not limited to lactic, glycolic and hydroxybutyric acids, polycaprolactones, and polyvalerolactones, can be synthesized or commercially obtained. For example, polyoxyalkylene copolymers are described in U.S. Patent Nos. 3,829,506, 3,535,307, 3,036,118, 2,979,578, 2,677,700 and 2,675,619. Polyoxyalkylene copolymers are sold, for example, by BASF under the tradename PLURONICSTM. These materials are applied as viscous solutions at room temperature or lower which solidify at the higher body temperature. Other materials with this behavior are known in the art, and can be utilized as described herein. These include KLUCELTM (hydroxypropyl cellulose), and purified konjac glucomannan gum.

Other suitable polymers are polymeric lacquer substances based on acrylates and/or methacrylates, commonly called EUDRAGITTM polymers (sold by Rohm America, Inc.). Specific EUDRAGITTM polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGITTM RL and EUDRAGITTM RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films, whereas EUDRAGITTM RL is freely permeable and EUDRAGITTM RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGITTM L is pH dependent. EUDRAGITTM L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable.

Polymer solutions that are liquid at an elevated temperature but solid or gelled at body temperature can also be utilized. A variety of thermoreversible polymers are known, including natural gel-forming materials such as agarose, agar, furcellaran, beta-carrageenan, beta-1,3-glucans such as curdlan, gelatin, or polyoxyalkylene containing compounds, as described above. Specific examples include thermosetting biodegradable

polymers for in vivo use described in U.S. Patent No. 4,938,763, the contents of which are incorporated herein by reference.

Polymer Blends with Monomers and/or Oligomers

5 Polymers with enhanced bioadhesive properties are provided by incorporating anhydride monomers or oligomers into one of the polymers listed above by dissolving, dispersing, or blending, as taught by U.S. Patent Nos. 5,955,096 and 6,156,348, the contents of which are incorporated herein by reference. The polymers may be used to form drug delivery systems which have improved ability to adhere to tissue surfaces, such as mucosal membranes. The anhydride oligomers are formed from organic diacid monomers, preferably the diacids normally found in the Krebs glycolysis cycle. Anhydride oligomers which enhance the bioadhesive properties of a polymer have a molecular weight of about 5000 or less, typically between about 100 and 5000 daltons, or include 20 or fewer diacid units linked by anhydride linkages and terminating in an anhydride linkage with a carboxylic acid monomer.

10 The oligomer excipients can be blended or incorporated into a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers, including those described above. In one embodiment, anhydride oligomers may be combined with metal oxide particles, such as those described above, to improve bioadhesion even more than with the organic additives alone. Organic dyes, because of their electronic charge and hydrophobicity or hydrophilicity, can either increase or decrease the bioadhesive properties of polymers when incorporated into the polymers.

15 As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. In one embodiment, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds have high chemical reactivity.

The oligomers can be formed in a reflux reaction of the diacid with excess acetic anhydride. The excess acetic anhydride is evaporated under vacuum, and the resulting oligomer, which is a mixture of species which include between about one to twenty diacid units linked by anhydride bonds, is purified by recrystallizing, for example, from toluene or other organic solvents. The oligomer is collected by filtration, and washed, for example, in ethers. The reaction produces anhydride oligomers of mono and poly acids with terminal carboxylic acid groups linked to each other by anhydride linkages.

The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). The anhydride bonds can be detected by Fourier transform infrared spectroscopy by the characteristic double peak at 1750 cm^{-1} and 1820 cm^{-1} , with a corresponding disappearance of the carboxylic acid peak normally at 1700 cm^{-1} .

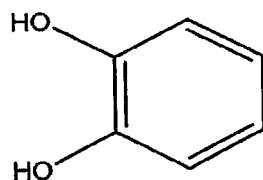
In one embodiment, the oligomers may be made from diacids described for example in U.S. Patent Nos. 4,757,128, 4,997,904 and 5,175,235, the disclosures of which are incorporated herein by reference. For example, monomers such as sebacic acid, bis(p-carboxy-phenoxy)propane, isophthalic acid, fumaric acid, maleic acid, adipic acid or dodecanedioic acid may be used.

Organic dyes, because of their electronic charge and hydrophilicity or hydrophobicity, may alter the bioadhesive properties of a variety of polymers when incorporated into the polymer matrix or bound to the surface of the polymer. A partial listing of dyes that affect bioadhesive properties include, but are not limited to: acid fuchsin, alcian blue, alizarin red s, auramine o, azure a and b, Bismarck brown y, brilliant cresyl blue ald, brilliant green, carmine, cibacron blue 3GA, congo red, cresyl violet acetate, crystal violet, eosin b, eosin y, erythrosin b, fast green fcf, giemsa, hematoxylin, indigo carmine, Janus green b, Jenner's stain, malachite green oxalate, methyl blue, methylene blue, methyl green, methyl violet 2b, neutral red, Nile blue a, orange II, orange G, orcein, paraosaniline chloride, phloxine b, pyronin b and y, reactive blue 4 and 72, reactive brown 10, reactive green 5 and 19, reactive red 120, reactive yellow 2,3, 13 and 86, rose bengal, safranin o, Sudan III and IV, Sudan black B and toluidine blue.

Polymers Functionalized with Hydroxy-Substituted Aromatic Groups

Polymers having an aromatic group which contains one or more hydroxyl groups grafted onto them or coupled to individual monomers are also suitable for use in the bioadhesive coatings of the invention, as described in U.S. Provisional Application No. 60/528,042, filed December 9, 2003, U.S. Patent Publication No. 2005/0201974, and WO 2005/056708, the contents of which are incorporated herein by reference. Such polymers can be biodegradable or non-biodegradable polymers. The polymer can be hydrophobic. Preferably, the aromatic group is catechol or a derivative thereof and the polymer contains reactive functional groups, so that a hydroxyl-substituted aromatic group can be readily attached. Typically, the polymer is a polyanhydride and the aromatic compound is the catechol derivative DOPA. These materials display bioadhesive properties superior to conventional bioadhesives used in therapeutic and diagnostic applications.

As used herein "catechol moiety" refers to a moiety with the following generic structure:



Catechol

The molecular weight of the suitable polymers and percent substitution of the polymer with the aromatic group may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 25%, 30%, 40%, or 50%, or up to 100% substitution. Generally, about 10% to about 40%, such as about 20% to about 30% of the monomers in the polymeric backbone are substituted with at least one aromatic group. Preferably, about 100% of the monomers in the polymeric backbone are substituted with at least one aromatic group. The resulting polymer typically has a molecular weight ranging from about 1 to 2,000 kDa.

The polymer that forms that backbone of the bioadhesive material can be a biodegradable polymer. Examples of preferred biodegradable polymers include synthetic polymers such as poly hydroxy acids, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid),
 5 poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides, collagen and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other
 10 modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, chitin, chitosan, pectin, amylopectin, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo* and by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers.

Suitable polymers can be formed by first coupling the aromatic compound to the
 15 monomer and then polymerizing. In this example, the monomers may be polymerized to form a polymer backbone, including biodegradable and non-biodegradable polymers. Suitable polymer backbones include, but are not limited to, polyanhydrides, polyamides, polycarbonates, polyalkylenes, polyalkylene oxides such as polyethylene glycol, polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols,
 20 polyvinyl ethers, polyvinyl esters, polyethylene, polypropylene, poly(vinyl acetate), poly(vinyl chloride), polystyrene, polyvinyl halides, polyvinylpyrrolidone, polyhydroxy acids, polysiloxanes, polyurethanes and copolymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-
 25 propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, and polyacrylates such as poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate),
 30 poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate).

A suitable polymer backbone can be a known bioadhesive polymer that is hydrophilic or hydrophobic. Hydrophilic polymers include CARBOPOL™, polycarbophil, cellulose esters, and dextran.

5 Non-biodegradable polymers, especially hydrophobic polymers are also suitable as polymer backbones. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(methacrylic acid), copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene maleic anhydride), polyamides, copolymers and mixtures thereof and dextran, cellulose and derivatives thereof.

10 Hydrophobic polymer backbones include polyanhydrides, poly(ortho)esters, and polyesters such as polycaprolactone. Preferably, the polymer is sufficiently hydrophobic that it is not readily water soluble, for example the polymer should be soluble up to less than about 1% w/w in water, preferably about 0.1% w/w in water at room temperature or body temperature. In the most preferred embodiment, the polymer is a polyanhydride, such as a poly(butadiene maleic anhydride) or another copolymer of maleic anhydride.
15 Polyanhydrides may be formed from dicarboxylic acids as described in U.S. Patent No. 4,757,128 to Domb et al., incorporated herein by reference. Suitable diacids include aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acid, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids, and aromatic and aliphatic
20 heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. Suitable monomers include sebacic acid (SA), fumaric acid (FA), bis(p-carboxyphenoxy)propane (UP), isophthalic acid (IPh), and dodecanedioic acid (DD).

25 A wide range of molecular weights are suitable for the polymer that forms the backbone of the bioadhesive material. The molecular weight may be as low as about 200 Da (for oligomers) up to about 2,000 kDa. Preferably the polymer has a molecular weight of at least 1,000 Da, more preferably at least 2,000 Da, most preferably the polymer has a molecular weight of up to 20 kDa or up to 200 kDa. The molecular weight of the polymer may be up to 2,000 kDa (e.g., 20 kDa to 1,000 kDa or 2,000 kDa).

30 The range of substitution on the polymer can vary greatly and depends on the polymer used and the desired bioadhesive strength. For example, a butadiene maleic

anhydride copolymer that is 100% substituted with DOPA will have the same number of DOPA molecules per chain length as a 67% substituted ethylene maleic anhydride copolymer. Typically, the polymer has a percentage substitution ranging from 10% to 100%, preferably ranging from 50% to 100%.

5 The polymers and copolymers that form the backbone of the bioadhesive material include reactive functional groups that interact with the functional groups on the aromatic compound.

 It is important that the polymer or monomer that forms the polymeric backbone contains accessible functional groups that easily react or interact with molecules
10 contained in the aromatic compounds, such as amines and thiols. In a preferred embodiment, the polymer contains amino reactive moieties, such as aldehydes, ketones, carboxylic acid derivatives, cyclic anhydrides, alkyl halides, aryl asides, isocyanates, isothiocyanates, succinimidyl esters or a combination thereof.

 Preferably, the aromatic compound containing one or more hydroxyl groups is
15 catechol or a derivative thereof. Optionally the aromatic compound is a polyhydroxy aromatic compound, such as a trihydroxy aromatic compound (e.g., phloroglucinol) or a multihydroxy aromatic compound (e.g., tannin). The catechol derivative may contain a reactive group, such as an amino, thiol, or halide group. The preferred catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine. Tyrosine, the
20 immediate precursor of DOPA, which differs only by the absence of one hydroxyl group in the aromatic ring, can also be used. Tyrosine is capable of conversion (e.g., by hydroxylation) to the DOPA form. A particularly preferred aromatic compound is an amine-containing aromatic compound, such as an amine-containing catechol derivative (e.g., dopamine).

25 Two general methods are used to form the polymer product. In one example, a compound containing an aromatic group which contains one or more hydroxyl groups is grafted onto a polymer. In this example, the polymeric backbone is a biodegradable polymer. In a second example, the aromatic compound is coupled to individual monomers and then polymerized.

30 Any chemistry which allows for the conjugation of a polymer or monomer to an aromatic compound containing one or more hydroxyl groups can be used, for example, if

the aromatic compound contains an amino group and the monomer or polymer contains an amino reactive group, this modification to the polymer or monomer is performed through a nucleophilic addition or a nucleophilic substitution reaction, such as a Michael-type addition reaction, between the amino group in the aromatic compound and the polymer or monomer. Additionally, other procedures can be used in the coupling reaction. For example, carbodiimide and mixed anhydride based procedures form stable amide bonds between carboxylic acids or phosphates and amino groups, bifunctional aldehydes react with primary amino groups, bifunctional active esters react with primary amino groups, and divinylsulfone facilitates reactions with amino, thiol, or hydroxy groups.

The aromatic compounds are grafted onto the polymer using standard techniques to form the bioadhesive material. In one example, L-DOPA is grafted to maleic anhydride copolymers by reacting the free amine in L-DOPA with the maleic anhydride bond in the copolymer.

A variety of different polymers can be used as the backbone of the bioadhesive material, as described above. Additional representative polymers include 1:1 random copolymers of maleic anhydride with ethylene, vinyl acetate, styrene, or butadiene. In addition, a number of other compounds containing aromatic rings with hydroxy substituents, such as tyrosine or derivatives of catechol, can be used in this reaction.

In another embodiment, the polymers are prepared by conjugate addition of a compound containing an aromatic group that is attached to an amine to one or more monomers containing an amino reactive group. In a preferred method, the monomer is an acrylate or the polymer is acrylate. For example, the monomer can be a diacrylate such as 1,4-butanediol diacrylate, 1,3-propanediol diacrylate, 1,2-ethanediol diacrylate, 1,6-hexanediol diacrylate, 2,5-hexanediol diacrylate or 1,3-propanediol diacrylate. In an example of the coupling reaction, the monomer and the compound containing an aromatic group are each dissolved in an organic solvent (e.g., THF, CH₂Cl₂, methanol, ethanol, CHCl₃, hexanes, toluene, benzene, CCl₄, glyme, diethyl ether, etc.) to form two solutions. The resulting solutions are combined, and the reaction mixture is heated to yield the desired polymer. The molecular weight of the synthesized polymer can be controlled by

the reaction conditions (e.g., temperature, starting materials, concentration, solvent, etc) used in the synthesis.

For example, a monomer, such as 1,4-phenylene diacrylate or 1,4-butanediol diacrylate having a concentration of 1.6 M, and DOPA or another primary amine containing aromatic molecule are each dissolved in an aprotic solvent such as DMF or DMSO to form two solutions. The solutions are mixed to obtain a 1:1 molar ratio between the diacrylate and the amine group and heated to 56 °C to form a bioadhesive material.

Non-Bioadhesive Polymers

In certain embodiments, optionally bioadhesive polymers, coatings and/or cylinders are non-bioadhesives. As used herein, a non-bioadhesive element of a formulation does not increase adhesion of a formulation to an endothelial (e.g, mucosal, gastrointestinal) surface or, unless otherwise indicated, minimally increases adhesion of a formulation to an endothelial surface. In certain embodiments, a non-bioadhesive coating adheres to a biological surface with an adherence of less than 5 N/m², less than 2 N/m², less than 1 N/m², less than 0.5 N/m², less than 0.1 N/m², less than 0.05 N/m², less than 0.01 N/m² or even less than 0.001 N/m². Preferably, such polymers, coatings and/or coating are rate-controlling or include a rate-controlling polymer.

Non-bioadhesive polymers suitable for use in the invention include water-soluble and water-insoluble polymers. Examples of suitable water-soluble polymers include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycol, copolymers of acrylic and methacrylic acid esters, and mixtures thereof. Examples of suitable water-insoluble polymers include ethyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl

isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethanes, and mixtures thereof. Exemplary polymers are ethylcellulose, polyacrylic acids (e.g., Eudragits™, Acryl-Eze™) hydroxypropyl cellulose, polyethylene oxide and polyvinylpyrrolidone.

5 Coatings

Preferred optionally bioadhesive coatings do not appreciably swell upon hydration, such that they do not substantially inhibit or block movement (e.g., of ingested food) through the gastrointestinal tract, as compared to the polymers disclosed by Duchene et al. Generally, polymers that do not appreciably swell upon hydration include
10 one or more hydrophobic regions, such as a polymethylene region (e.g., $(CH_2)_n$, where n is 4 or greater). The swelling of a polymer can be assessed by measuring the change in volume when the polymer is exposed to an aqueous solution. Polymers that do not appreciably swell upon hydration expand in volume by 50% or less when fully hydrated. Preferably, such polymers expand in volume by less than 25%, less than 20%, less than
15 15%, less than 10% or less than 5%. In certain embodiments, bioadhesive coatings are mucophilic.

In one embodiment, a polymer that does not appreciably swell upon hydration (e.g., a hydrophobic polymer) is mixed or blended with a polymer that does swell or a hydrophilic substance (e.g., Carbopol™, poly(acrylic acid), small organic acids such as
20 citric acid, maleic acid, fumaric acid, hydrophilic drugs, ionic and non-ionic detergents, sugars, salts such as NaCl, disintegrants). In certain embodiments, the amount of swelling or hydration in the polymer does not substantially interfere with bioadhesiveness. In certain embodiments, the amount of swellable polymer or hydrophilic substance is selected to sufficiently hydrate the non-swellable polymer to
25 enhance its bioadhesiveness. In certain such embodiments, the weight ratio of swellable to non-swellable polymer or hydrophilic substance to non-swellable polymer can be varied in order to obtain a coating that combines a desired amount of swelling (e.g., for faster adhesion) with longer-lasting adhesion, such as from 5:1 to 1:5 or 2:1 to 1:2. For example, the swellable polymer and/or hydrophilic substance can comprise about 1% to
30 about 30% by weight of a bioadhesive coating.

In one embodiment, the optionally bioadhesive polymeric coating consists of two layers, an inner optionally bioadhesive layer that does not substantially swell upon hydration and an outer optionally bioadhesive layer that is readily hydratable and optionally bioerodable, such as one comprised of Carbopol™.

5 The optionally bioadhesive polymers discussed above can be mixed with one or more plasticizers or thermoplastic polymers. Such agents typically increase the strength and/or reduce the brittleness of polymeric coatings. Examples of plasticizers include dibutyl sebacate, polyethylene glycol, triethyl citrate, dibutyl adipate, dibutyl fumarate, diethyl phthalate, ethylene oxide-propylene oxide block copolymers such as Pluronic™
10 F68 and di(sec-butyl) fumarate. Examples of thermoplastic polymers include polyesters, poly(caprolactone), polylactide, poly(lactide-co-glycolide), methyl methacrylate (e.g., EUDRAGIT™), cellulose and derivatives thereof such as ethyl cellulose, cellulose acetate and hydroxypropyl methyl cellulose (HPMC) and large molecular weight polyanhydrides. The plasticizers and/or thermoplastic polymers are mixed with a
15 optionally bioadhesive polymer to achieve the desired properties. Typically, the proportion of plasticizers and thermoplastic polymers, when present, is from 0.5% to 40% by weight.

In certain embodiments, bioadhesive and/or mucoadhesive polymers may be combined with suitable (e.g., biocompatible) non-bioadhesive/mucoadhesive polymers to
20 vary the adhesiveness (e.g., fracture strength) of the coating. The combination may be a purely physical combination (by blending, mixing, codissolving, etc.), or may be a chemical one (e.g., by crosslinking the polymers, or by copolymerizing monomers of a bioadhesive/mucoadhesive polymer with monomers of a non-bioadhesive/mucoadhesive polymer).

25 In one embodiment, the optionally bioadhesive polymer coating, in a dry packaged form of a tablet, is a hardened shell.

A tablet or a drug eluting device can have one or more coatings in addition to the optionally bioadhesive polymeric coating, e.g., covering the surface of the optionally bioadhesive coating. These coatings and their thickness can, for example, be used to
30 control where in the gastrointestinal tract the optionally bioadhesive coating becomes

exposed. In one example, the additional coating prevents the optionally bioadhesive coating from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine (e.g., an enteric coating).

Examples of coatings include methylmethacrylates, zein, cellulose acetate, cellulose phthalate, HMPC, sugars, enteric polymers, gelatin and shellac. Premature dissolution of a tablet in the mouth can be prevented with hydrophilic polymers such as HPMC or gelatin.

Coatings used in tablets of the invention typically include a pore former such that the coating is permeable to the drug.

Excipients

The cores of tablets and drug eluting devices of the invention may contain one or more excipients, carriers or diluents. These excipients, carriers or diluents can be selected, for example, to control the disintegration rate of a tablet or drug eluting device. In particular, it is advantageous for the disintegration time to be less than the gastric (or small/large intestinal) retention time. In one embodiment, the disintegration time of a tablet is at least 25% of the gastric retention time, at least 50% of the gastric retention time or at least 75% of the gastric retention time.

It will be understood by those skilled in the art that any vehicle or carrier conventionally employed and which is inert with respect to the active agent, and in certain embodiments does not interfere with bioadhesiveness, may be utilized for preparing and administering the pharmaceutical compositions of the present invention. Illustrative of such vehicles and carriers are those described, for example, in Remington's Pharmaceutical Sciences, 18th ed. (1990), the disclosure of which is incorporated herein by reference.

The formulations of the present invention for use in a subject comprise one or more drugs, optionally together with one or more acceptable carriers or diluents therefor and optionally other therapeutic ingredients. The carriers or diluents must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy.

All methods include the step of bringing into association the drug with the carrier or diluent which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the agent with the carriers and then, if necessary, dividing the product into unit dosages thereof.

5 Examples of carriers and diluents include pharmaceutically accepted hydrogels such as alginate, chitosan, methylmethacrylates, cellulose and derivatives thereof (microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, ethylcellulose), agarose and PovidoneTM, kaolin, magnesium stearate, starch, lactose, sucrose, density-controlling agents such as barium sulfate and oils,
10 dissolution enhancers such as aspartic acid, citric acid, glutamic acid, tartartaric acid, sodium bicarbonate, sodium carbonate, sodium phosphate, glycine, tricine and TRIS.

 For multi-layer tablets in particular, the tablet typically includes at least one polymer or excipient. The polymer may be degradable or non-degradable. Suitable
15 degradable polymers include polyesters, such as poly(lactic acid) (p[LA]), poly(lactide-co-glycolide) (p[LGA]), poly(caprolactone) (p[CL]); polyanhydrides such as poly(fumaric-co-sebacic anhydride) (p[FASA]) in molar ratios of 20:80 to 90:10,
poly(carboxyphenoxypropane-co-sebacic anhydride) (p[CPPSA]), poly(adipic anhydride) (p[AA]); polyorthoesters; polyamides; and polyimides. Other suitable polymers include
hydrogel-based polymers such as agarose, alginate, and chitosan. Suitable non-degradable
20 polymers include polystyrene, polyvinylphenol, and polymethylmethacrylates (EudragitsTM).

 The excipients, carriers or diluents can also be selected to control the time until a tablet or drug eluting device detaches from a mucosal membrane. In particular, the
25 addition of one or more disintegrating agents will reduce the time until a tablet or drug eluting device detaches. Alternatively or in combination with the disintegrating agents, an agent that interferes with the mucosa-tablet/device adhesion can be used to control the time until detachment occurs.

 Suitable excipients include stabilizers, plasticizers, wetting agents, antitack agents, tack agents, foam agents, antifoam agents, binders, fillers, extenders, flavorants,
30 dispersants, surfactants, solubilizers, solubilization inhibitors, glidants, lubricants, antiadherents, adherents, coatings, protective agents, sorbents, suspending agents,

crystallization inhibitors, recrystallization inhibitors, disintegrants, acidulants, diluents, alkalizing agents, antioxidants, preservatives, colorants, electrolytes, solvents, antisolvents, accelerating agents, and/or retarding agents. Examples include alginate, chitosan, methylmethacrylates (Eudragits™), celluloses (especially microcrystalline
5 cellulose, hydroxypropylmethylcellulose, ethylcellulose etc), agarose, Povidone™, lactose, microcrystalline cellulose, kaolin starch, magnesium stearate, stearic acid, glycerol monostearate, sucrose, compressible sugar, lactose and barium sulfate.

The present invention can be further understood by reference to the following non-limiting examples.

EXEMPLIFICATION

Example 1: Longitudinally Compressed Tablets Containing 250 mg Valacyclovir HCl (Lot # 502-094)

15 Longitudinally compressed core tablets (LCT) were prepared by using a pair of 0.2618" dies (Natoli Engineering). The compound die was filled with 250 mg of a Valacyclovir immediate release (IR) dry blend. The tablets were prepared by direct compaction at 500 psi for 1 second using standard 0.2618" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained
20 250 mg Valacyclovir. The composition of core tablets is provided in Table 1.

The core tablets were first coated peripherally with an impermeable, solvent-cast film of polycaprolactone (PCL, MW 200 kDa) that was attached to the tablet by heat sealing at 40-60°C. Then, a second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first
25 film. Fumaric anhydride oligomer, polycaprolactone (MW 200 kDa) and dibutyl sebacate, in the 40%:50%:10% w/w ratio, were co-dissolved in dichloromethane and a film was prepared by solvent-casting on a tray. After 24 hrs of drying, the dry, cut film was applied over the existing, impermeable, PCL coating and the edges of the film were joined by heating. The longitudinal-section of these dosage forms is illustrated in Figure

30 1.

Table 1: Composition of Valacyclovir HCl 250 mg Core Tablet Formulation

Ingredients	IR Layer
Valacyclovir *	277.8
Hydroxypropyl cellulose	75.0
Compressible Sugar	132.7
Crospovidone, NF	12.5
Magnesium Stearate	2.0
Total	500.0

* 277.8 mg Valacyclovir HCl is equivalent to 250 mg Valacyclovir

The bioadhesive-coated tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. 50% of the valacyclovir is released in 30 minutes, and all of it is released by 2 hours.

It should be evident to those skilled in the art that drug release from LCT's covered with an impermeable first coat of PCL (or other impermeable polymer such as ethyl cellulose, cellulose acetate, zein etc) and a second, overlying, bioadhesive coat of PCL and Spheromer™ II should be identical to that of LCT's coated only with a single layer of impermeable polymer. The bioadhesive coating facilitates intimate contact of the dosage form with GI mucosa, enabling prolonged retention in GIT and shortened diffusion distances for drug absorption.

Example 2: Longitudinally Compressed Tablets Containing 400 mg Gabapentin (Lot # 411-104, 412-047 and 412-006)

Longitudinally compressed core tablets (LCTs) were prepared by using a pair of 0.2900" dies (Natoli Engineering). The dies were carefully aligned and firmly joined together to form a compound die. The compound die was filled with 800 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2900" upper/lower punches and a GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 400 mg Gabapentin. The composition of core tablets is provided in Table 2.

The LCTs were coated peripherally first with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive

Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 1.

Table 2: Composition of Gabapentin 400 mg LCT Core Tablet Formulations

Ingredients	Weight (mg)		
	411-104	412-047	412-006
Gabapentin	400.0	400.0	400.0
Hydroxypropyl cellulose	200.0	200.0	200.0
Polyethylene oxide	120.0	80.0	80.0
Hydroxypropylmethyl cellulose	0	40.0	60.0
Lactose	72.8	72.8	52.8
Polyvinylpyrrolidone	4.0	4.0	4.0
Magnesium Stearate	3.2	3.2	3.2
Total	800.0	800.0	800.0

Coated Gabapentin tablets were tested for release profile in 0.1 HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 35% of the gabapentin in the Lot # 411-104 formulation is released in 2 hours, 70% by 4 hours, about 95% by 6 hours, and all of it is released by 8 hours. The release profile of the Lot # 412-047 gabapentin formulation is about 25% of the drug by 2 hours, almost 50% by 4 hours, 80% by 8 hours, and all of it by 12 hours. Gabapentin is released from the third formulation (Lot # 412-006) in the following manner: 20% by 4 hours, about 40% by 8 hours, about 70% by 16 hours, and 100% by 24 hours.

Example 3: Longitudinally Compressed Tablets Containing 500 mg Gabapentin (Lot # 411-029, 411-106 and 411-108)

Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The compound die was filled with 800 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2900" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 500 mg Gabapentin. The compositions of core tablets are provided in Table 3.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 2. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers) or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 1.

Table 3: Composition of Gabapentin 500 mg Core Tablet Formulations

Ingredients	Weight (mg)		
	411-029	411-106	411-108
Gabapentin	500.0	500.0	500.0
Hydroxypropyl cellulose	200.0	200.0	200.0
Hydroxypropylmethyl cellulose	60.0	40.0	20.0
Polyethylene oxide	36.8	56.8	76.8
Magnesium Stearate	3.2	3.2	3.2
Total	800.0	800.0	800.0

Coated Gabapentin tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. A little more than 20% of the gabapentin in the Lot # 411-108 formulation is released in 1 hour, 35% by 2 hours, about 70% by 4 hours, and all of it is released by 6 hours. The release profile of the Lot # 411-

106 gabapentin formulation is about almost 30% of the drug by 2 hours, almost 50% by 4 hours, almost 80% by 8 hours, and all of it by 12 hours. Gabapentin is released from the third formulation (Lot # 411-029) in the following manner: 10% by 1 hour, a little more than 25% by 4 hours, almost 50% by 8 hours, a little more than 60% by 12 hours, about
5 75% by 16 hours, and 100% by 24 hours.

Example 4: Longitudinally Compressed Tablets Containing 225 mg Valacyclovir (Lot # 502-063, 502-065 and 502-067)

10 Longitudinally compressed core tablets were prepared by using a pair of 0.2618" dies (Natoli Engineering). The compound die was filled with 500 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2618" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 225 mg Valacyclovir. The
15 compositions of core tablets are provided in Table 4.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers
20 comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 1.

Table 4: Composition of Valacyclovir 225 mg LCT Core Tablet Formulations

Ingredients	Weight (mg)		
	502-063	502-065	502-067
Valacyclovir HCl*	250.0	250.0	250.0
Hydroxypropyl cellulose	125.0	125.0	125.0
Lactose	58.0	45.5	33.0
Polyethylene oxide	50.0	50.0	50.0
Hydroxypropylmethyl cellulose	12.5	25.0	37.5
Polyvinylpyrrolidone	2.5	2.5	2.5
Magnesium Stearate	2.0	2.0	2.0
Total	500.0	500.0	500.0

* Equivalent to 225 mg Valacyclovir

Coated Valacyclovir HCl tablets were tested for release profiles in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 25% of the valacyclovir in the Lot # 502-063 formulation is released in 1 hour, almost 50% by 2 hours, about 75% by 4 hours, and all of it is released by 8 hours. The release profile of the Lot # 502-065 valacyclovir formulation is a little more than 20% of the drug by 1 hour, a little more than 30% by 2 hours, almost 60% by 4 hours, about 95% by 8 hours, and all of it by 12 hours. Valacyclovir is released from the third formulation (Lot # 502-067) in the following manner: about 15% by 1 hour, almost 25% by 2 hours, a little more than 40% by 4 hours, about 75% by 8 hours, and 100% by 16 hours.

Example 5: Longitudinally Compressed Tablets Containing 450 mg Valacyclovir (Lot # 502-069, 502-071 and 502-073)

Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The compound die was filled with 800 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2900" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 500 mg Valacyclovir HCl. The compositions of core tablets are provided in Table 5.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 1.

Table 5: Composition of Valacyclovir 450 mg Core Tablet Formulations

Ingredients	Weight (mg)		
	502-069	502-071	502-073
Valacyclovir HCl *	500.0	500.0	500.0
Hydroxypropyl cellulose	200.0	200.0	200.0
Polyethylene oxide	96.8	76.8	56.8
Hydroxypropylmethyl cellulose	-	20.0	40.0
Magnesium Stearate	3.2	3.2	3.2
Total	800.0	800.0	800.0

* Equivalent to 450 mg Valacyclovir

Coated Valacyclovir HCl tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 20% of the valacyclovir in the Lot # 502-069 formulation is released in 1 hour, about 40% by 2 hours, about 65% by 4 hours, and all of it is released by 8 hours. The release profile of the Lot # 502-071 valacyclovir formulation is about 20% of the drug in 1 hour, about 50% by 4 hours, almost 90% by 8 hours, and all of it by 12 hours. Valacyclovir is released from the third formulation (Lot # 502-073) in the following manner: about 10% by 1 hour, a little more than 30% by 4 hours, 80% in 12 hours, and 100% by 16 hours.

Example 6: Longitudinally Compressed Tablets containing 500 mg Metformin HCl (Lot # 412-089, 412-091, 412-093 and 412-099)

Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The die was filled with 800 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2900" upper/lower punches and a GlobePharma Manual Tablet Compaction Machine (model MTCM-1). Each tablet contained 500 mg Metformin HCl. The core compositions of tablets are provided in Table 6.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers) or combinations of these polymers can also be applied over the impermeable coating. The cross-section of this dosage form is illustrated in Figure 1.

Table 6: Composition of Metformin HCl 500 mg Core Tablet Formulations

Ingredients	Weight (mg)			
	412-089	412-091	412-093	412-099
Metformin HCl	500.0	500.0	500.0	500.0
Hydroxypropyl cellulose	200.0	200.0	200.0	200.0
Hydroxypropylmethyl cellulose	76.8	56.8	60.0	60.0
Polyethylene oxide	20.0	40.0	36.8	-
Polyvinylpyrrolidone (Povidone)	-	-	-	36.8
Magnesium Stearate	3.2	3.2	3.2	3.2
Total	800.0	800.0	800.0	800.0

Coated metformin tablets were tested for release profiles in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. 30% of the metformin HCl in the Lot # 412-093 formulation is released in 1 hour, a little more than 50% by 2 hours, almost 80% by 4 hours, almost 90% by 6 hours, and all of it is released by 24 hours.

Example 7: Longitudinally Compressed Tablets containing 30 mg Pioglitazone HCl (Lot # 503-036)

Longitudinally compressed tablets were prepared by using a pair of 0.2618" dies joined together in a similar fashion to the method described in Example 1. The compound die was filled with 500 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 500 psi for 1 second using a standard 0.2618" lower punch, a special 0.2618" upper punch (2" tip length), and a manual tablet press in a similar fashion to the method described in Example 1. Each tablet contained 30 mg Pioglitazone HCl. The core composition of tablet is provided in Table 7.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release.

Table 7: Composition of Pioglitazone HCl 30 mg Core Tablet Formulation

Ingredients	Weight (mg)
Pioglitazone HCl	30.0
Lactose	325.0
Hydroxypropyl cellulose	125.0
Hydroxypropylmethyl cellulose	17.5
Magnesium Stearate	2.5
Total	500.0

Coated pioglitazone tablets were tested for release profiles in 0.1 N HCl buffer containing 0.3 N KCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. Almost 20% of the Pioglitazone in the Lot # 503-036 formulation is released in 30

minutes, a little more than 20% in 1 hour, 50% by 8 hours, 80% by 16 hours, and all of it is released by 24 hours.

Example 8: Longitudinally Compressed Tablet containing 30 mg Pioglitazone HCl
(Lot # 503-203)

Longitudinally compressed tablets were prepared by using a pair of 0.2618" dies joined together in a similar fashion to the method described in Example 1. The compound die was filled with 300 mg of a dry blend of drug and excipients. The tablets were prepared by direct compaction at 500 psi for 1 second using a standard 0.2618" lower punch, a special 0.2618" upper punch (2" tip length), and a manual tablet press described in Example 1. Each tablet contained 30 mg Pioglitazone HCl.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 1. The core composition of tablet is provided Table 8.

Table 8: Composition of Pioglitazone HCl 30 mg Core Tablet Formulation

Ingredients	Weight (mg)
Pioglitazone HCl	30.0
Lactose	261.0
Croscarmellose Sodium	7.5
Magnesium Stearate	1.5
Total	300.0

Coated pioglitazone tablets were tested for release profile in 0.1 N HCl buffer containing 0.3 N KCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm.

Almost 80% of the Pioglitazone is released in 10 minutes, a little more than 90% in 20 minutes, and the release profile plateaus at 30 minutes.

Example 9: Longitudinally Compressed Tablets Containing 500 mg Valacyclovir HCl (Lot # 501-213)

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Longitudinally compressed bilayer core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The compound die was filled first with 650 mg of a Valacyclovir controlled release (CR) dry blend, and then with 150 mg of a Valacyclovir immediate release (IR) dry blend. The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2900" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 450 mg Valacyclovir HCl.

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The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 2. The core composition of tablet is provided in Table 9.

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Table 9: Composition of Valacyclovir HCl 500 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	CR Layer	IR Layer
Valacyclovir HCl *	400.00	100.00
Hydroxypropyl cellulose	162.50	-
Hydroxypropylmethyl cellulose	48.75	-
Polyethylene oxide	36.14	-
Compressible Sugar	-	26.90
Polyvinylpyrrolidone	-	22.50
Magnesium Stearate	2.60	0.60
Total	650.0	150.0

* Equivalent to 450 mg Valacyclovir

Coated tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the
 5 USP II dissolution apparatus at 100 rpm. About 20% of the valacyclovir in the Lot # 501-
 213 formulation is released in 30 minutes, about 25% in 1 hour, 50% by 8 hours, almost
 80% by 16 hours, and all of it is released by 24 hours.

**Example 10: Longitudinally Compressed Bilayer Tablets containing 2.5 mg
 10 Glipizide and 500 mg Metformin HCl (Lot # 502-105)**

Longitudinally compressed bilayer tablets were prepared by using a pair of
 0.2900" dies, standard 0.2900" upper/lower punches, and a manual tablet press described
 in Example 1. The compound die was filled first with 700 mg of a dry blend of
 15 Metformin HCl and excipients (layer 1), and then with 100 mg of a dry blend of Glipizide
 and excipients (layer 2). The bilayer core tablets were compacted at 4000 psi for 1
 second. Each tablet contained 2.5 mg Glipizide and 500 mg Metformin HCl.

The LCTs were coated peripherally with a single layer of impermeable PCL film
 that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer
 20 II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the
 first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers
 comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers

blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 2. The core composition of tablet is provided in Table 10.

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Table 10: Composition of Glipizide/Metformin HCl, 2.5 mg/500 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	Layer 1	Layer 2
Metformin HCl	500.0	-
Glipizide	-	2.5
Hydroxypropyl cellulose	140.0	20.0
Hydroxypropylmethyl cellulose	35.0	-
Polyethylene oxide	22.2	-
Compressible Sugar	-	74.6
Polyvinylpyrrolidone (Crospovidone)	-	2.5
Magnesium Stearate	2.8	0.4
Total	700.0	100.0

10 Bioadhesive longitudinally compressed Glipizide-Metformin HCl tablets were tested for release profile in phosphate buffered saline (PBS) solution (pH 6.8) at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 30% of the glipizide in the Lot # 502-105 formulation is released in 30 minutes, almost 70% by 2 hours, and 80% by 4 hours, and plateaus at almost 90% by 8 hours. The release profile for metformin is as follows: a little more than 10% in 30 minutes, about 25% in 2 hours, about 70% in 8
15 hours, and 100% by 16 hours.

Example 11: Longitudinally Compressed Tablets Containing 250 mg Gabapentin and 250 mg Sodium Valproate (Lot # 412-010)

20 Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The die was filled first with 400 mg of a dry blend of Gabapentin and excipients, and then with 400 mg of a dry blend of Sodium Valproate and excipients. The tablets were prepared by direct compaction at 4000 psi for 1 second using

standard 0.2900" upper/lower punches and the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 250 mg Gabapentin and 250 mg Sodium Valproate. The composition of core tablets is provided in Table 11.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of these dosage forms is illustrated in Figure 2.

Table 11: Composition of Gabapentin/Sodium Valproate 250 mg / 250 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	Gabapentin Layer	Sod. Valproate
Gabapentin	250.0	-
Sodium Valproate	-	250.0
Hydroxypropyl cellulose	100.0	100.0
Polyvinylpyrrolidone	-	23.6
Hydroxypropylmethyl	30.0	12.0
Polyethylene oxide	18.4	-
Lactose	-	12.8
Magnesium Stearate	1.6	1.6
Total	400.0	400.0

Coated tablets were tested for release profile in phosphate buffered saline (PBS) solution, pH 6.8, at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 35% of the sodium valproate in the Lot # 412-010 formulation is released in 30 minutes, about 65% by 2 hours, and 100% by 6 hours. The release profile for gabapentin is as

follows: almost 10% in 30 minutes, almost 25% in 2 hours, about 45% in 8 hours, a little more than 80% by 16 hours, and 100% by 24 hours.

Example 12: Longitudinally Compressed Bilayer Tablets containing 4 mg

5 Rosiglitazone Maleate and 500 mg Metformin HCl (Lot # 503-167)

Longitudinally compressed bilayer tablets were prepared by using a pair of 0.2900" dies joined together as described previously. The compound die was filled first with 800 mg of a dry blend of Metformin HCl and excipients (layer 1), and then with 100
10 mg of a dry blend of Rosiglitazone Maleate and excipients (layer 2). The tablets were prepared by direct compaction at 500 psi for 1 second using a standard 0.2900" lower punch, a special 0.2900" upper punch (2" tip length) using a manual tablet press.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer
15 II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride
20 polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 2.

Each tablet contained 4 mg Rosiglitazone Maleate and 500 mg Metformin HCl. The core composition of tablet is provided in Table 12.

Table 12: Composition of Metformin HCl/Rosiglitazone Maleate, 4 mg/500 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	Layer 1	Layer 2
Metformin HCl	500.0	-
Rosiglitazone Maleate	-	4.0
Hydroxypropyl cellulose	256.0	8.0
Hydroxypropylmethyl cellulose	40.0	-
Compressible Sugar	-	85.0
Croscarmellose Sodium	-	2.5
Magnesium Stearate	4.0	0.5
Total	800.0	100.0

Coated tablets were tested for dissolution in 0.1 N HCl buffer at 37 ± 0.5 °C, in the USP II dissolution apparatus at 100 rpm. About 90% of the rosiglitazone in the Lot # 503-167 formulation is released in 30 minutes, and it plateaus at about 95% at 2 hours. The release profile for metformin is as follows: almost 20% in 1 hour, about 30% in 2 hours, almost 70% in 8 hours, and 100% by 16 hours.

Example 13: Longitudinally Compressed Bilayer Tablets containing 45 mg Pioglitazone HCl and 500 mg Metformin HCl (Lot # 501-237)

Longitudinally compressed bilayer tablets were prepared by using a pair of 0.2900" dies joined together as described in Example 1. The compound die was filled first with 700 mg of a dry blend of Metformin HCl and excipients (layer 1), and then with 100 mg of a dry blend of Pioglitazone HCl and excipients (layer 2). The tablets were prepared by direct compaction at 500 psi for 1 second using a standard 0.2900" lower punch, a special 0.2900" upper punch (2" tip length), and a manual tablet press described in Example 1.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers

blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 2. Each tablet contained 45 mg Pioglitazone HCl and 500 mg Metformin HCl. The core composition of tablet is provided in Table 13:

Table 13: Composition of Pioglitazone HCl/ Metformin HCl, 45 mg/500 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	Layer 1	Layer 2
Metformin HCl	500.0	-
Pioglitazone HCl	-	45.0
Hydroxypropyl cellulose	140.0	15.0
Hydroxypropylmethyl cellulose	35.0	-
Polyethylene oxide	22.2	-
Compressible Sugar	-	37.6
Polyvinylpyrrolidone (Crospovidone)	-	2.0
Magnesium Stearate	2.8	0.4
Total	700.0	100.0

Example 14: Bioadhesive Longitudinally Compressed Bilayer Tablets containing 4 mg Rosiglitazone Maleate and 500 mg Metformin HCl (Lot 504-060)

Longitudinally compressed bilayer tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The dies were carefully aligned and firmly joined together to form a compound die. The compound die was filled first with 800 mg of a dry blend of Metformin HCl and excipients (layer 1), and then with 100 mg of a dry blend of Rosiglitazone Maleate and excipients (layer 2). The tablets were prepared by direct compaction at 250 psi for 1 second using a standard 0.2900" lower punch, a special 0.2900" upper punch (2" tip length), and a GlobePharma Manual Tablet Compaction Machine (model MTCM-1).

A 0.4375" set of die and upper/lower punches was used for press-coating the core tablet. The tablet was placed vertically in the center of 0.4375" die and 600 mg of a Spheromer™ III polymer blend with ethylcellulose was poured around the tablet inside

the die. The core tablet and the polymer were pressed together at 3000 psi for 1 s. The longitudinal-section of this dosage form is illustrated in Figure 2.

Each tablet contained 4 mg Rosiglitazone Maleate and 500 mg Metformin HCl. The core and coating compositions of tablet are provided in the Tables 14A and 14B.

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Table 14A: Core Tablet Formulation

Ingredients	Weight (mg)	
	Layer 1	Layer 2
Metformin HCl	500.0	-
Rosiglitazone Maleate	-	4.0
Hydroxypropyl cellulose (Klucel EF Pharm)	276.0	4.0
Hydroxypropylmethyl cellulose (Hypromellose 4K cps)	20.0	-
Compressible Sugar	-	89.0
Croscarmellose Sodium	-	2.5
Mg Stearate	4.0	0.5
Total	800.0	100.0

Table 14B: Coating Formulation

Ingredients	Weight (mg)
Spheromer™ III, L-Dopa/BMA	352.0
Ethylcellulose (Ethocel STD 100 FP)	85.8
Mg Stearate	2.2
Total	440.0

10 Bioadhesive longitudinally compressed Rosiglitazone Maleate-Metformin HCl tablets were placed in 0.1N HCl at 37±0.5°C, in the USP II dissolution apparatus at 100 rpm. About 90% of the rosiglitazone in the Lot # 504-060 formulation is released in 30 minutes, and it plateaus at about 95% at 1 hour. The release profile for metformin is as follows: almost 20% in 1 hour, about 55% in 4 hours, and almost 100% by 8 hours.

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Example 15: Longitudinally Compressed Trilayer Tablet Formulation containing 30 mg Pioglitazone HCl (Lot # 503-038)

20 Longitudinally compressed trilayer core tablets were prepared by using a pair of 0.2618" dies joined together in a similar fashion to the method described in Example 1.

The compound die was filled first with 250 mg of a dry blend of Pioglitazone and excipients (layer 1), second with 100 g of compressible sugar (layer 2), and then with 250 mg of a dry blend of Pioglitazone and excipients (layer 3). The tablets were prepared by direct compaction at 4000 psi for 1 second using standard 0.2618" upper/lower punches and a manual tablet press in a similar fashion to the method described in Example 1. Each tablet contained a total of 30 mg Pioglitazone HCl. The core composition of tablet is provided in Table 15.

The core tablets were coated peripherally on layer1 and layer 3 with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. Layer 2 was left uncoated. The longitudinal-section of this dosage form is illustrated in Figure 6.

Table 15: Composition of Pioglitazone HCl, 30 mg Core Tablet Formulation

Ingredients	Weight (mg)		
	Layer 1	Layer 2	Layer 3
Pioglitazone HCl	15.0	-	15.0
Lactose	162.5	-	162.5
Hydroxypropyl cellulose	62.5	-	62.5
Hydroxypropylmethyl cellulose	8.75	-	8.75
Magnesium Stearate	1.25	-	1.25
Compressible sugar	-	100.0	-
Total	250.0	100.0	250.0

Coated tablets were tested for dissolution in 0.1 N HCl buffer containing 0.3 N KCl at 37±0.5°C, in the USP II dissolution apparatus at 100 rpm. About 20% of the pioglitazone in the Lot # 503-308 formulation is released in 30 minutes, about 45% in 2 hours, almost 70% in 4 hours, about 90% by 6 hours, and 100% by 8 hours.

Example 16: Longitudinally Compressed Tablets containing 45 mg Pioglitazone HCl (Lot # 502-041, 502-043, 502-045 and 502-047)

Longitudinally compressed tablets were prepared by using a pair of 0.2618" dies, standard 0.2618" upper/lower punches, and a manual tablet press in a similar fashion to the method described in Example 1. Each core tablet weighed 750 mg.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 1. Each tablet contained 45 mg Pioglitazone HCl. The core compositions of tablets are provided in Table 16.

Table 16: Composition of Pioglitazone HCl 45 mg Core Tablet Formulations

Ingredients	Weight (mg)			
	502-041	502-043	502-045	502-047
Pioglitazone HCl	45.00	45.00	45.00	45.00
Lactose	536.25	461.25	585.00	510.00
Hydroxypropyl cellulose	150.00	150.00	75.00	75.00
Polyvinylpyrrolidone (Crospovidone)	15.00	15.00	-	-
Croscarmellose sodium	-	-	41.25	41.25
Citric Acid	-	75.00	-	75.00
Mg Stearate	3.75	3.75	3.75	3.75
Total	750.00	750.00	750.00	750.00

Coated tablets were tested for release profiles in 0.1 N HCl buffer containing 0.3 N KCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. A little more than 35% of the pioglitazone in the Lot # 502-045 formulation is released in 30 minutes, almost 80% in 2 hours, and nearly 100% by 4 hours.

Example 17: Longitudinally Compressed Tablets with Two Pre-compressed Inserts containing 30 mg Pioglitazone HCl and 500 mg Metformin HCl (Lot # 503-053)

Longitudinally compressed tablets were prepared by using a pair of 0.2900" dies (and a 0.2618" die), standard 0.2900" upper/lower (and 0.2618") punches, and a manual tablet press described in Example 1. The 0.2618" die was filled with 100 mg of a dry blend of Pioglitazone and excipients, and the blend was compacted at 250 psi at 1 s. The 0.2900" die was filled first with 200 mg of a dry blend of Metformin HCl and excipients. The first pre-compressed Pioglitazone tablet (insert) was placed horizontally on the Metformin layer in the die and 300 mg of Metformin blend was added. The second pre-compressed Pioglitazone tablet was placed horizontally on the top of Metformin layer and another 250 mg of Metformin blend was added. The tablets were compacted at 4000 psi for 1 sec. according to the method described in Example 1.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer IITM (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive SpheromerTM polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 8, although the tablet contains two inserts instead of three.

Each tablet contained 30 mg Pioglitazone HCl and 500 mg Metformin HCl. The core composition of tablet is provided in Table 17.

Table 17: Composition of Pioglitazone HCl/ Metformin HCl, 30 mg/500 mg Core Tablet Formulation

Ingredients	Weight (mg)		
	Matrix	Insert 1	Insert 2
Metformin HCl	500.0	-	-
Pioglitazone HCl	-	15.0	15.0
Hydroxypropyl cellulose	200.0	20.0	20.0
Hydroxypropylmethyl cellulose	20.0	-	-
Polyethylene oxide	76.8	-	-
Compressible sugar	-	54.6	54.6
Croscarmellose sodium	-	10.0	10.0
Magnesium Stearate	3.2	0.4	0.4
Total	800.0	100.0	100.0

Example 18: Longitudinally Compressed Tablets with Pre-compressed Insert containing 15 mg Pioglitazone HCl and 250 mg Metformin HCl (Lot # 503-051)

Longitudinally compressed core tablets were prepared by using a 0.2900" (and 0.2618") die, standard 0.2900" (and 0.2618") upper/lower punches, and a manual tablet press described in Example 1. The 0.2618" die was filled with 100 mg of a dry blend of Pioglitazone and excipients, and the blend was compacted at 250 psi at 1 s. The 0.2900" die was filled first with 200 mg of a dry blend of Metformin HCl and excipients. The pre-compressed Pioglitazone tablet (insert) was placed horizontally on the Metformin layer in the die and another 200 mg of Metformin blend was added. The tablets were compacted at 1000 psi for 1 second according to the method described in Example 1.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 8, although the tablet contains two inserts instead of three.

Each tablet contained 15 mg Pioglitazone HCl and 250 mg Metformin HCl. The core composition of tablet is provided in Table 18.

Table 18: Composition of Pioglitazone HCl/ Metformin HCl, 15 mg/250 mg Core Tablet Formulation

Ingredients	Weight (mg)	
	Matrix	Insert
Metformin HCl	250.0	-
Pioglitazone HCl	-	15.0
Hydroxypropyl cellulose	100.0	20.0
Hydroxypropylmethyl cellulose	10.0	-
Polyethylene oxide	38.4	
Compressible sugar	-	54.6
Croscarmellose sodium	-	10.0
Mg Stearate	1.6	0.40
Total	400.0	100.0

Example 19: Longitudinally Compressed Osmotic Tablets Containing 500 mg Valacyclovir (Lot # 505-018)

Longitudinally compressed tablets were prepared by using a special 0.2900" die, two times longer than ordinary dies (Natoli Engineering). The die was filled with 700 mg of a dry blend of drug and excipients. A special punch, 2" tip length, was used as the upper punch and to dislodge the tablets from the die. The tablets were prepared by direct compaction at 500 psi for 1 second using the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 500 mg Valacyclovir. The compositions of core tablets are provided in Table 19.

The longitudinally compressed tablets were first coated completely with a cellulose acetate (CA 398-10) plus PEG 400 based semi-permeable coating. A passageway, 500 μ m in size, on the cellulose acetate film was made on each side of the tablet by using a micro-drill.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the

first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 9.

Table 19: Composition of Valacyclovir HCl, 500 mg Core Tablet Formulation

Ingredients	Weight (mg)
Valacyclovir HCl*	555.8
Hydroxypropyl cellulose	141.4
Magnesium Stearate	2.8
Total	700.0

* Equivalent to 500 mg Valacyclovir

Coated tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. Almost 15% of the valacyclovir in the Lot # 5085-018 formulation is released in 3 hours, about 25% in 6 hours, almost 55% in 10 hours, about 95% by 12 hours, and 100% by 14 hours.

Example 20: Longitudinally Compressed Tablets Containing 250 mg Valacyclovir (Lot # 504-027)

Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The die was filled initially with 100 mg of ethylcellulose composition (Plug II), subsequently with 250 mg of a Valacyclovir immediate release (IR II) dry blend, followed with 100 mg of hydroxypropyl cellulose (Plug I), and finally with 150 mg of a Valacyclovir immediate release (IR I) dry blend. A special punch, 2" tip length, was used as the upper punch to dislodge the tablets from the die. The tablets were prepared by direct compaction at 500 psi for 1 second using the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 250 mg Valacyclovir HCl. The compositions of core tablets are provided in Table 20.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer IITM (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive SpheromerTM polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 5.

Table 20: Composition of Valacyclovir, 250 mg Core Tablet Formulation

Ingredients	Weight (mg)			
	IR I	Plug I	IR II	Plug II
Valacyclovir HCl *	138.9	-	138.9	-
Compressible Sugar	103.85	-	103.85	-
Croscarmellose Sodium	6.25	-	6.25	-
Magnesium Stearate	1.00	-	1.00	-
Hydroxypropyl Cellulose	-	100.0	-	-
Ethylcellulose	-	-	-	100.0
Total	250.0	100.0	250.0	100.0

* Equivalent to 250 mg Valacyclovir

Coated tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. Almost 50% of the valacyclovir in the Lot # 504-027 formulation is released in 30 minutes, and the dissolution profile remains at 50% until 11.5 hours, at which point about 85% of drug has been released. By 12 hours, all the drug has been released.

Example 21: Longitudinally Compressed Tablets Containing 250 mg Valacyclovir (Lot # 504-079 and 504-081)

Longitudinally compressed core tablets were prepared by using a special 0.2900" die. The dies were filled initially with 100 mg of hydroxypropyl cellulose (Plug II),

subsequently with 500 mg of a Valacyclovir immediate release (IR) dry blend, and finally with 100 mg of hydroxypropyl cellulose (Plug I). A special punch, 2" tip length, was used as the upper punch to dislodge the tablets from the die. The tablets were prepared by direct compaction at 500 psi for 1 second using the GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 250 mg Valacyclovir. The compositions of core tablets are provided in Table 21.

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer II™ (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive Spheromer™ polymer layers comprising either Spheromer I (anhydride polymers), Spheromer II (anhydride oligomers blended with pharmaceutical polymers), Spheromer III (catechol-grafted anhydride polymers), or combinations of these polymers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 11.

Table 21: Composition of Valacyclovir HCl, 250 mg Core Tablet Formulation

Ingredients	Weight (mg)					
	504-079			504-081		
	Plug I	IR	Plug II	Plug I	IR	Plug II
Valacyclovir HCl *	-	277.8	-	-	277.8	-
Compressible Sugar	-	207.7	-	-	207.7	-
Croscarmellose Sodium	-	12.5	-	-	12.5	-
Magnesium Stearate	-	2.0	-	-	2.0	-
Hydroxypropyl Cellulose (Klucel LF Pharm)	100.0	-	100.0	-	-	-
Hydroxypropyl Cellulose (Klucel EF Pharm)	-	-	-	100.0	-	100.0
Total	100.0	500.0	100.0	100.0	500.0	100.0

* Equivalent to 250 mg Valacyclovir

Coated tablets were tested for release profile in 0.1 N HCl at 37±0.5 °C, in the USP II dissolution apparatus at 100 rpm. No valacyclovir in Lot # 504-081 is released until about 5 hours, at which point about 5% of drug is released. Almost 30% of drug is

released by 5.5 hours, 75% by 6 hours, and 100% by 7 hours. The valacyclovir in Lot # 504-079 is not released until 8 hours, at which point about 5% of drug is released. Almost 20% is released in 8.5 hours, about 45% in 9 hours, 80% in 9.5 hours, and all the drug by 10 hours.

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Example 22: Bioadhesive Longitudinally Compressed Tablets Containing 200 mg Levodopa and 50 mg Carbidopa (Lot 507-041)

Longitudinally compressed tablets were prepared by using a special 0.2618" die, two times longer than ordinary dies (Natoli Engineering). The die was filled with 800 mg of a dry blend of spheronized drug particulates and excipients. Levodopa-Carbidopa particulates ranged from 250 to 425 μ m in diameter. A special punch, 2" tip length, was used as the upper punch and to dislodge the tablets from the die. The tablets were prepared by direct compaction at 2000 psi for 1 second using the GlobePharma Manual Tablet Compaction Machine (MTCM-1).

The LCTs were coated peripherally with a single layer of impermeable PCL film that was heat-sealed to the tablet core. A second film comprising bioadhesive Spheromer IITM (Fumaric Anhydride Oligomer) blended in polycaprolactone was applied over the first film as in Example 1. Optionally, bioadhesive SpheromerTM polymer layers comprising either SpheromerTM I (anhydride polymers), SpheromerTM II (anhydride oligomers blended with pharmaceutical polymers), SpheromerTM III (catechol-grafted anhydride polymers) or else combinations of these polymers layers can also be applied over the impermeable coating without affecting drug release. The longitudinal-section of this dosage form is illustrated in Figure 13.

Each tablet contained 200 mg Levodopa and 50 mg Carbidopa anhydrous. The composition of particulates and that of core matrix are provided in Table 22A and Table 22B, respectively.

TABLE 22A: Composition of Levodopa-Carbidopa Multiparticulate Formulation

Ingredients	Wt%
Levodopa	44.0
Carbidopa, Monohydrate	11.9
Emocel 90M (Microcrystalline cellulose)	26.0
Ac-Di-Sol (Croscarmellose Sodium)	6.1
Klucel EF Pharm (HPC)	5.0
Fast-Flo no. 316 (Lactose, Monohydrate)	5.0
Citric acid	1.0
SLS	1.0
Total	100.0

5 TABLE 22B: Composition of Levodopa-Carbidopa Spheres in Tablet Formulation

Ingredients	Wt%	Weight (mg)
Levodopa-Carbidopa Spheres	58.25	466
Polyox WSR 301	41.25	330
Mg Stearate	0.50	4
Total	100.00	800.00

10 Bioadhesive longitudinally compressed Levodopa-Carbidopa tablets were placed in 0.1N HCl at 37±0.5°C, in the USP II dissolution apparatus at 50 rpm. About 20% of drug is release in 1 hour, 40% in 4 hours, almost 80% in 10 hours, and almost all of it by 16 hours.

15 **Example 23: Bioadhesive Longitudinally Compressed Trilayer Tablets containing 200 mg Levodopa and 50 mg Carbidopa (Lot 506-047)**

Longitudinally compressed trilayer tablets were prepared by using a special 0.2618" die (Natoli Engineering), two times longer than the ordinary dies. The die was filled with three layers of different dry blend formulations of Levodopa, Carbidopa and excipients. The tablets were prepared by direct compaction at 250 psi for 1 second using a standard 0.2618" lower punch, a special 0.2618" upper punch (2" tip length), and a
20 GlobePharma Manual Tablet Compaction Machine (model MTCM-1).

A 0.3287" x 0.8937" capsule shape punch set was used for press-coating the core tablet. A first layer of Spheromer™ III polymer blend with ethylcellulose comprising 200

mg dry powder was added to the die. The pre-compressed tablet was placed horizontally on the polymer bed such that one end of the tablet (layer 1) was positioned in the center in line with the concave edge of the die. A second layer of bioadhesive polymer comprising 240 mg polymer powder was then added to cover the tablet. The core tablet and the polymer layers were then compressed together at 3500 psi for 1 s. The longitudinal-section of this dosage form is illustrated in Figure 14.

Each tablet contained 200 mg Levodopa and 50 mg Carbidopa anhydrous. The core and coating compositions of tablets are provided in the following tables.

Table 23A:

Core Tablet Formulation

Ingredients	Weight (mg)		
	Layer 1	Layer 2	Layer 3
Levodopa	40.0	120.0	40.0
Carbidopa, Monohydrate	10.8	32.4	10.8
Hypromellose 100 cps (HPMC)	-	10.0	-
Methocel E5 Prem LV (HPMC)	-	90.0	-
Glutamic Acid HCl	-	3.1	-
Corn Starch	-	3.1	-
Ludipress®	98.45	-	98.45
Mg Stearate	0.75	1.4	0.75
Total	150.0	260.0	150.0

Table 23B:

Coating Formulation

Ingredients	Weight (mg)
Spheromer™ III, L-Dopa/BMA	352.0
Ethylcellulose (Ethocel STD 100 FP)	85.8
Mg Stearate	2.2
Total	440.0

Bioadhesive longitudinally compressed Levodopa-Carbidopa tablets were placed in 0.1N HCl at 37±0.5°C, in the USP II dissolution apparatus at 50 rpm. About 20% of drug is release in 1 hour, about 35% in 4 hours, almost 60% in 10 hours, 80% in 10 hours, and almost all of it by 12 hours.

Example 24: Preparation of the Extended Release (ER) Formulation

Applicants produced an extended release (ER) formulation, which is based on a novel **BIO**adhesive **Regulated Oral Drug** delivery (**BIOROD™**) system containing 600 mg of therapeutic agent. This system consists of a longitudinally compressed tablet core that contains uniformly dispersed drug. An impermeable and optionally a bioadhesive polymer based inactive coat surrounds all of the surfaces of the core except the surface of the cylindrical face. The drug release occurs only from the cylindrical face, whose surface area controls the rate of release of drug. By maintaining constant surface area and uniform drug erosion rate, a constant drug dissolution rate can be achieved. The tablet includes an immediate release portion that releases about 25% of the drug in first hour and an extended release portion that prolongs the release of remaining 75% of the drug over 8-16 hours. Preparation of immediate release or extended release granules involved the following steps:

- (1) Weighing Therapeutic agent and pharmaceutically acceptable excipients.
- (2) Blending Therapeutic agent with pharmaceutically acceptable excipients in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a dry mix.
- (3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluid was primarily comprised of a fluid selected from a group consisting of purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, an alcohol, a hydro-alcoholic mixture, or an alcoholic or hydro-alcoholic solution of a polymeric composition.
- (4) Drying the granulation from step (3) in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C.
- (5) Blending the dried granules with a super disintegrant such as croscarmellose sodium (Acdisol™) and a lubricant, i.e., magnesium stearate, using a V-shell blender.

These granules were then compressed into a bilayer tablet using a manual tablet press. A special 0.2900" diameter die, a longer than ordinary die, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch, 2" tip length, was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: IR and ER. The ingredients were then compressed into a tablet at 300-600 psi for 1 s. These compressed tablets were then dip coated manually using a 10% w/v solution of ethylcellulose 10 cps and dried using a hot air gun. This process was repeated several times in order to achieve a uniform film coating around the periphery of longitudinally compressed tablet. The top and bottom portion were then scrapped off using a revolving blade such that the two layers are completely exposed on one side for the drug to diffuse out. Optionally, the compressed tablets can be pan coated in an O'Hara pan coater using ethyl cellulose 10 cps solution prepared using dehydrated alcohol until 10% weight gain is achieved.

Example 25: Production of Immediate Release (IR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 701-012.

IR granules were produced with low shear granulation method as described in Example 1 consisting of the following processes.

- (1) Weighing Therapeutic agent and pharmaceutically acceptable excipients.
- (2) Blending Therapeutic agent with pharmaceutically acceptable excipients in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a dry mix. The weight and composition of therapeutic agent IR granules are given in Table 24.
- (3) Granulating the dry mix from step (2) under low shear with a granulation fluid made with polyox N 10 (0.5% w/v) in 70% v/v isopropanol forming a wet granulation.
- (4) Drying the granulation from step (3) in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-250 lpm (liters per minute) and an inlet air temperature of 35-40°C.

- (5) Blending the dried granules with a super disintegrant such as acdisol and lubricant i.e. magnesium stearate using a V-shell blender.

Table 24. Weight and Composition of IR granules, Sub-lot # 701-012

Ingredients	Percent
Therapeutic agent	69.06
Anhydrous lactose	5.00
Ascorbic acid	4.50
Disodium Edetate	0.50
Acdisol	15.00
Sodium lauryl sulfate	5.00
Polyox N 10	0.60
Magnesium stearate	0.34
Total	100.00

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Example 26: Production of Extended Release (ER) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 701-017.

ER granules were produced using a low shear granulation method as described in example 24 consisting of the following processes.

- 10 (1) Weighing Therapeutic agent and pharmaceutically acceptable excipients.
- (2) Blending Therapeutic agent with pharmaceutically acceptable excipients in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a dry mix. The weight and composition of therapeutic agent ER granules are given in Table 25.
- 15 (3) Granulating the dry mix from step (2) under low shear with a granulation fluid made with polyox N 10 (0.5% w/v) in 70% v/v isopropanol, forming a wet granulation.
- (4) Drying the granulation from step (3) in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-250 lpm (liters per minute) and an inlet air temperature of 35-40°C.
- 20 (5) Blending the dried granules with a super disintegrant such as AcdisolTM and lubricant i.e. magnesium stearate using a V-shell blender.

Table 25. Weight and Composition of ER granules, Sub-lot # 701-017

Ingredients	Percent
Therapeutic agent	67.07
Ascorbic acid	2.50
Polyox N 10	5.11
Disodium Edetate	0.50
Polyox WSR coagulant	1.00
Anhydrous lactose	9.13
Sodium lauryl sulfate	5.28
Magnesium stearate	0.35
Citric acid	4.30
Acdisol	4.76
Total	100.00

Example 27: Production of IR/ER Trilayer Tablets, 600mg Lot # 701-009, 701-030 and 701-042.

IR/ER tablets were produced using a GlobePharma manual tablet press as described in Example 24.

A special 0.2900" diameter die, longer than ordinary dies, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch, 2" tip length, was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: IR, ER and IR. The ingredients were then compressed into a tablet using a compression force of 600 psi for 1 second.

The weight and composition of IR/ER tablets are given in Table 26.

Coating of Longitudinally Compressed Tablets (LCT's):

These tablets were coated with 3.2% w/w OPADRY® Clear (YS-1-19025-A). These OPADRY® coated capsules were subsequently coated with ethylcellulose in a pan coater (O'Hara). A 10% w/v solution of ethylcellulose was prepared in ethanol and sprayed on IR/ER tablets so as to achieve a final weight gain of 10.0% w/w. The top and the bottom portion were then scrapped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out. These ethylcellulose coated tablets were subsequently coated with a bioadhesive polymer

composition comprising of either Spheromer III and succinic acid (lot# 701-030) to achieve a weight gain of 19.7% w/w or Carbopol 974P (lot# 701-042) to achieve a weight gain of 19.8% w/w.

5 **Table 26. Weight and Composition of IR/ER tablets, lot # 701-009.**

Ingredients	Weight (%)	Weight Per tablet (mg)
IR granules (Layer 1)	12.5	111
ER granules (Layer 2)	75	663
IR granules (Layer 3)	12.5	111
Total	100	885

Example 28: Preparation of Extended Release (XR) Formulation

10 An extended release (XR) formulation, which is based on a novel **POLYmer Regulated Oral Drug delivery (POLYROD™)** system containing 600 mg of therapeutic agent, was produced. This system includes a longitudinally compressed tablet core that contains uniformly dispersed drug. An impermeable polymer based inactive coat surrounds all of the surfaces of the core except the surface of the cylindrical face. The drug release occurs only from the cylindrical face, whose surface area controls the rate of release of drug. By maintaining a constant surface area and uniform drug erosion rate, a constant drug dissolution rate can be achieved. The tablet includes an immediate release portion that releases about 25% of the drug in first hour and an extended release portion that prolongs the release of remaining 75% of the drug over 8-16 hours. The immediate release portion was prepared by weighing and blending therapeutic agent and

15 pharmaceutically acceptable excipients. The resulting mixture was wet massed using purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, an alcohol, a hydro-alcoholic mixture, or an alcoholic or hydro-alcoholic solution of a polymeric composition. These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally the

20

25

dried granules were tumble mixed with a super disintegrant such as Acdisol™ and lubricant, i.e. magnesium stearate, using a V-shell blender.

These granules were then compressed into a bilayer tablet using a manual tablet press. A special 0.2900" diameter die, longer than ordinary die was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: IR and XR. The ingredients were then compressed into a tablet at 300-600 psi for 1 second. These compressed tablets were then dip coated manually using a 10% w/v solution of ethylcellulose 10 cps and dried using a hot air gun. This process was repeated several times in order to achieve a uniform film coating around the periphery of the longitudinally compressed tablet. The top and bottom portion were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out. Optionally, the compressed tablets can be pan coated in O'Hara pan coater, using an ethyl cellulose 10 cps solution prepared using dehydrated alcohol, until a 10% weight gain is achieved.

Example 29: Production of Immediate Release (IR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 608-093.

IR granules were produced using the low shear granulation method described in Example 28.

67 g of therapeutic agent were weighed and mixed with 5 g of dipac sugar, 5 g of Avicel PH 101, 0.01 g of butylated hydroxytoluene, 0.1 g of aerosil, 7.5 g of Acdisol™, 4 g of sodium lauryl sulfate and blended using a low shear mixer. The resulting mixture was wet massed using a 3% w/v solution of methocel LV E5 prepared using purified water.

These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 7.5 g of Acdisol™ and 0.34 g of magnesium stearate using a V-shell blender.

Example 30: Production of Extended Release (XR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 608-157.

XR granules were produced using the low shear granulation method described in Example 28.

5 77 g of therapeutic agent were weighed and mixed with 6 g of hydroxypropylcellulose (Klucel EF Pharm), 7.5 g of hydroxypropylcellulose (Klucel HXF Pharm), 6 g of compressible sugar, 0.01 g of butylated hydroxytoluene, 3 g of sodium lauryl sulfate and blended using a low shear mixer. The resulting mixture was wet massed using purified water.

10 These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 0.4 g of magnesium stearate using a V-shell blender.

15 **Example 31: Production and In Vitro Dissolution of IR/XR Bilayer Tablets, Lot # 608-164.**

IR/XR tablets were produced using a GlobePharma manual tablet press, as described in Example 28.

20 A special 0.2900" diameter die, which is longer than ordinary dies, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: 224 grams of IR granules and 584 grams of XR granules. The ingredients were then compressed into a tablet using compression force of 600 psi for 1
25 second.

Coating of Longitudinally Compressed Tablets (LCT's):

The tablets were dip coated with an ethycellulose (10% w/v) solution and dried using a hot air gun. This process was repeated two more times in order to form a uniform film around the periphery of the LCT's. The top and the bottom portions were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out. The longitudinal-section of this dosage form is illustrated in Figure 2.

In Vitro Dissolution of IR/XR Tablets, Lot # 608-164

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 32.

Example 32: Production and In Vitro Dissolution of IR/XR Bilayer Tablets, Lot # 609-025.

IR granules, subplot # 608-093 (Example 29), were used for the manufacture of these tablets and XR granules, subplot # 609-006, were prepared as below.

70 g of therapeutic agent were weighed and mixed with 6.5 g of anhydrous citric acid, 0.01 g of disodium edetate, 0.01 g of butylated hydroxytoluene, 5.9 g of hydroxypropylcellulose (Klucel EF Pharm), 8.3 grams of hydroxypropylcellulose (Klucel HXF Pharm), 5.9 g of compressible sugar, 3 g of sodium lauryl sulfate and blended using a low shear mixer. The resulting mixture was wet massed using purified water.

These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 0.4 g of magnesium stearate using a V-shell blender.

IR/XR tablets were produced using a GlobePharma manual tablet press, as described in Example 28. The tablet ingredients were poured into the die and gently tapped in the following order: 224 mg of IR granules and 642 grams of XR granules. The

ingredients were then compressed into a tablet using a compression force of 600 psi for 1 second.

Coating of Longitudinally Compressed Tablets (LCT's):

5 The tablets were subsequently dip coated with an ethylcellulose (10% w/v) solution and dried using a hot air gun. This process was repeated two more times in order to form a uniform film around the periphery of the LCT's. The top and the bottom portion were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out.

10 In Vitro Dissolution of IR/XR Tablets, Lot # 609-025

 The *in vitro* dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at
15 predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 33.

Example 33: *In vivo* Pharmacokinetic Performance of IR/XR Bilayer Tablet, 600 mg (lot#609-025)

20 The *in vivo* performance of an XR Tablet, 600 mg (lot#609-025), was evaluated in beagles. The XR tablet was administered to cohorts of six beagle dogs in the fed state and plasma levels of therapeutic agent were measured using LC-MS/MS analysis. Figure 34 shows the plasma concentration profiles of therapeutic agent. The pharmacokinetic data, including the area under the plasma therapeutic agent vs. time curve (AUC),
25 maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}), are provided in Table 27.

**Table 27. Pharmacokinetic Performance of IR/XR tablet, 600 mg (lot#609-025)
Given Once Daily in Fed Beagles.**

Formulation	AUC ₀₋₄₈ ($\mu\text{g/mL/hr}$)	C _{max} ($\mu\text{g/mL}$)	T _{max} (hrs)
IR/XR tablet, 600 mg	47.04 $\pm$ 4.3	6.35 $\pm$ 0.4	9.7 $\pm$ 1.7

Example 34: *In Vitro* Dissolution of IR/XR Bilayer Tablets, Lot # 609-070

IR/XR tablets were prepared identically to lot #609-025 as described in Example 32 and evaluated for their *in vitro* dissolution performance at different paddle speeds. These tests for IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 60, 75 or 100 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 35.

Example 35: Production and *In Vitro* Dissolution of IR/XR Trilayer Tablets, Lot # 609-136, 609-137, 609-138 and 609-139.

IR granules, subplot # 608-093 (Example 29) and XR granules, subplot # 609-006, were used for the manufacturing of the tablets and were prepared as described in Example 30.

IR/XR tablets were produced using a GlobePharma manual tablet press, as described in Example 28. The tablet ingredients were poured into the die and gently tapped in the following order: IR, HPC (Klucel LXF Pharm) and XR. The ingredients were then compressed into a tablet using a compression force of 600 psi for 1 second. The longitudinal-section of this dosage form is illustrated in Figure 30. The weight and composition of IR/XR tablets are shown in Tables 28-31.

Table 28: Composition of IR/XR tablets (Lot # 609-136)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Hydroxypropyl cellulose (Klucel LXF Pharm) (Layer 2)	150
XR granules (Layer 3)	642
Total	1016

Table 29: Composition of IR/XR tablets (Lot # 609-137)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Hydroxypropyl cellulose (Klucel LXF Pharm) (Layer 2)	200
XR granules (Layer 3)	642
Total	1066

5 Table 30: Composition of IR/XR tablets (Lot # 609-138)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Hydroxypropyl cellulose (Klucel LXF Pharm) (Layer 2)	100
XR granules (Layer 3)	642
Total	966

Table 31: Composition of IR/XR tablets (Lot # 609-139)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Hydroxypropyl cellulose (Klucel LXF Pharm) (Layer 2)	50

XR granules (Layer 3)	642
Total	916

Coating of Longitudinally Compressed Tablets (LCT's):

The tablets were dip coated with an ethycellulose (10% w/v) solution and dried using a hot air gun. This process was repeated two more times in order to form a uniform film around the periphery of the LCT's. The top and the bottom portion were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out.

In Vitro Dissolution of IR/XR Tablets, Lot # 609-136, 609-137, 609-138 and 609-139

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 36.

Example 36: Production and *In Vitro* Dissolution of IR/XR Trilayer Tablets, Lot # 610-024, 610-025 and 610-026.

IR/XR tablets were prepared as described in Example 35. The weight and composition of IR/XR tablets are shown in Tables 32-34. The longitudinal section of this dosage form is illustrated in Figure 30.

Table 32: Composition of IR/XR tablets (Lot # 610-024)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Glyceryl monostearate+Lactose mix (Layer 2)	50
XR granules (Layer 3)	642
Total	916

Table 33: Composition of IR/XR tablets (Lot # 610-025)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Glyceryl monostearate +Lactose mix (Layer 2)	100
XR granules (Layer 3)	642
Total	956

Table 34: Composition of IR/XR tablets (Lot # 610-026)

Ingredients	Weight per tablet (mg)
IR granules (Layer 1)	224
Glyceryl monostearate +Lactose mix (Layer 2)	200
XR granules (Layer 3)	642
Total	1066

5 **In Vitro Dissolution of IR/XR Trilayer Tablets, Lot # 610-024, 610-025 and 610-026.**

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets
10 obtained from UV spectrophotometer analysis is shown in Figure 37.

Example 37: Production of Immediate Release (IR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 701-092.

IR granules were produced using a low shear granulation method.
15 71 g of therapeutic agent were weighed and mixed with 2.3 g of anhydrous lactose, 4.4 g of ascorbic acid, 0.5 g of disodium edetate, 6.5 g of Acdisol™, 5.1 g of sodium lauryl sulfate, 3 g of polyox N10 and blended using a low shear mixer. The resulting mixture

was wet massed using a 2% w/v solution of polyox N10 prepared using isopropanol and purified water (70:30).

These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 7.5 g of Acdisol™ and 0.34 g of magnesium stearate using a V-shell blender.

Example 38: Production of Extended Release (XR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 701-046.

XR granules were produced using a low shear granulation method as described below.

68 g of therapeutic agent were weighed and mixed with 2.7 grams of ascorbic acid, 0.04 g of butylated hydroxytoluene, 0.5 g of disodium edetate, 3 g of polyox wsr coagulant, 0.16 g of anhydrous lactose, 11 g of polyox N10, 5.3 g of sodium lauryl sulfate, 4.3 g of citric acid, 2.2 g of Acdisol™ and blended using a low shear mixer. The resulting mixture was wet massed using a 0.67% w/v polyox N 10 solution prepared in isopropanol: water (70:30).

These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 2 g of Acdisol™ and 0.3 g of magnesium stearate using a V-shell blender.

Example 39: Production and In Vitro Dissolution of IR/XR Trilayer Tablets, Lot # 701-105.

IR/XR tablets were produced using a GlobePharma manual tablet press as described below.

A special 0.2900" diameter die, which is longer than ordinary dies, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: 106 mg of IR granules, 664 mg of XR granules and 106 mg of IR

granules. The ingredients were then compressed into a tablet using a compression force of 300 psi for 1 second.

Coating of Longitudinally Compressed Tablets (LCT's):

5 These tablets were coated with 3.1 % w/w OPADRY® Clear (YS-1-19025-A). These OPADRY coated capsules were subsequently coated with ethylcellulose in a pan coater (O'Hara). 10% w/v solution of ethylcellulose was prepared in ethanol and sprayed on IR/XR tablets so as to achieve a final weight gain of 11.3% w/w. The top and the bottom portion were then scraped off using a revolving blade such that the two layers are
10 completely exposed on one side for the drug to diffuse out. The longitudinal-section of this dosage form is illustrated in Figure 31.

In Vitro Dissolution of IR/XR Tablets, Lot # 701-105

15 *In vitro* dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 38.

20 **Example 40: Production of Immediate Release (IR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 610-183.**

 IR granules were produced using a low shear granulation method. 69 g of therapeutic agent were weighed and mixed with 5.0 g of anhydrous lactose, 4.5 g of ascorbic acid, 0.5 g of disodium edetate, 7.5 g of Acdisol™, 5.0 grams of sodium
25 lauryl sulfate and blended using a low shear mixer. The resulting mixture was wet massed using a 0.5% w/v solution of polyox N10 prepared using isopropanol and purified water (70:30).

 These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and
30 an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 7.5 g of Acdisol™ and 0.34 g of magnesium stearate using a V-shell blender.

Example 41: Production of Extended Release (XR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 611-002.

XR granules were produced using a low shear granulation method as described
5 below.

67 g of therapeutic agent were weighed and mixed with 2.5 g of ascorbic acid, 0.04 g of butylated hydroxytoluene, 0.5 g of disodium edetate, 1 g of polyox wsr coagulant, 9.13 g of anhydrous lactose, 4.4 g of polyox N10, 5.3 g of sodium lauryl sulfate, 4.3 g of citric acid, 2.4 g of Acdisol™ and blended using a low shear mixer. The
10 resulting mixture was wet massed using a 0.5% w/v polyox N 10 solution prepared in isopropanol: water (70:30).

The granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with
15 2.4 g of Acdisol™ and 0.35 g of magnesium stearate using a V-shell blender.

Example 42: Production and In Vitro Dissolution of IR/XR Trilayer Tablets, Lot # 611-006

IR/XR tablets were produced using a GlobePharma manual tablet press as
20 described below.

A special 0.2900" diameter die, which is longer than ordinary dies, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the
25 following order: 111 grams of IR granules, 663 grams of XR granules and 111 grams of IR granules. The ingredients were then compressed into a tablet using a compression force of 600 psi for 1 second.

Coating of Longitudinally Compressed Tablets (LCT's):

30 The tablets were coated with 4.4% w/w OPADRY® Clear (YS-1-19025-A). The OPADRY® coated capsules were subsequently coated with ethylcellulose in a pan coater

(O'Hara). A 10% w/v solution of ethylcellulose was prepared in ethanol and sprayed on IR/XR tablets to achieve a final weight gain of 11.3% w/w. The top and the bottom portion were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out. The longitudinal-section of this dosage form is illustrated in Figure 30.

In Vitro Dissolution of IR/XR Tablets, Lot # 611-006

The *in vitro* dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 39.

Example 43: *In vivo* Pharmacokinetic Performance of IR/XR 600mg Tablets in Fed Beagle Dogs, Lot # 611-006

The *in vivo* performance of IR/XR 600mg Tablets was evaluated in beagle dogs. Tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of therapeutic agent were measured using LC-MS/MS analysis. Figure 40 shows the plasma concentration profiles of therapeutic agent. The pharmacokinetic data including the area under the plasma therapeutic agent vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 35.

Table 35: Pharmacokinetic Data for of IR/XR 600mg Tablets, Lot # 611-006 in Fed Beagles; the area under the plasma therapeutic agent vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	AUC ₀₋₃₆ ($\mu\text{g/mL/hr}$)	C_{max} ($\mu\text{g/mL}$)	T_{max} (hrs)
IR/XR 600mg Tablets	54.5 $\pm$ 8.7	5.7 $\pm$ 0.9	12.7 $\pm$ 4.2

Example 44: Production and In Vitro Dissolution of IR/XR Trilayer Tablets, Lot # 611-035

IR/XR tablets were produced using a GlobePharma manual tablet press, as described in Example 42. The tablet ingredients were poured into the die and gently tapped in the following order: 106 mg of IR granules, 665 mg of XR granules and 106 mg of IR granules. The ingredients were then compressed into a tablet using a compression force of 600 psi for 1 second. The longitudinal section of this tablet is illustrated in Figure 31. The weight and composition of IR/XR tablets are shown in Table 36.

Table 36: Weight and Composition of IR/XR tablets, Lot # 611-035

Components	% w/w
Therapeutic agent	58.5
Anhydrous Lactose	7.1
Ascorbic Acid	2.7
Disodium EDTA	0.4
Croscarmellose Sodium (Acdisol™)	5.5
Sodium Lauryl Sulfate	4.5
Polyox N 10	3.1
Magnesium Stearate	0.4
Polyox WSR coagulant	0.6
Citric Acid	2.7
Opadry Clear (YS-1-19025-A)	4.4
Ethylcellulose 10 cps	9.6
Dibutyl Sebacate	0.5
Alcohol Dehydrated	*
Isopropanol 99%	*
Purified Water	*
Total	100

* Evaporated during drying process

5 In Vitro Dissolution of IR/XR Tablets, Lot # 611-035

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets
10 obtained from UV spectrophotometer analysis is shown in Figure 41.

Example 45: Production and In Vitro Dissolution of IR/XR Trilayer Tablets, Lot # 611-027

IR/XR tablets were produced using a GlobePharma manual tablet press as
15 described in Example 42. The tablet ingredients were poured into the die and gently

tapped in the following order: 101 mg of IR granules, 650 mg of XR granules and 101 mg of IR granules. The ingredients were then compressed into tablet using a compression force of 600 psi for 1 second. The longitudinal section of this tablet is illustrated in Figure 31. The weight and composition of IR/XR tablets are given in Table 37.

5

Table 37. Weight and Composition of IR/XR tablets, Lot # 611-027

Components	Percent w/w
Therapeutic agent	58.4
Anhydrous Lactose	5.8
Ascorbic Acid	2.6
Disodium EDTA	0.4
Croscarmellose Sodium (Acdisol™)	5.4
Sodium Lauryl Sulfate	4.5
Polyox N 10	3.1
Magnesium Stearate	0.3
Polyox WSR coagulant	1.9
Citric Acid	2.8
Opadry Clear (YS-1-19025-A)	4.2
Ethylcellulose 10cps.	10.1
Dibutyl Sebacate	0.5
Alcohol Dehydrated	*
Isopropanol 99%	*
Purified Water	*
Total	100

* Evaporated during drying process

In Vitro Dissolution of IR/XR Tablets, Lot # 611-027

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 42.

Example 46: Production of Extended Release (XR) Granules with Low Shear Granulation and Fluid Bed Drying, Lot# 609-098.

XR granules were produced using a low shear granulation method as described below. 70 g of therapeutic agent were weighed and mixed with 0.01 g of butylated hydroxytoluene, 0.01 g of disodium edetate, 5.9 g of compressible sugar, 5.9 g of pladone K29/32, 8.3 g of pladone K90, 3 g of sodium lauryl sulfate, 6.5 g of anhydrous citric acid and blended using a low shear mixer. The resulting mixture was wet massed using purified water.

These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 0.4 g of magnesium stearate using a V-shell blender.

Example 47: Production and In Vitro Dissolution of IR/XR Bilayer Tablets, Lot # 609-107

IR/XR tablets were produced using a GlobePharma manual tablet press as described below.

A special 0.2900" diameter die, which is longer than ordinary dies, was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: IR (Example 29) and XR. The ingredients were then compressed into tablet using a compression force of 600 psi for 1 second.

Coating of Longitudinally Compressed Tablets (LCT's):

These tablets were coated with 4.9% w/w OPADRY® Clear (YS-1-19025-A). These OPADRY coated capsules were subsequently coated with ethylcellulose in a pan coater (O'Hara). A 10% w/v solution of ethylcellulose was prepared in ethanol and sprayed on IR/XR tablets to achieve a final weight gain of 11.9% w/w. The top and the bottom portion were then scraped off using a revolving blade such that the two layers were completely exposed on one side for the drug to diffuse out.

In Vitro Dissolution of IR/XR Tablets, Lot # 609-107

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37°C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The dissolution profile of the tablets obtained from UV spectrophotometer analysis is shown in Figure 43.

Example 48: Longitudinally Compressed Tablets containing 600 mg therapeutic agent.

A 2 pulse POLYROD system containing 600 mg of therapeutic agent was prepared. This system consists of a longitudinally compressed tablet core that contains uniformly dispersed drug. An impermeable polymer based inactive coat surrounds all of the surfaces of the core except the surface of the cylindrical face. The drug release occurs only from the cylindrical face, whose surface area controls the rate of release of drug. By maintaining a constant surface area and uniform drug erosion rate, a constant drug dissolution rate can be achieved.

Longitudinally compressed core tablets were prepared by using a pair of 0.2900" dies (Natoli Engineering). The die was filled initially with 100 mg of ethylcellulose composition (Plug II), subsequently with 422 mg of therapeutic agent immediate release (IR II) granules (Lot # 611-010), followed with 100 mg of hydroxypropyl cellulose (Plug I), and finally with 422 mg of therapeutic agent immediate release (IR I) granules. A special punch having a 2" tip length was used as the upper punch to dislodge the tablets from the die. The tablets were prepared by compaction at 600 psi for 1 second using the

GlobePharma Manual Tablet Compaction Machine (MTCM-1). Each tablet contained 600 mg therapeutic agent. These tablets were coated with 4.9% w/w OPADRY® Clear (YS-1-19025-A). These OPADRY® coated capsules were subsequently coated with ethylcellulose in a pan coater (O'Hara). A 10% w/v solution of ethylcellulose was prepared in ethanol and sprayed on IR/XR tablets to achieve a final weight gain of 11.9% w/w. The top and the bottom portion were then scraped off using a revolving blade such that the two layers are completely exposed on one side for the drug to diffuse out. The longitudinal-section of this dosage form is illustrated in Figure 3. The weight and composition of IR/XR tablets are shown in Table 38.

Table 38: Composition of 600 mg Core Tablet Formulation

Ingredients	Weight (mg)			
	IR I	Plug I	IR II	Plug II
IR granules *	422	-	422	-
Hydroxypropyl Cellulose	-	100.0	-	-
Ethylcellulose	-	-	-	100.0
Total	422.0	100.0	422.0	100.0

* Equivalent to 600 mg therapeutic agent

Example 49: Preparation of Extended Release (XR), 500mg Formulation.

The tablet includes an immediate release portion that releases about 25% of the drug in first hour and an extended release portion that prolongs the release of remaining 75% of the drug over 8-16 hours. Preparation of immediate release or extended release granules involved the following steps.

IR granules (lot # 701-109) were produced using a low shear granulation method.

71 g of therapeutic agent were weighed and mixed with 2.3 g of anhydrous lactose, 4.4 g of ascorbic acid, 0.5 g of disodium edetate, 6.5 g of Acdisol™, 5.1 g of sodium lauryl sulfate, 3.1 g of polyox N 10 and blended using a low shear mixer. The resulting mixture was wet massed using a 2.6% w/v solution of polyox N10 prepared

using isopropanol and purified water (70:30). These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 6.4 g of Acdisol™ and 0.4 g of magnesium stearate using a V-shell blender.

XR granules (lot # 701-110) were produced using a low shear granulation method as described below.

68 g of therapeutic agent were weighed and mixed with 9.2 g of anhydrous lactose, 2.7 g of ascorbic acid, 0.04 g of butylated hydroxytoluene, 0.5 g of disodium edetate, 2.2 g of Acdisol™, 5.3 g of sodium lauryl sulfate, 4.5 g of polyox N 10, 1 g of Polyox WSR coagulant, 4.3 g of citric acid and blended using a low shear mixer. The resulting mixture was wet massed using a 0.6% w/v solution of polyox N10 prepared using isopropanol and purified water (70:30). These granules were dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 50-300 lpm (liters per minute) and an inlet air temperature of 35-40 °C. Finally, the dried granules were tumble mixed with 2.1 g of Acdisol™ and 0.3 g of magnesium stearate using a V-shell blender.

The granules were then compressed into a bilayer tablet using a manual tablet press. A 0.2900" diameter die longer than ordinary die was used. The upper and lower punches of 0.2900" diameter were inserted in the tablet press. A special punch having a 2" tip length was used as the upper punch and to dislodge the tablets from the dies. The tablet ingredients were poured into the die and gently tapped in the following order: 88.5 mg of IR granules, 553 mg of XR granules and 88.5 mg of IR granules. The ingredients were then compressed into a tablet at 300-600 psi for 1 s. These compressed tablets were pan coated with OPADRY® Clear (YS-1-19025-A) in an O'Hara pan coater to achieve a weight gain of 3.0% w/w and subsequently coated using an ethyl cellulose 10 cps solution prepared using dehydrated alcohol until a 14% weight gain was achieved. The top portion was then scraped off using a revolving blade such that the immediate release layer was completely exposed for the drug to diffuse out. The longitudinal section of this tablet is illustrated in Figure 14.

In Vitro Dissolution of IR/XR Tablets, Lot # 701-116

In vitro dissolution tests of IR/XR tablets were performed in 900 mL of purified water containing 1% SLS in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 60 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed. The dissolution profile obtained is shown in Figure 44.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. An oral dosage formulation, comprising a compressed inner core comprising a therapeutic, prophylactic, or diagnostic agent and an outer polymeric layer disposed over at least a portion of the surface of the core.
2. The formulation of claim 1, wherein the polymeric layer comprises a water-soluble polymer.
3. The formulation of claim 1, wherein the polymeric layer comprises a water-insoluble polymer.
4. The formulation of claim 1, wherein the polymeric layer comprises a polymer selected from hydroxypropyl cellulose, polyethylene oxide and polyvinylpyrrolidone.
5. The formulation of claim 1, wherein the therapeutic agent is selected from valacyclovir, gabapentin, metformin, pioglitazone, glipizide, sodium valproate, rosiglitazone, levodopa, and carbidopa.
6. The formulation of claim 5, wherein the therapeutic agent is L-3,4-dihydroxyphenylalanine (levodopa).
7. The formulation of claim 1, wherein the agent is in the form of particles.
8. The formulation of claim 7, wherein the particles are microspheres that release at least 40% of the drug into a fluid of the gastrointestinal tract or into water in less than 30 minutes.
9. The formulation of claim 1, wherein the inner core comprises more than one therapeutic, prophylactic, or diagnostic agent.

10. The formulation of claim 1, wherein the inner core comprises one or more excipients.
11. The formulation of claim 1, wherein the inner core comprises one or more absorption enhancers.
12. The formulation of claim 1, wherein the inner core consists essentially of the therapeutic, prophylactic, or diagnostic agent.
13. The formulation of claim 1, wherein the inner core is a compressed tablet.
14. The formulation of claim 13, wherein the formulation is an immediate release formulation.
15. The formulation of claim 13, wherein the formulation is an extended release formulation.
16. The formulation of claim 13, wherein the formulation comprises an ascending release formulation.
17. The formulation of claim 13, wherein the formulation comprises a combination of immediate release and extended release formulation portions.
18. The formulation of claim 13, wherein the formulation comprises a combination of extended release formulation portions.
19. A method for preparing a dosage formulation, comprising applying to a compressed inner core comprising a therapeutic, prophylactic, or diagnostic agent, an outer polymeric layer.

20. The method of claim 19, wherein the polymeric layer comprises hydroxypropyl cellulose, polyethylene oxide or polyvinyl pyrrolidone.
21. The method of claim 19, wherein the compressed inner core is a tablet.
22. The method of claim 19, wherein the polymer is applied to the core by thermal extrusion of the polymer around the compressed core.
23. The method of claim 19, wherein the polymer is applied to the core by compression coating.
24. The method of claim 23, wherein compression coating comprises adding a portion of the polymeric layer to a die, positioning the compressed core in a flat position in the die adjacent to the portion, adding a second portion of the polymeric layer to the die adjacent to the core, and compressing the polymeric layers and core.
25. The method of claim 23, wherein compression coating comprises adding the polymeric layer to a die, inserting the core, and compressing the polymeric layer and core together.
26. The method of claim 19, wherein the polymer is applied to the core by spray coating.
27. The method of claim 19, wherein the polymeric layer is applied to the core by wrapping a film comprising the polymer around at least one surface of the core.
28. A rate-controlled dosage formulation prepared by the method of any of claims 19-23.
29. The dosage formulation of claim 28, further comprising an enteric coating.

30. A method for administering an agent to a patient, comprising administering to the patient a dosage formulation of claim 1.
31. The method of claim 30, wherein the dosage formulation is targeted for delivery to the small intestine or colon.
32. The method of claim 30, wherein the dosage formulation is administered orally, rectally, or vaginally.
33. The dosage formulation of claim 28, wherein the polymeric layer further comprises one or more pore formers.
34. The dosage formulation of claim 28, wherein the polymeric layer further comprises one or more entero-soluble polymers.
35. The dosage formulation of claim 28, wherein the inner core has a hardness between 2 kp – 30 kp.
36. The formulation of claim 1, wherein the oral dosage formulation is rate-controlled.
37. The formulation of claim 1, wherein the formulation is an immediate release formulation.
38. The formulation of claim 1, wherein the formulation is an extended release formulation.
39. The formulation of claim 1, wherein the formulation comprises an ascending release formulation.

40. The formulation of claim 1, wherein the formulation comprises a combination of immediate release and extended release formulation portions.
41. The formulation of claim 1, wherein the formulation comprises a combination of extended release formulation portions.
42. The formulation of claim 9, wherein the agents are different.
43. The formulation of claim 9, wherein the agents are the same.
44. The formulation of claim 43, wherein the agents are released in three or more pulses.
45. The formulation of claim 42, wherein at least one agent is highly aqueous-soluble and at least one agent is poorly aqueous-soluble.
46. A drug-eluting device, comprising a reservoir having a compressed core comprising a therapeutic, diagnostic, or prophylactic agent, an outer polymeric layer disposed over at least a portion of the surface of the core, and one or more areas uncoated by the polymeric layer through which agent from the core can elute from the device.
47. An oral dosage formulation, comprising a compressed inner core comprising a therapeutic, prophylactic, or diagnostic agent and an outer polymeric layer disposed over at least a portion of the surface of the core, wherein one agent is a drug formulated for extended release in a charge-neutral form of the drug and one agent is the drug formulated for immediate release in a salt form of the drug.
48. The formulation of claim 47, wherein the charge-neutral form of the drug is a carboxylic acid or amine free base.

49. The formulation of claim 48, wherein the charge neutral form of the drug is selected from valproic acid and acyclovir.
50. The formulation of any one of claims 47 to 49, wherein the salt form of the drug is a carboxylate salt or amine salt.
51. The formulation of claim 50, wherein the salt form of the drug is selected from sodium valproate and sodium acyclovir.
52. The formulation of claim 47, wherein the polymeric layer is bioadhesive.
53. The formulation of claim 47, wherein the polymeric layer is non-bioadhesive.
54. An oral dosage formulation, comprising a slow-eroding inner core comprising a therapeutic, prophylactic, or diagnostic agent and an outer polymeric layer disposed over at least a portion of the surface of the core.
55. The formulation of claim 54, wherein the polymeric layer is bioadhesive.
56. The formulation of claim 54, wherein the polymeric layer is non-bioadhesive.
57. The formulation of claim 1, wherein the polymeric layer is non-bioadhesive.
58. The formulation of claim 57, wherein the polymeric layer is rate-controlling.
59. The formulation of claim 1, wherein the polymeric layer is rate-controlling.
60. The method of claim 19, wherein the polymeric layer is non-bioadhesive.
61. The method of claim 60, wherein the polymeric layer is rate-controlling.

62. The method of claim 19, wherein the polymeric layer is rate-controlling.

FIGURE 1

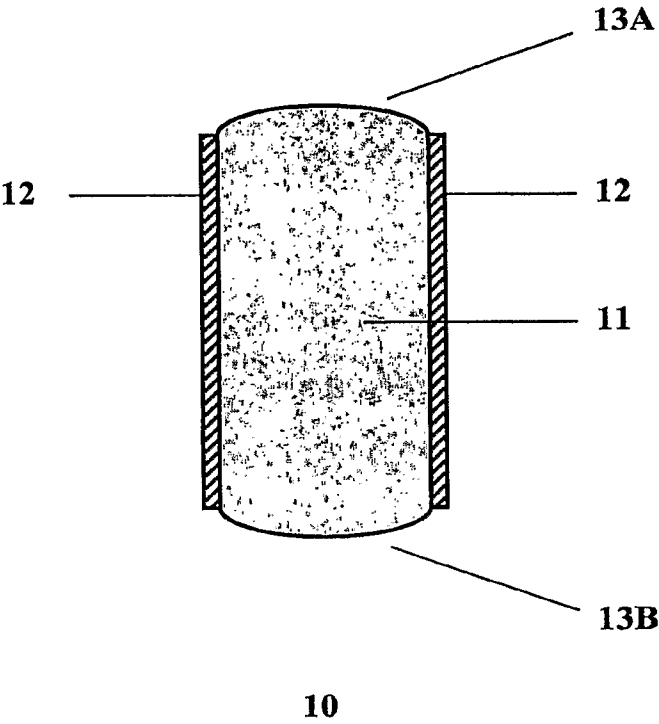


FIGURE 2

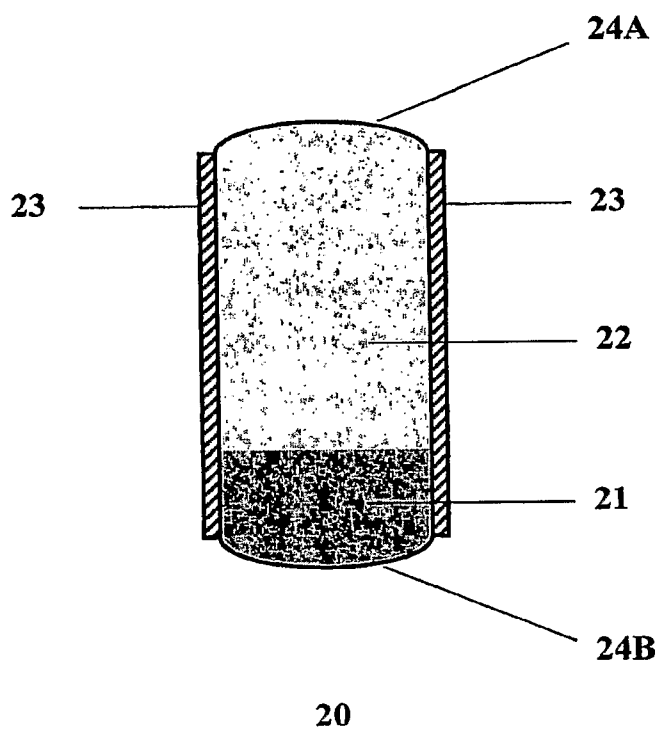


FIGURE 3

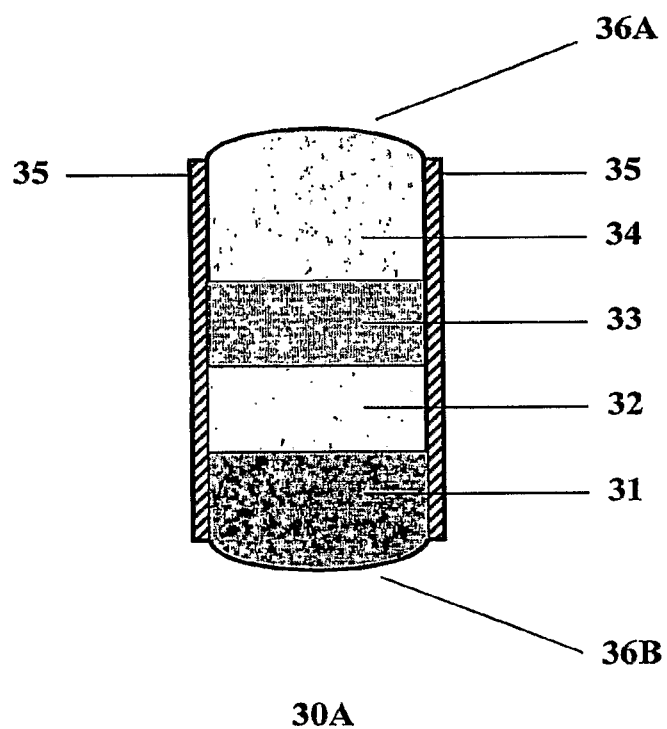


FIGURE 4

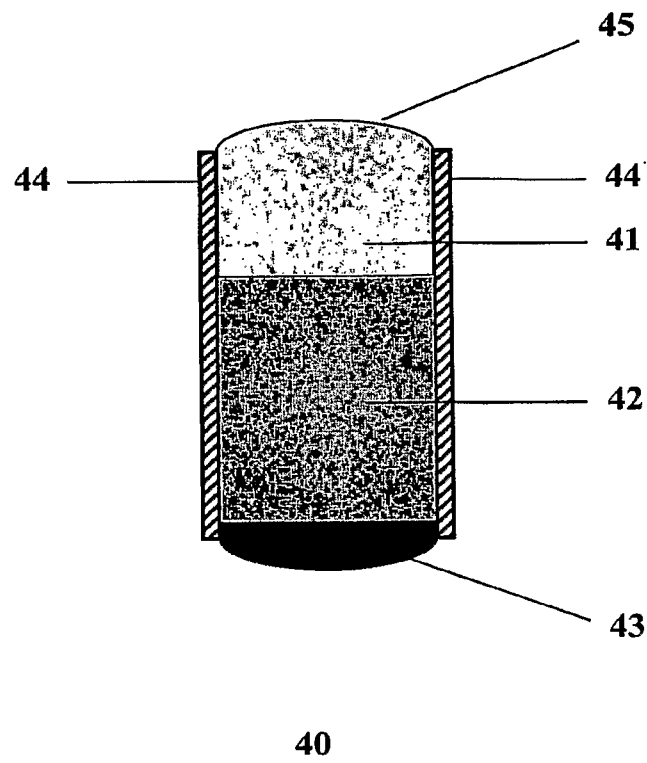


FIGURE 5

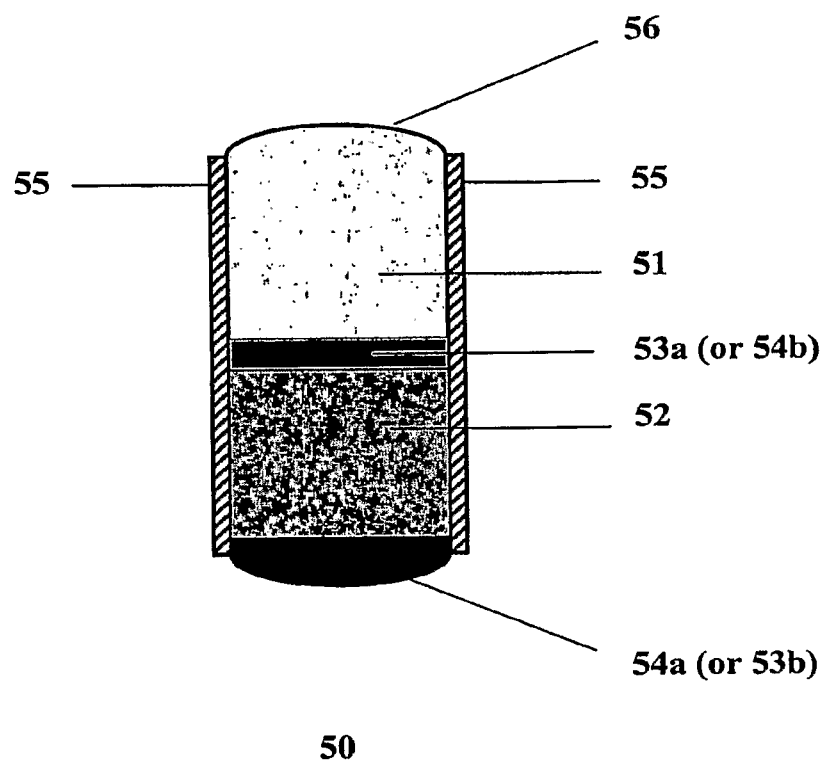


FIGURE 6

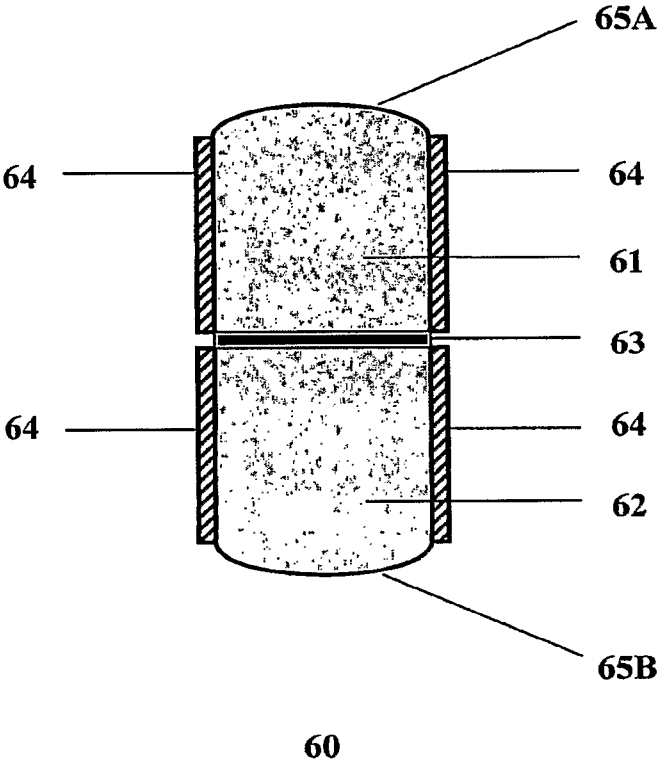


FIGURE 7

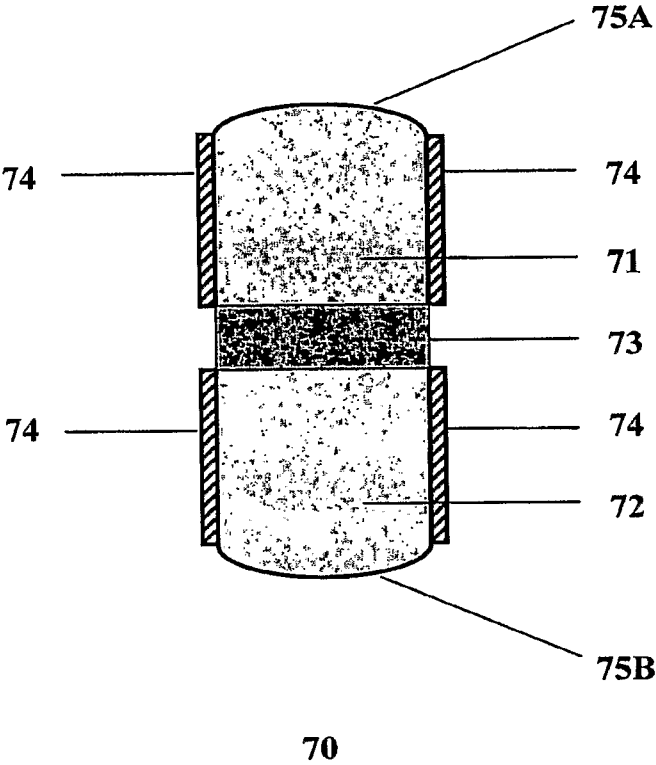


FIGURE 8

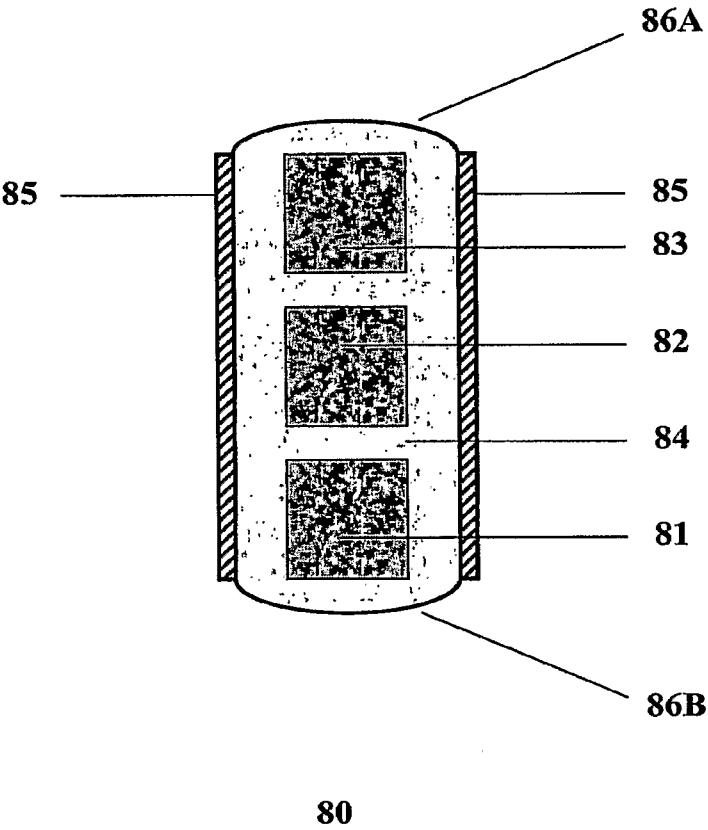


FIGURE 9

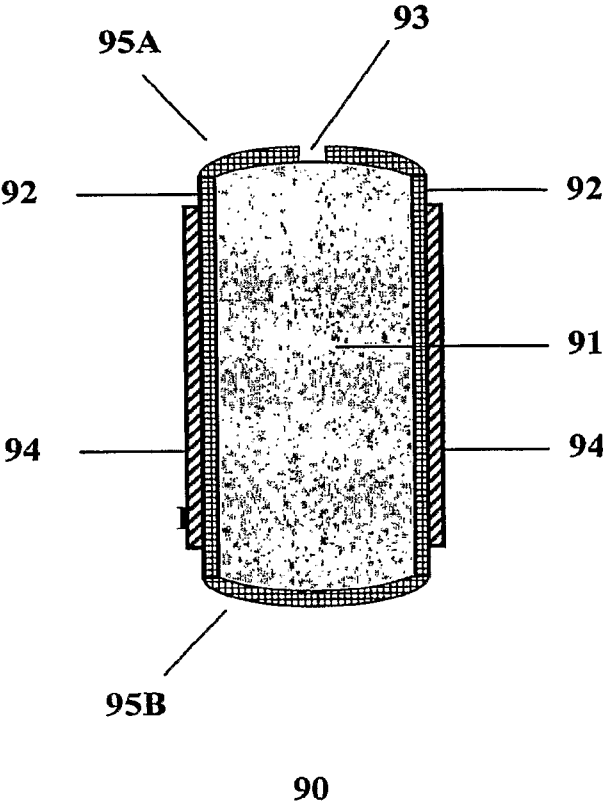
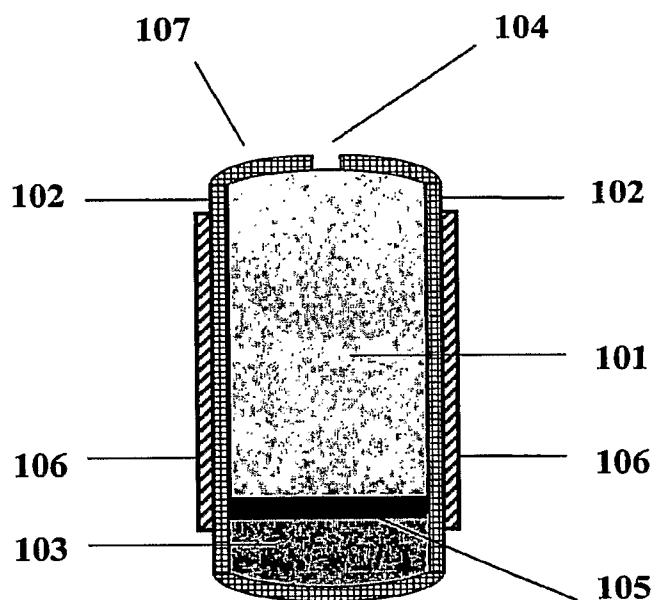


FIGURE 10



100A

FIGURE 11

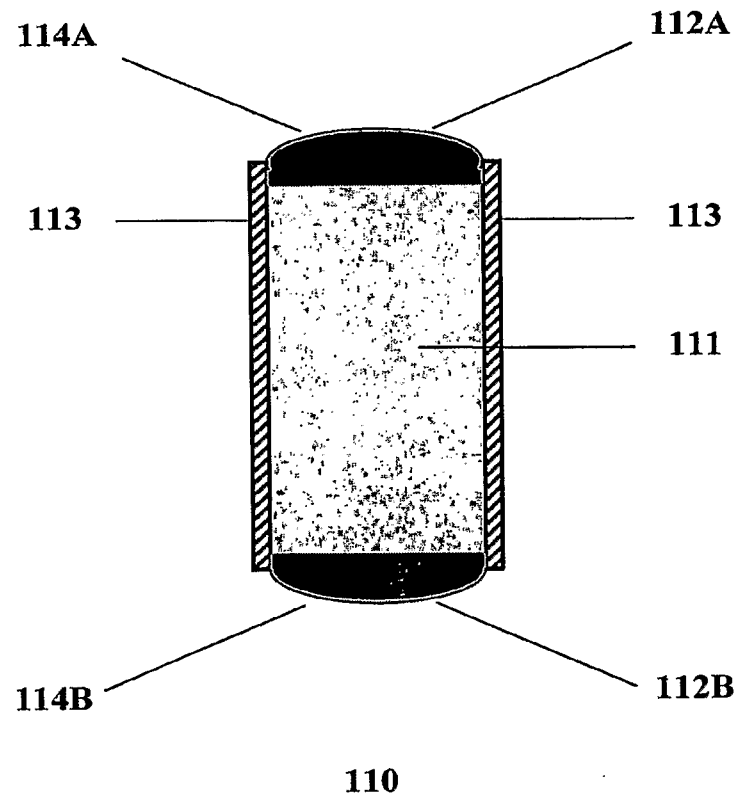


FIGURE 12

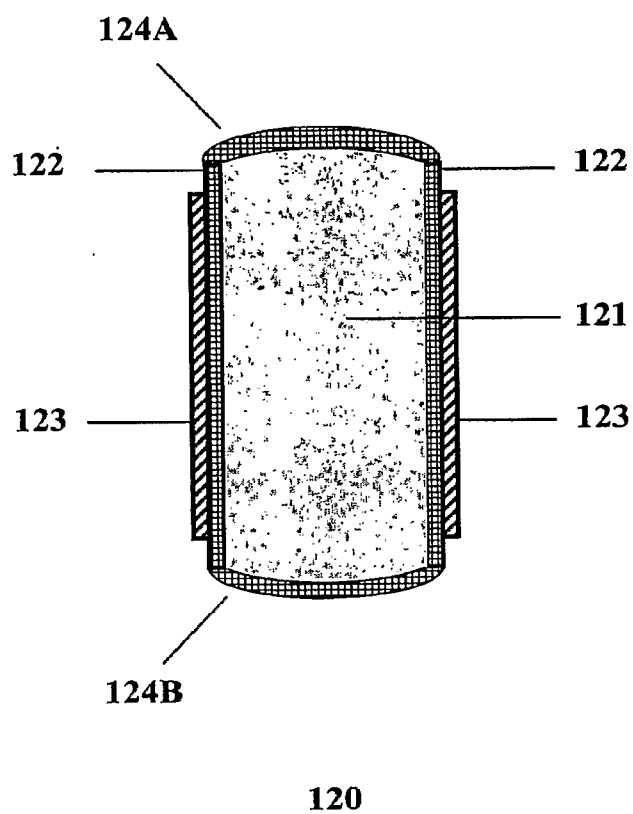


FIGURE 13

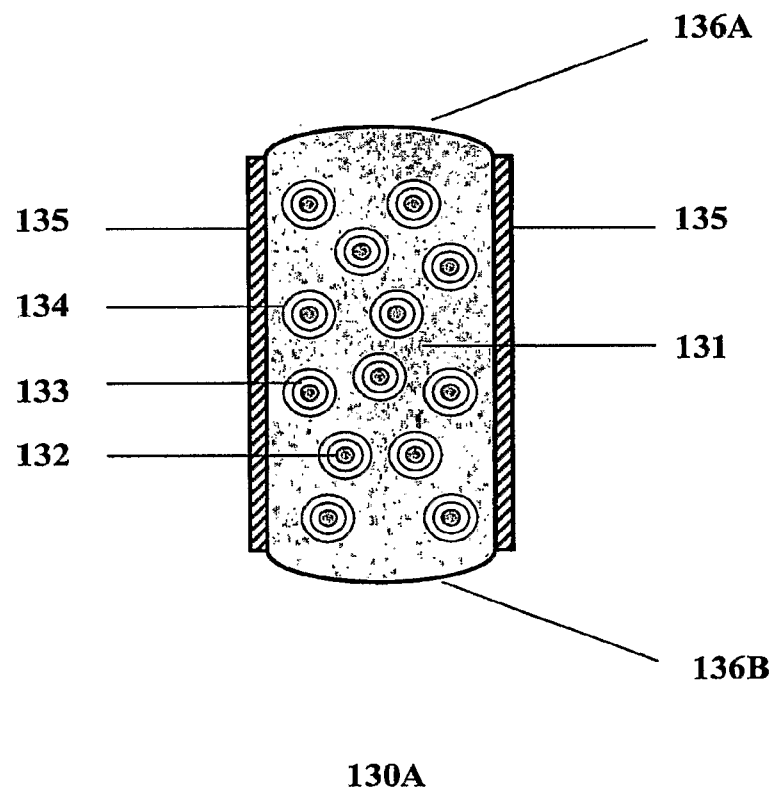


FIGURE 14

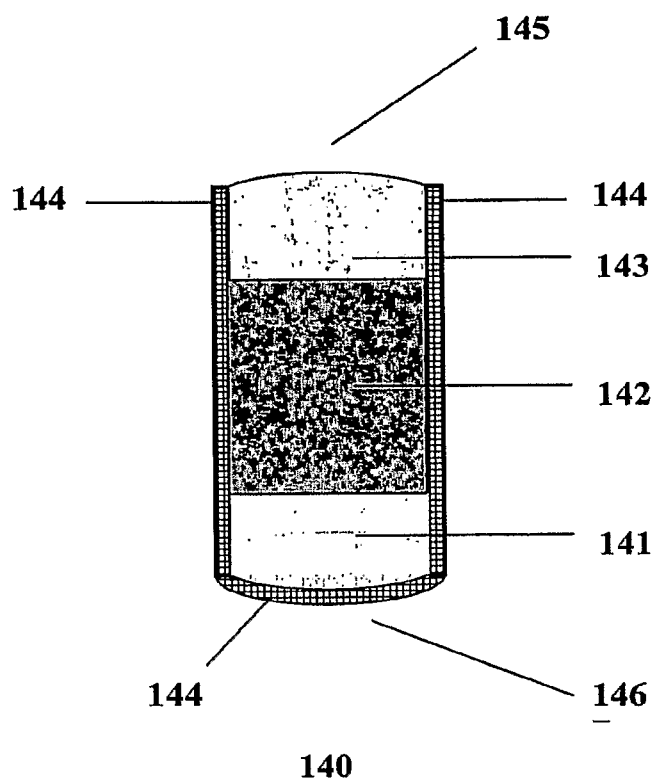
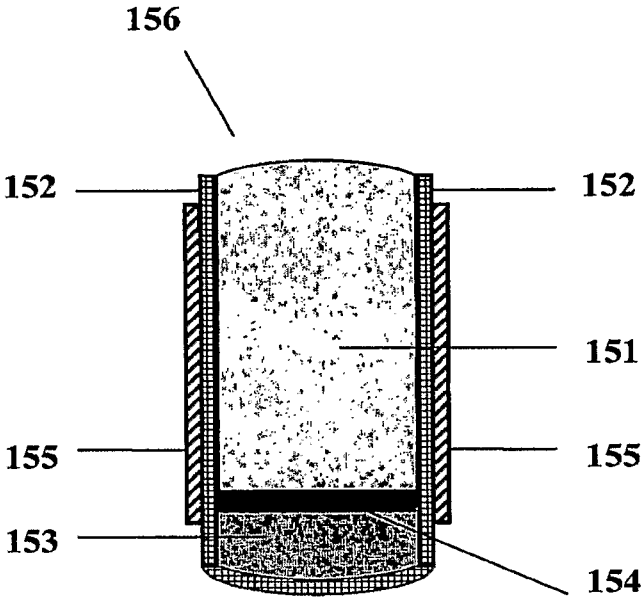


FIGURE 15



150

FIGURE 16

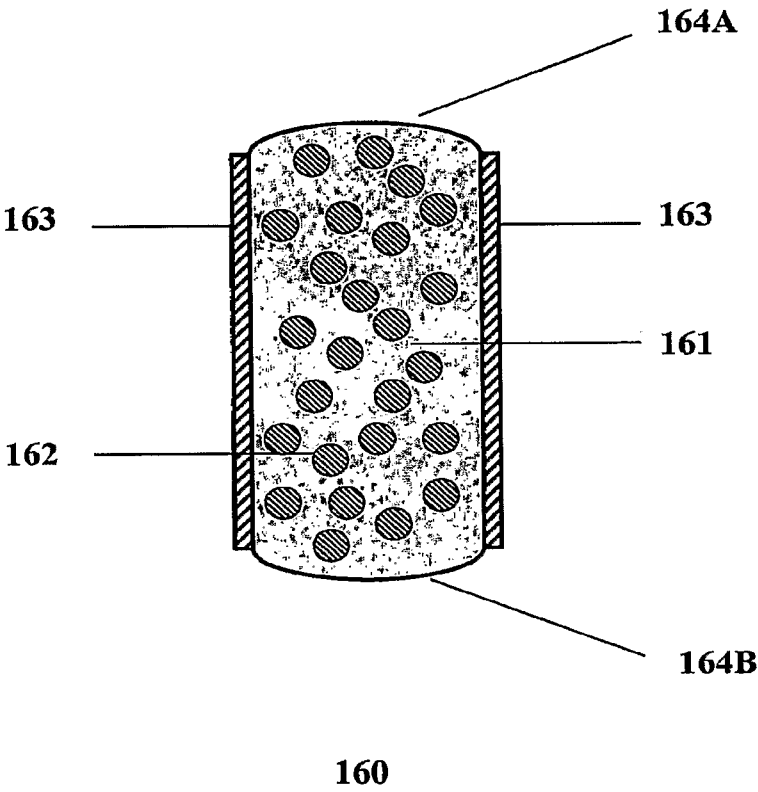


FIGURE 17

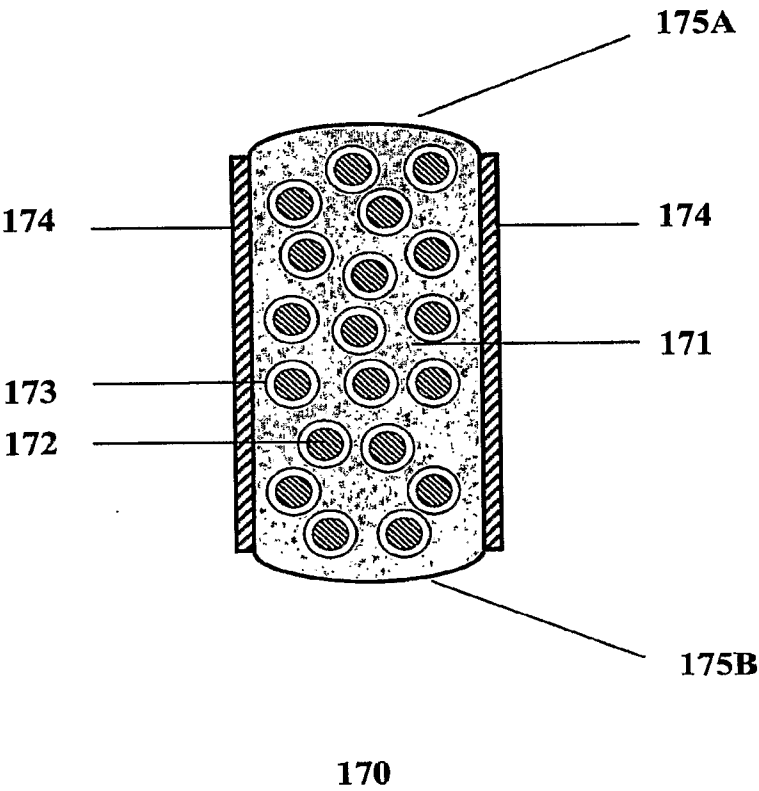


FIGURE 18

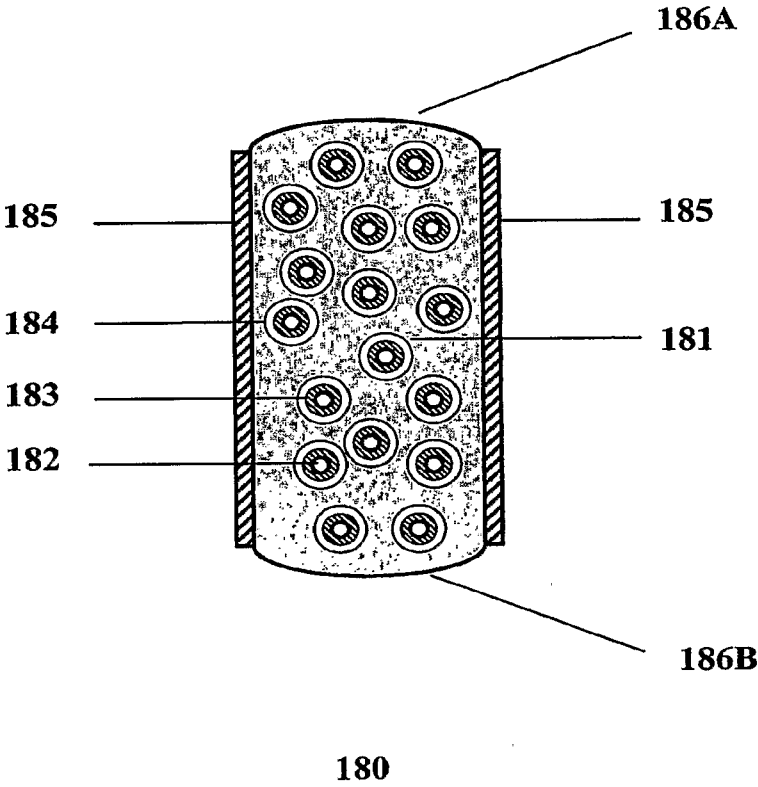


FIGURE 19

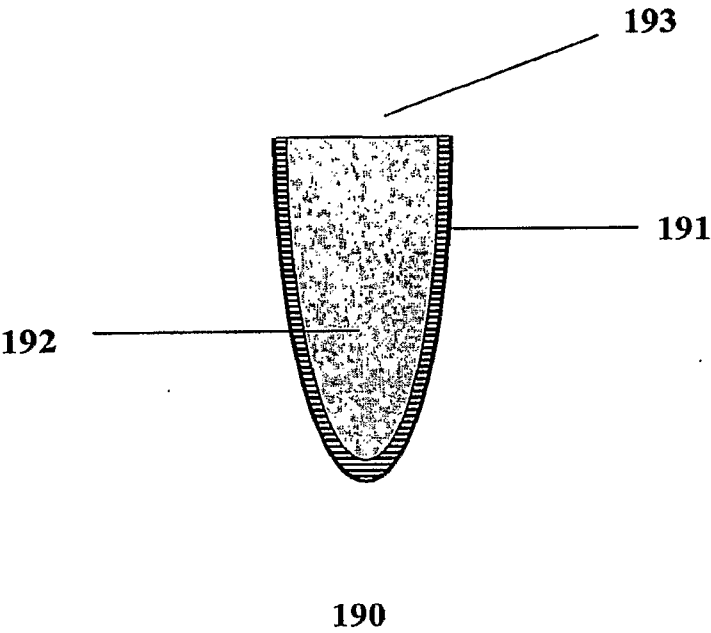
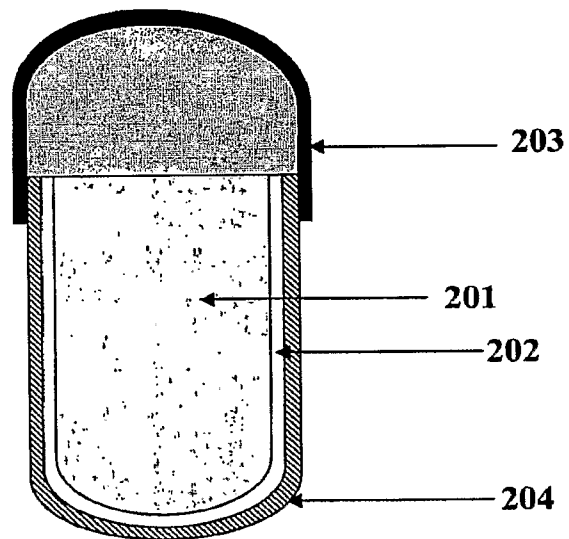
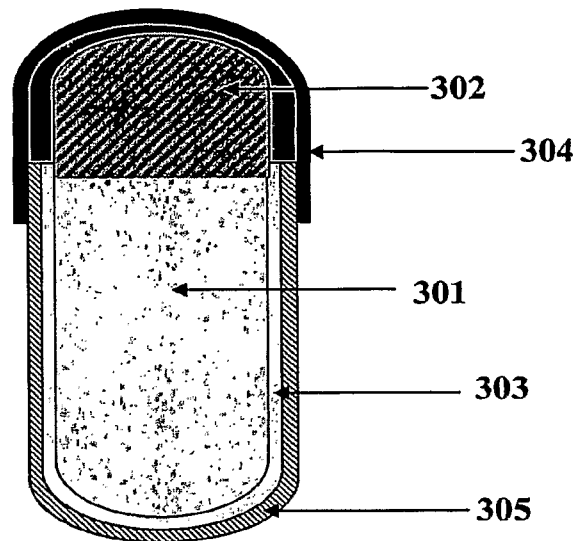


FIGURE 20



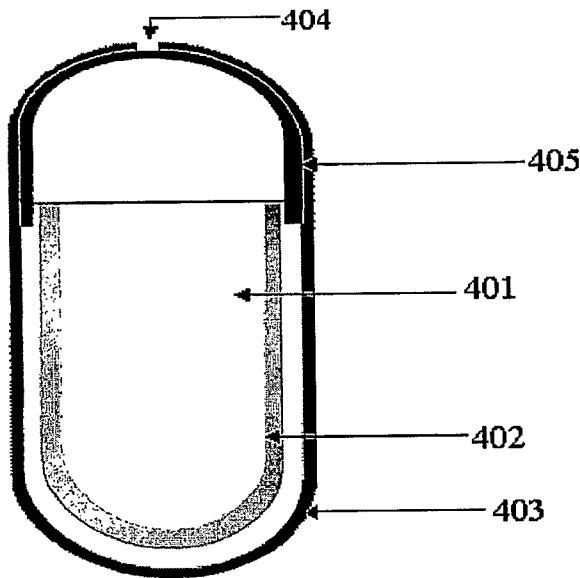
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FIGURE 21



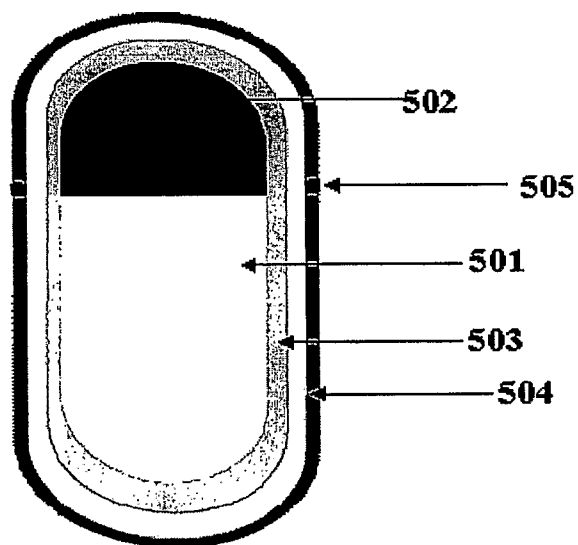
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FIGURE 22



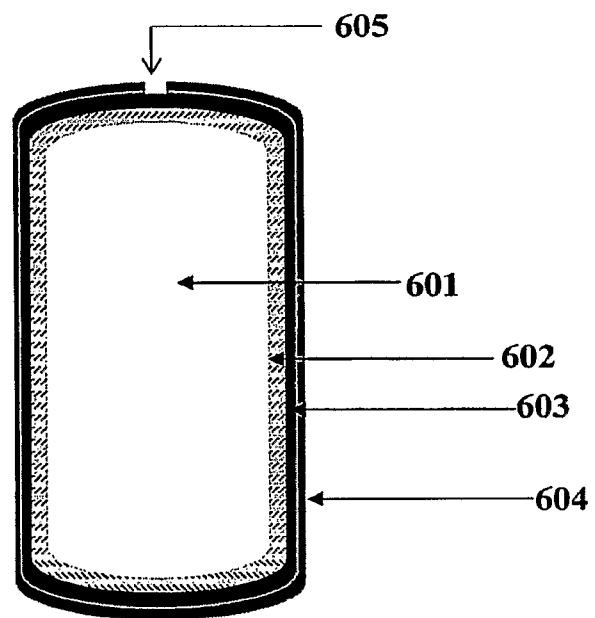
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FIGURE 23



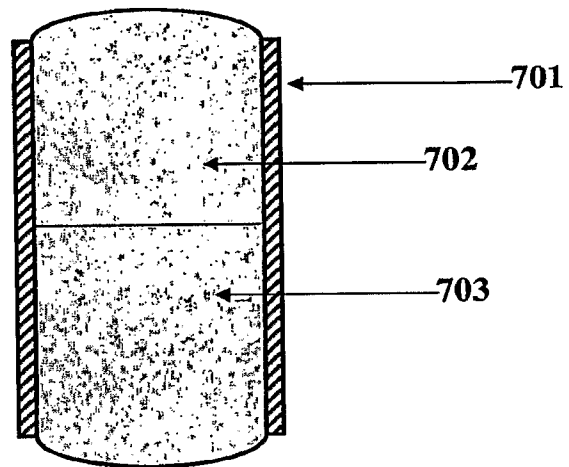
500

FIGURE 24



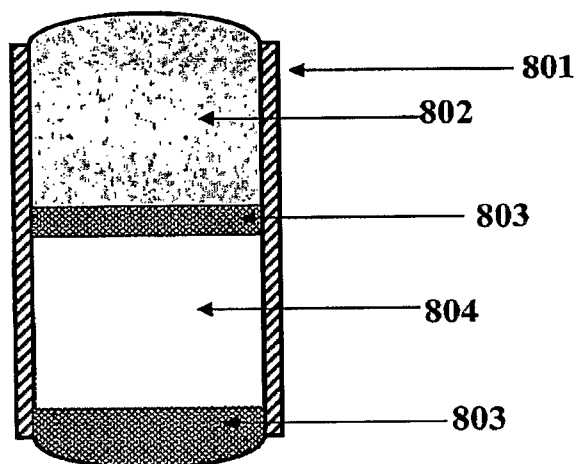
600

FIGURE 25



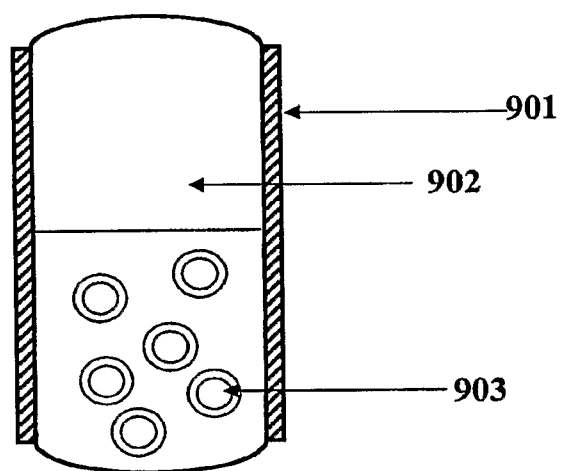
700

FIGURE 26



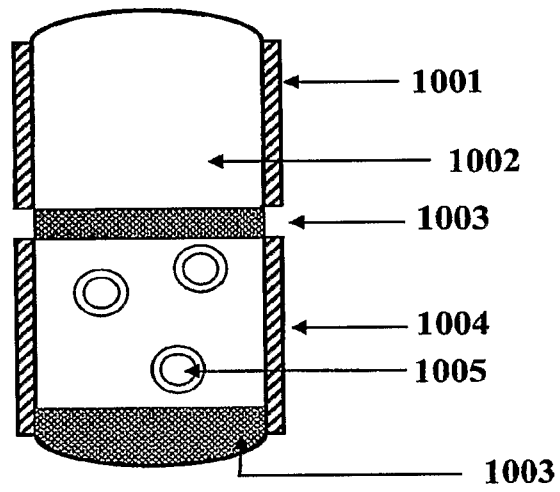
800

FIGURE 27



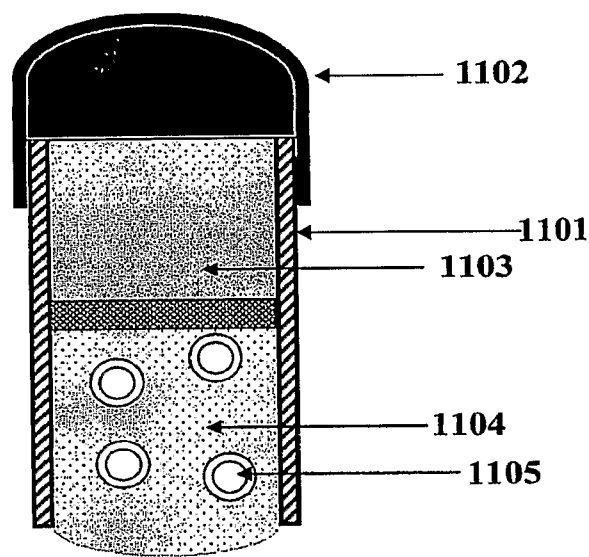
900

FIGURE 28



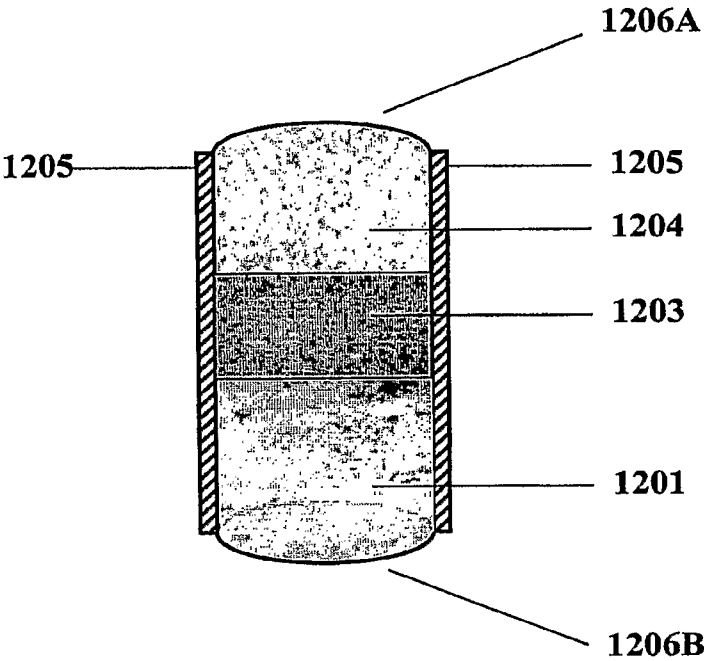
1000

FIGURE 29



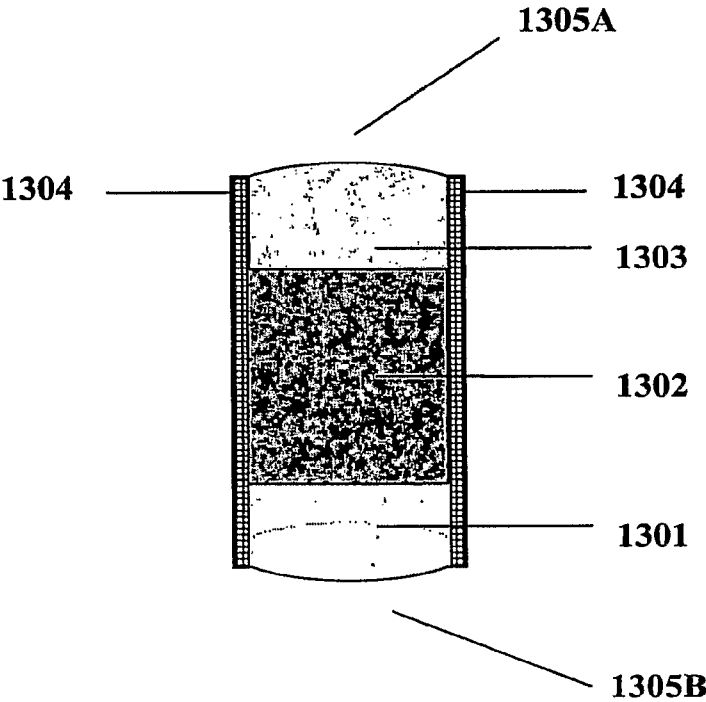
1100

FIGURE 30



1200

FIGURE 31



1300

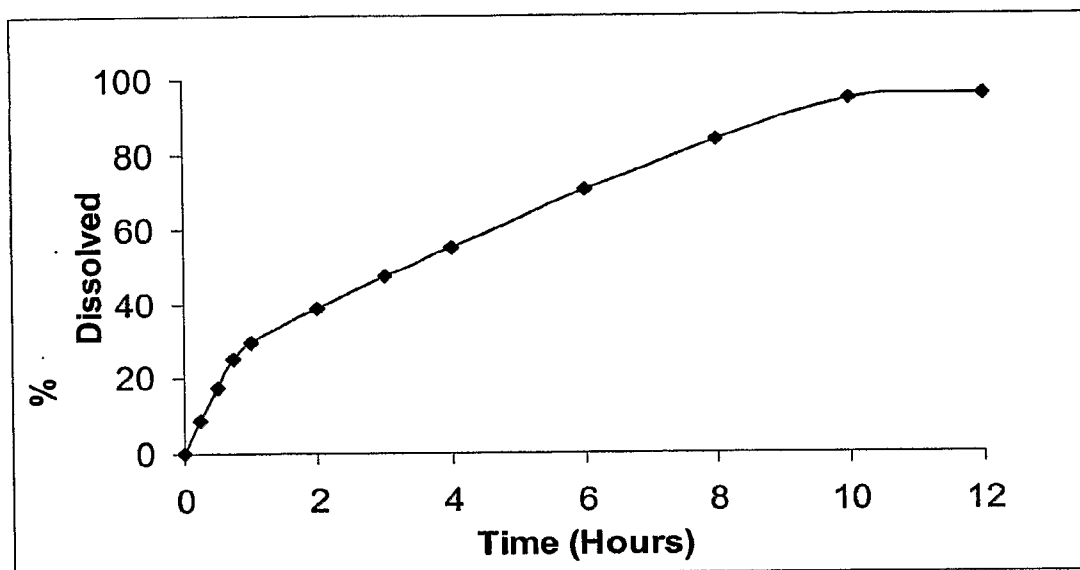
FIGURE 32

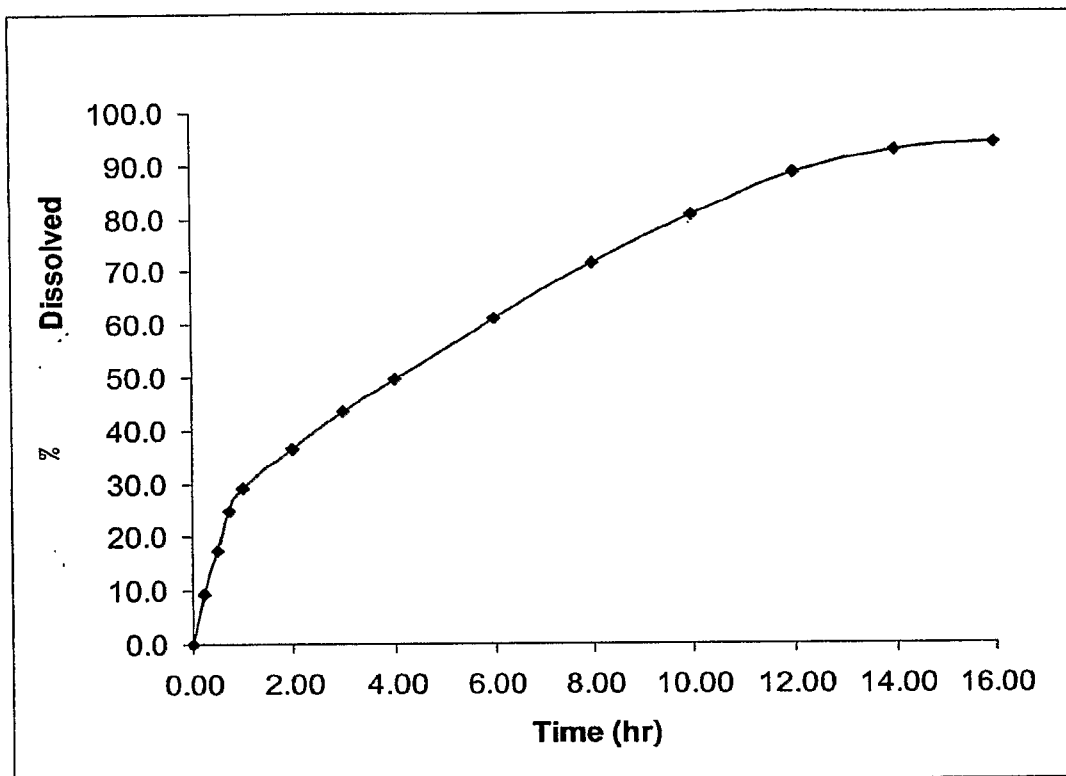
FIGURE 33

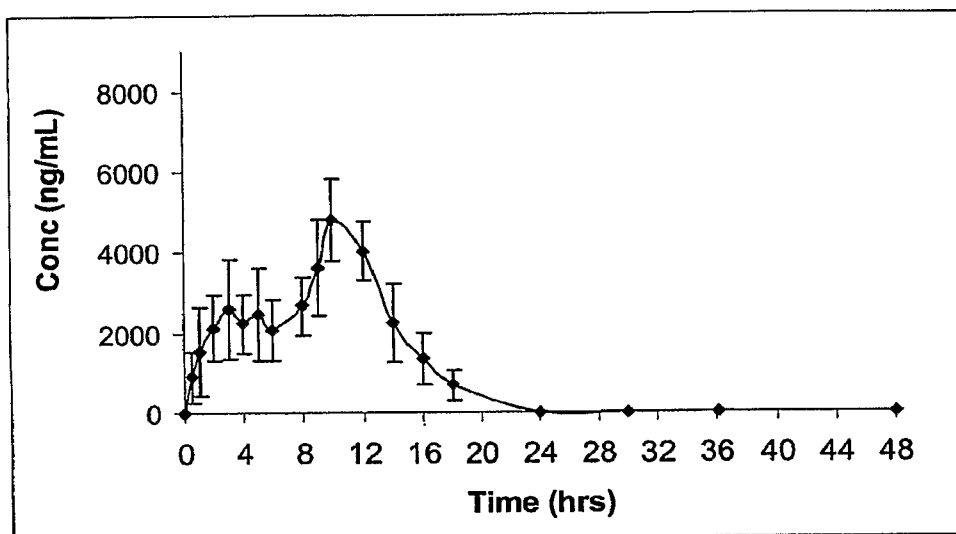
FIGURE 34

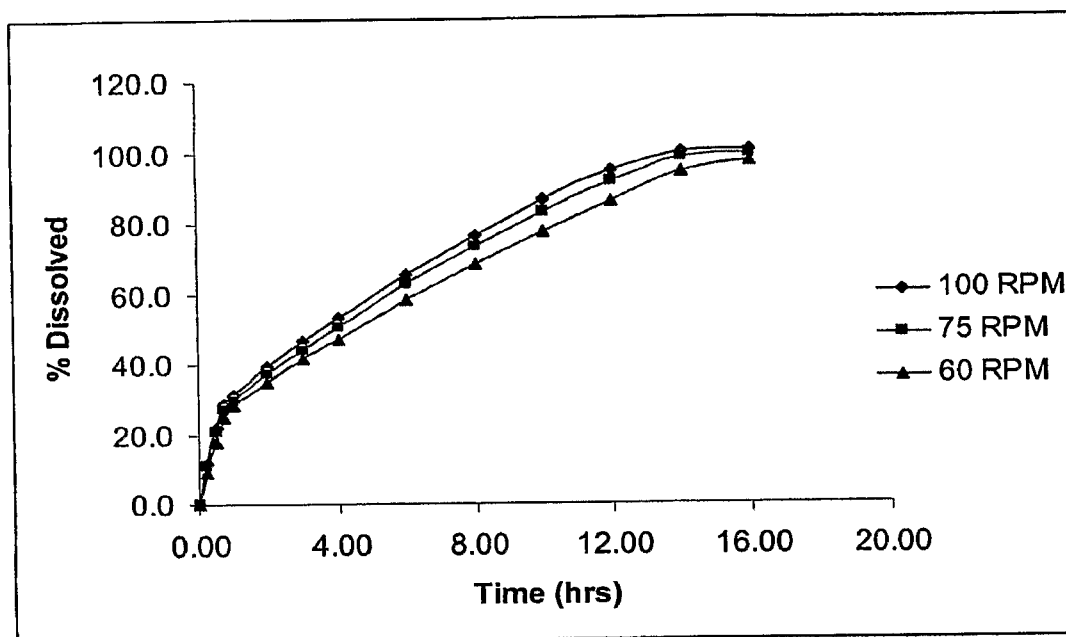
FIGURE 35

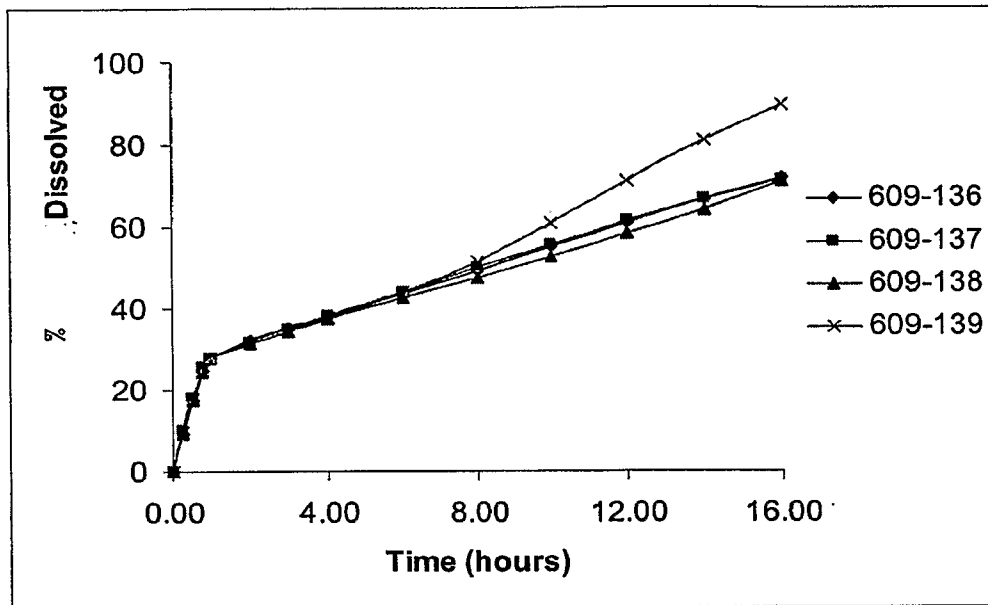
FIGURE 36

FIGURE 37

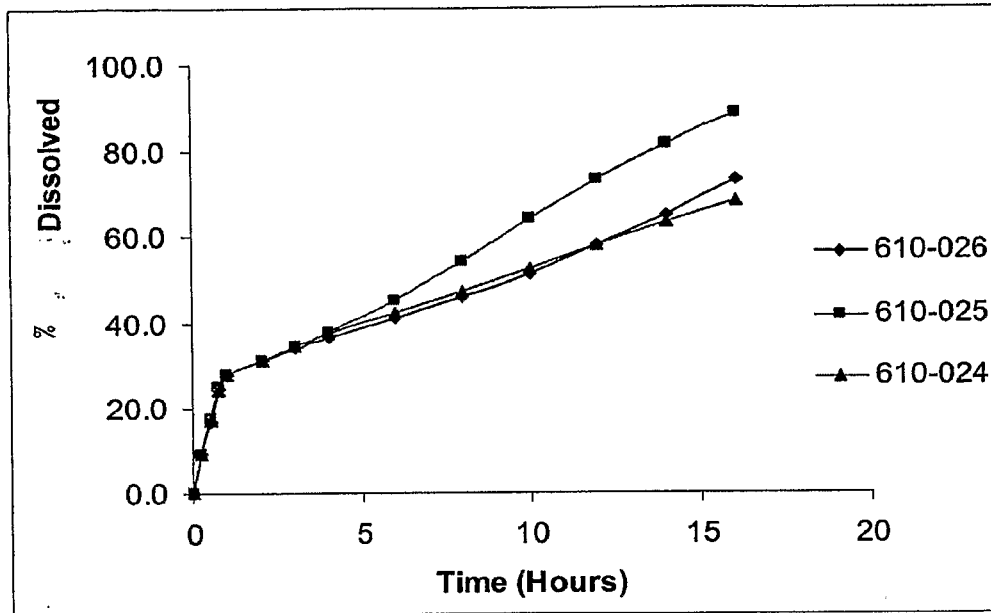


FIGURE 38

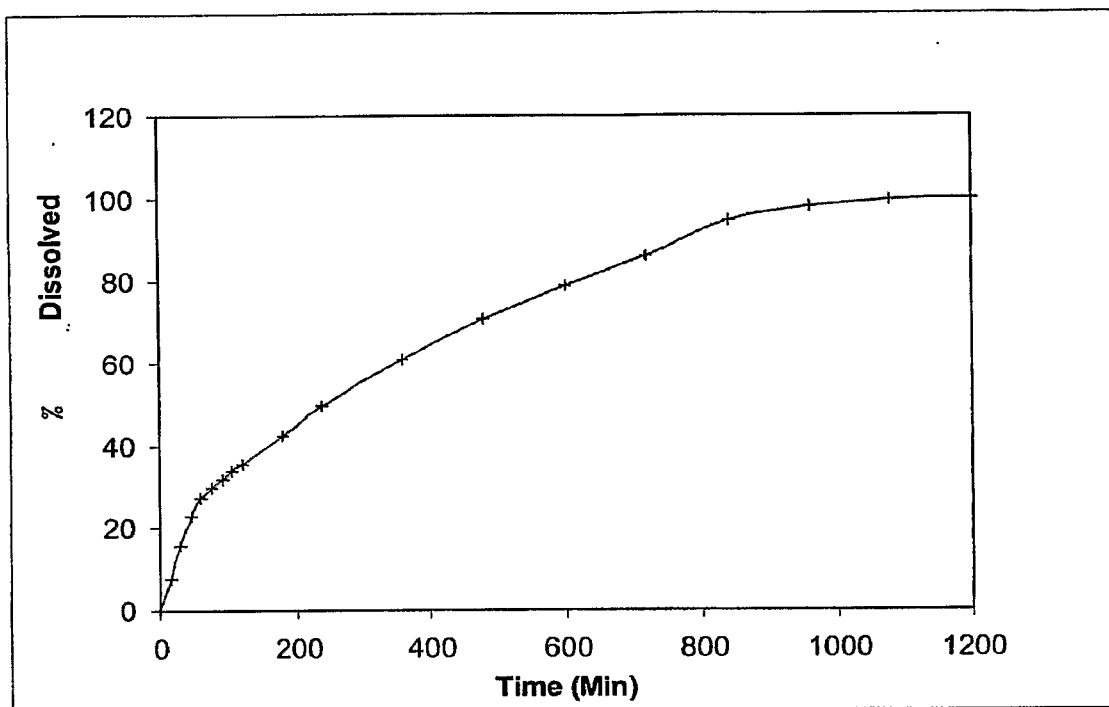


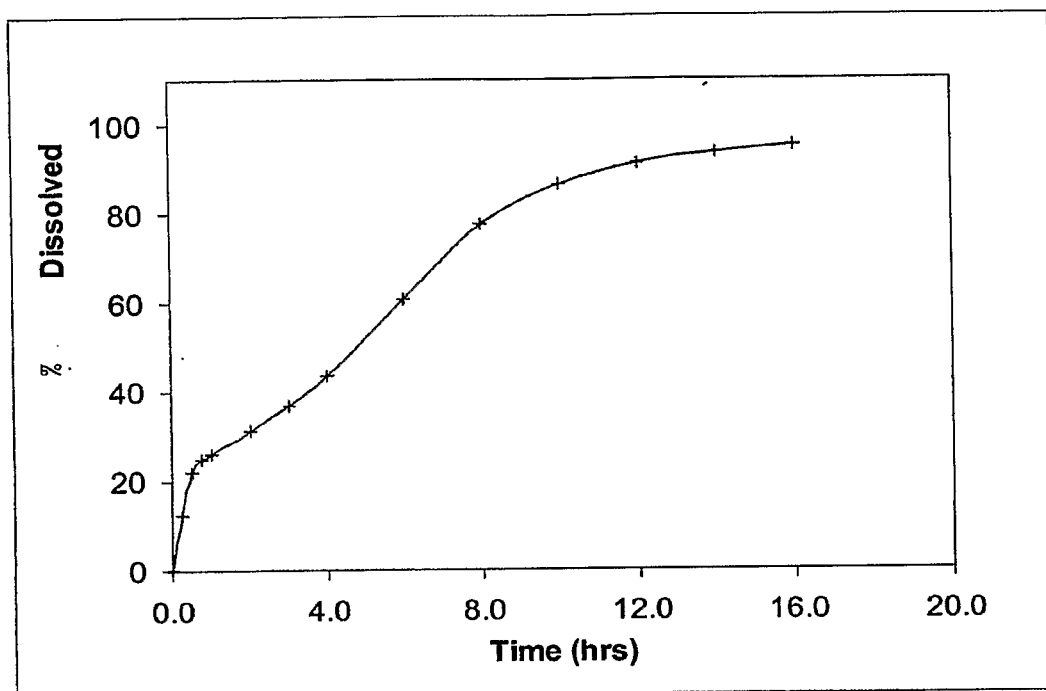
FIGURE 39

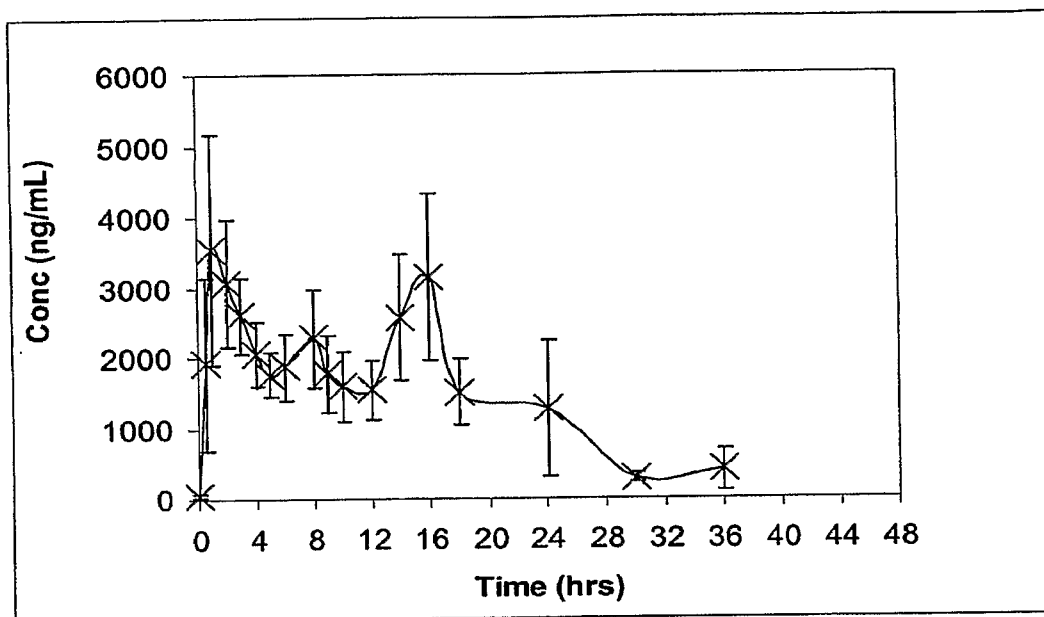
FIGURE 40

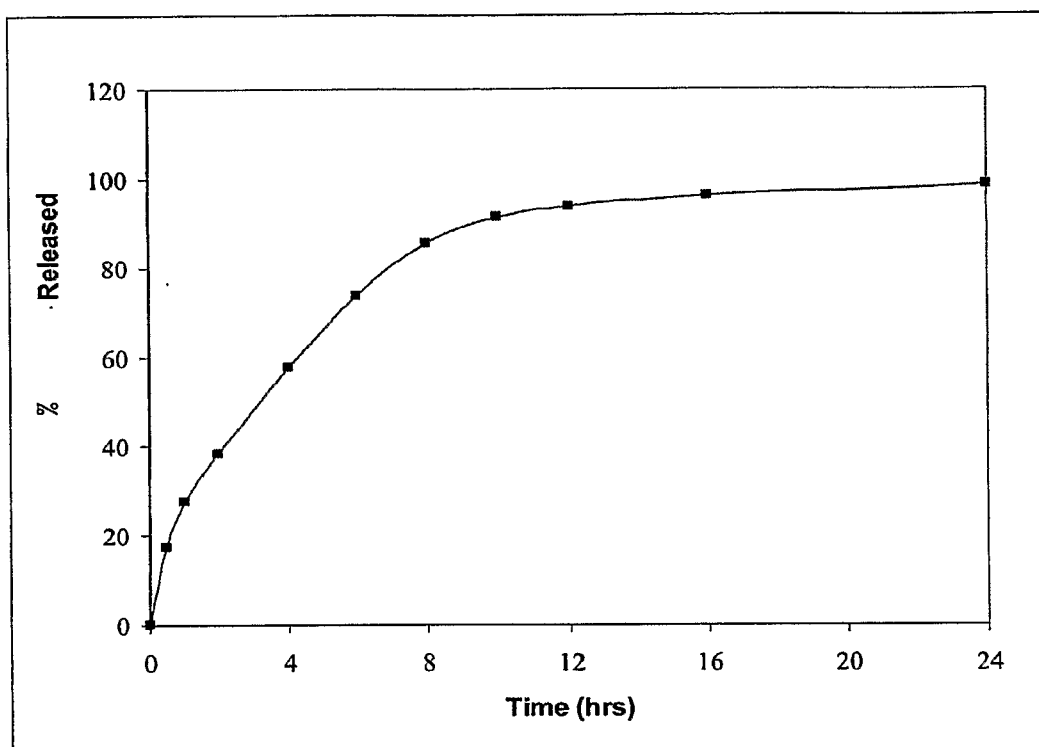
FIGURE 41

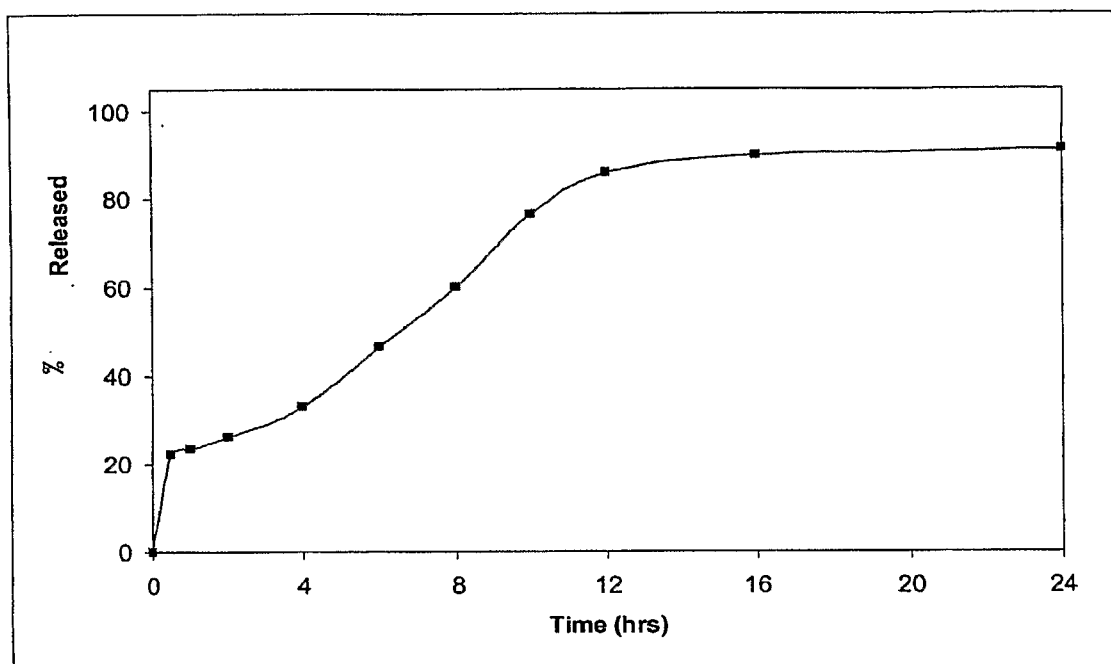
FIGURE 42

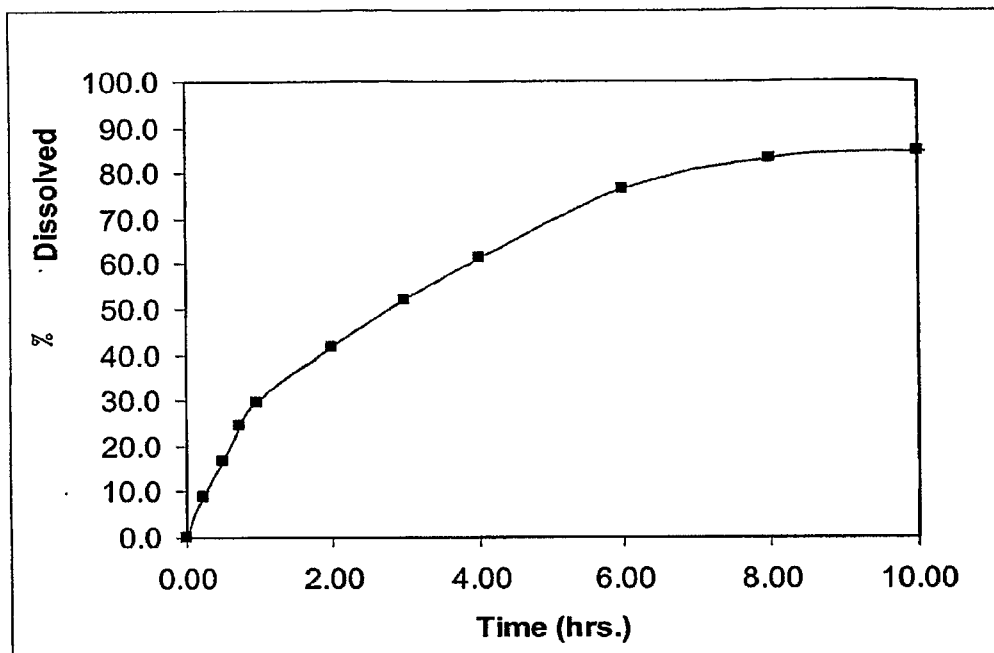
FIGURE 43

FIGURE 44