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(54) **MODIFIED RELEASE DOSAGE FORMS**

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and which is a continuation-in-part of application No.
09/966,497, filed on Sep. 28, 2001, and which is a
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filed on Sep. 28, 2001, and which is a continuation-
in-part of application No. 09/966,450, filed on Sep.
28, 2001.

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(52) **U.S. Cl.** **424/473**

(57) **ABSTRACT**

A dosage form comprises: (a) at least one active ingredient;
(b) a core having an outer surface; and (c) a shell which
resides upon at least a portion of the core outer surface,
wherein at least a portion of the shell is semipermeable, such
that the liquid medium diffuses through the semipermeable
shell or shell portion to the core due to osmosis. The shell
also provides for delivery of the active ingredient to a liquid
medium outside the shell after contacting of the dosage form
with the liquid medium. The dosage form delivers one or
more active ingredients in a controlled manner upon con-
tacting of the dosage form with a liquid medium. The dosage
form may be employed to provide a burst release of the
active ingredient, or to provide release of the active ingre-
dient at an ascending release rate over an extended time
period upon contacting of the dosage form with a liquid
medium.

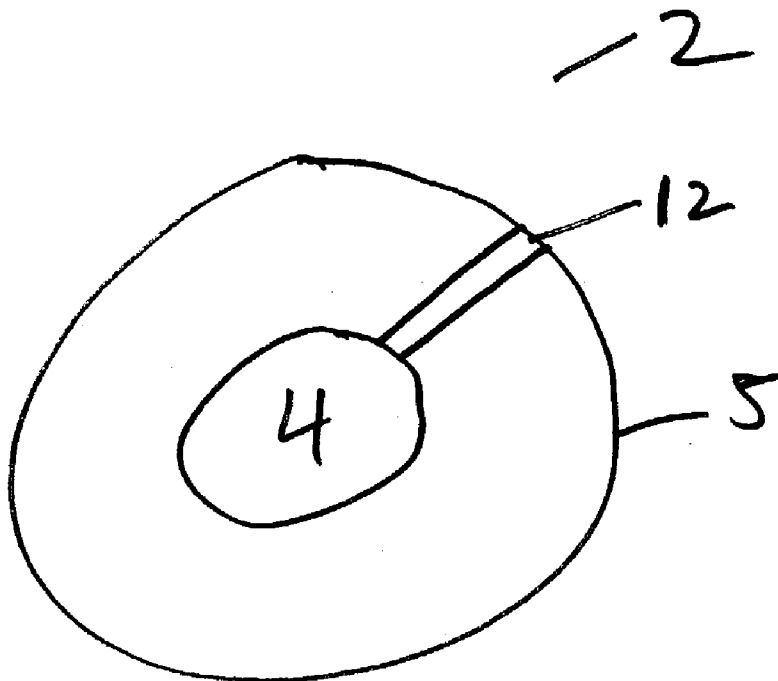


Fig. 1A

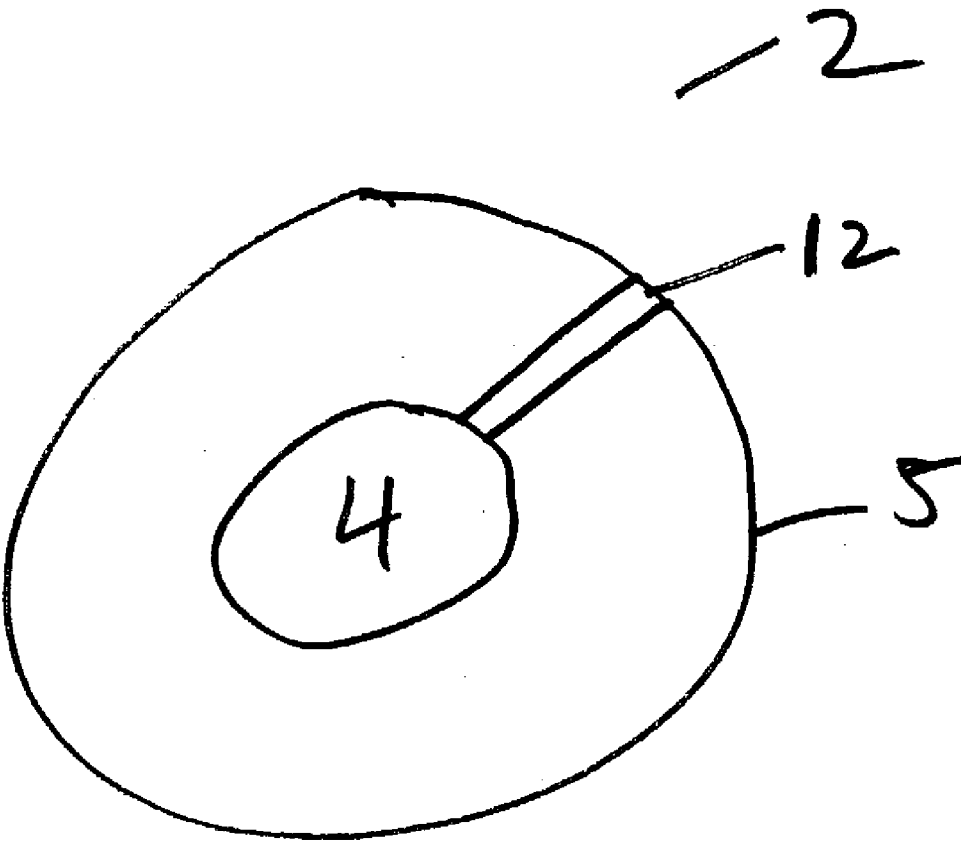


Fig. 1B

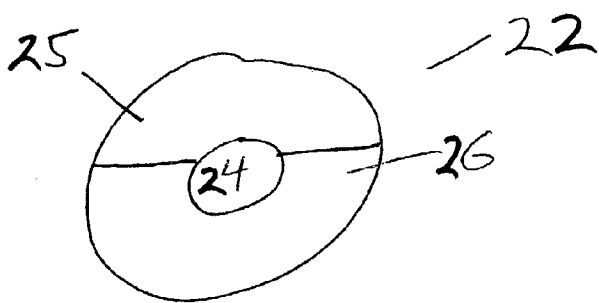


Fig. 2

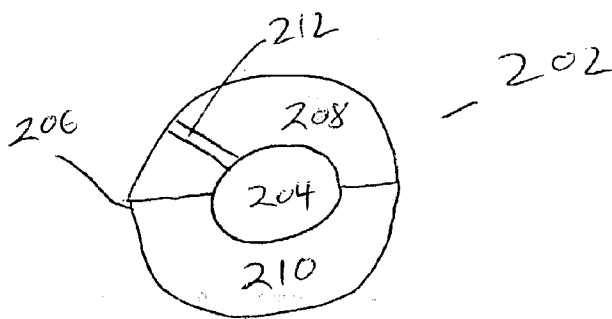


Fig. 3

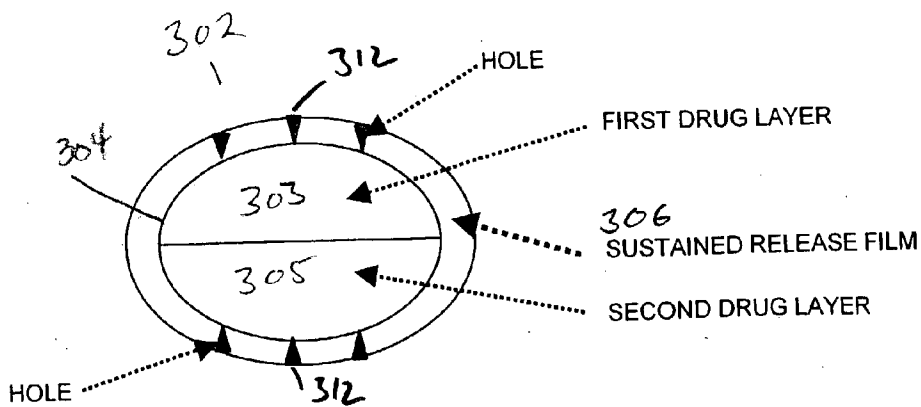


Fig. 4

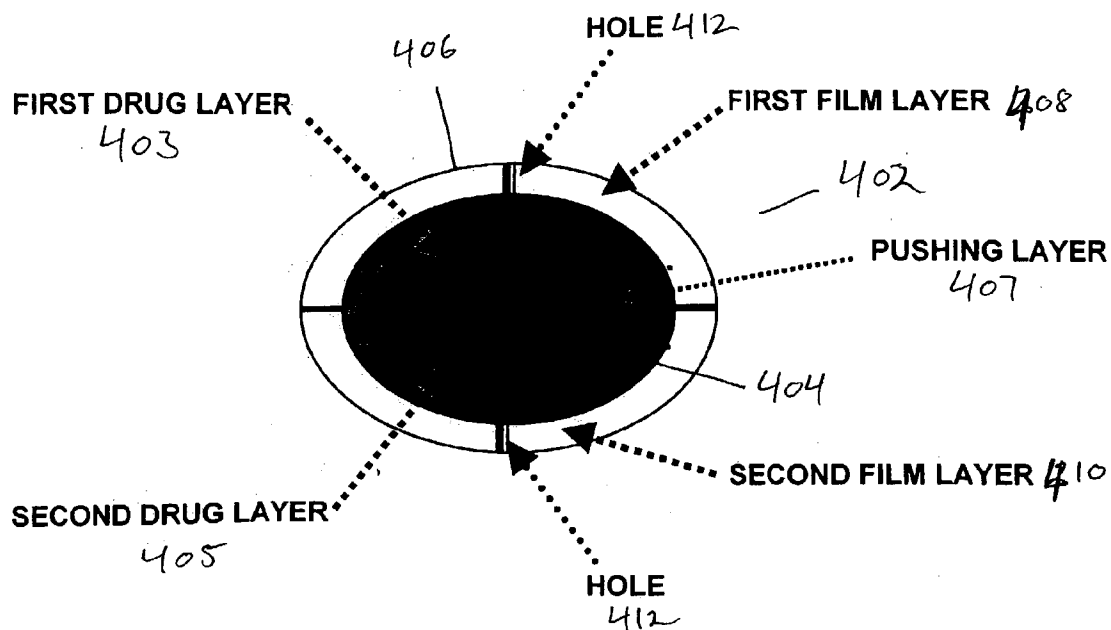


Fig. 5

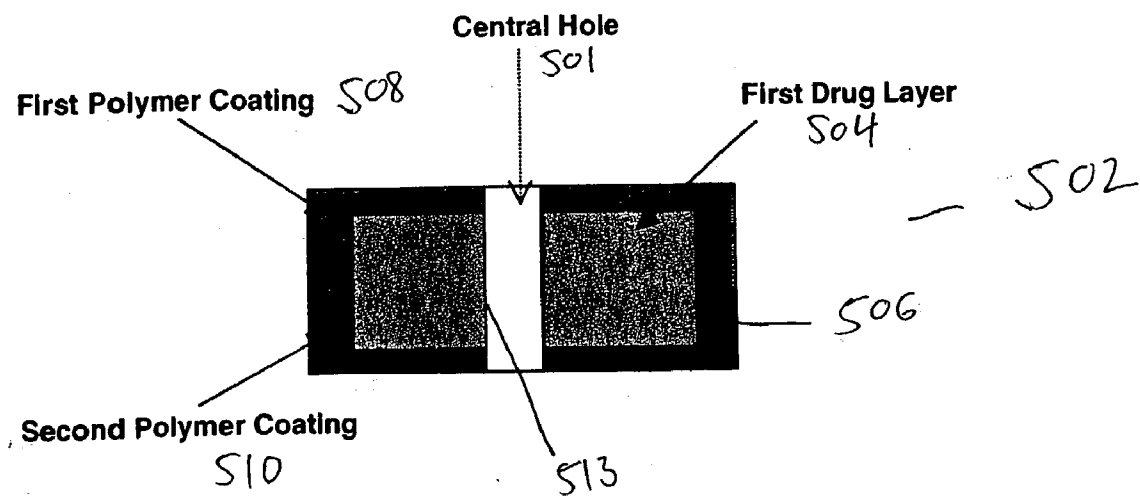
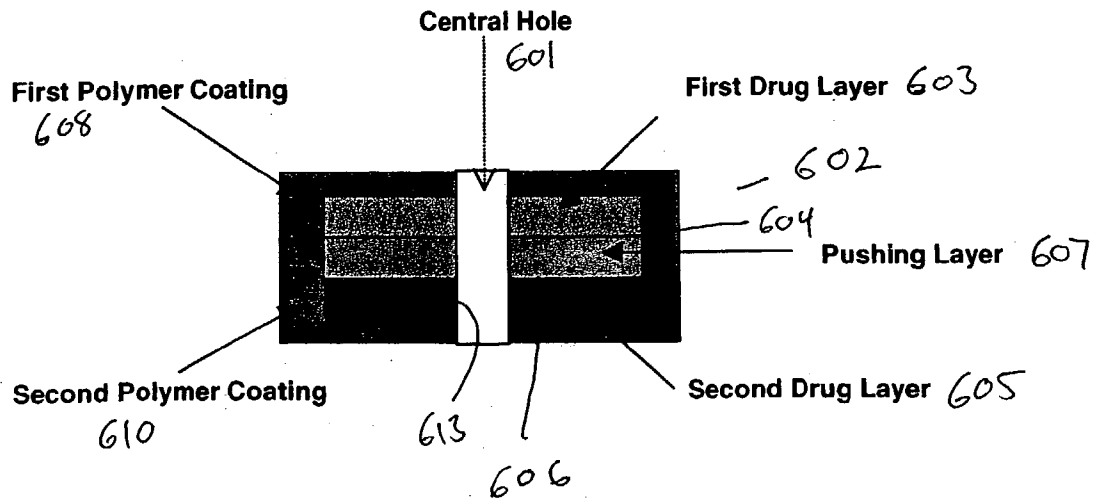


Fig. 6



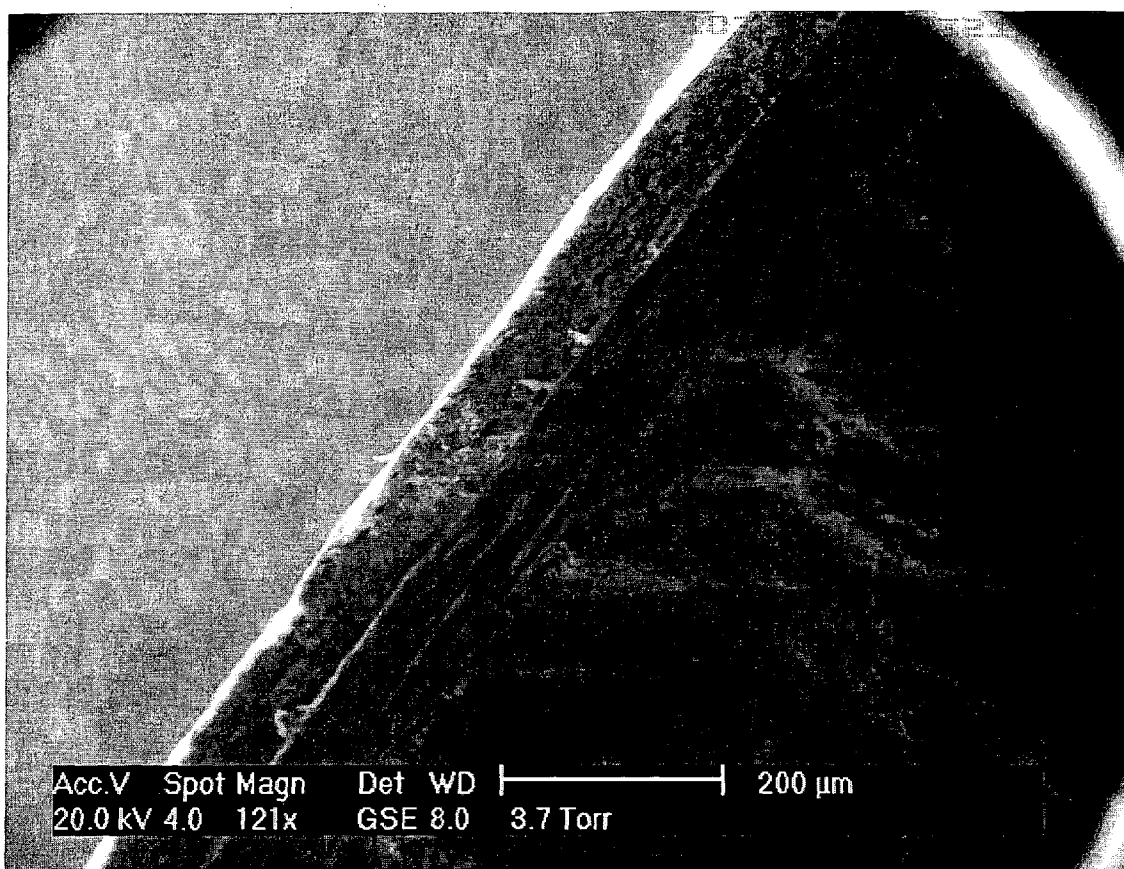


Fig. 7A

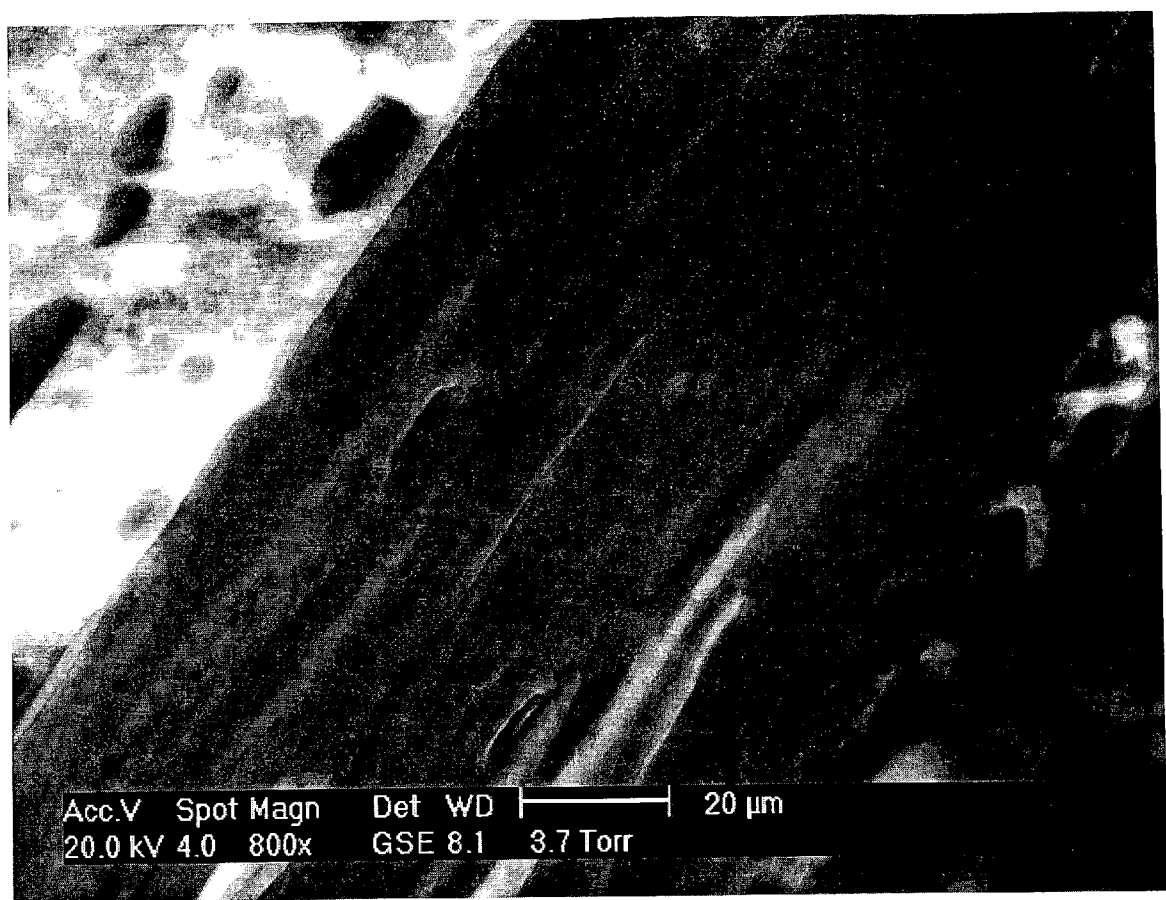


Fig. 7B

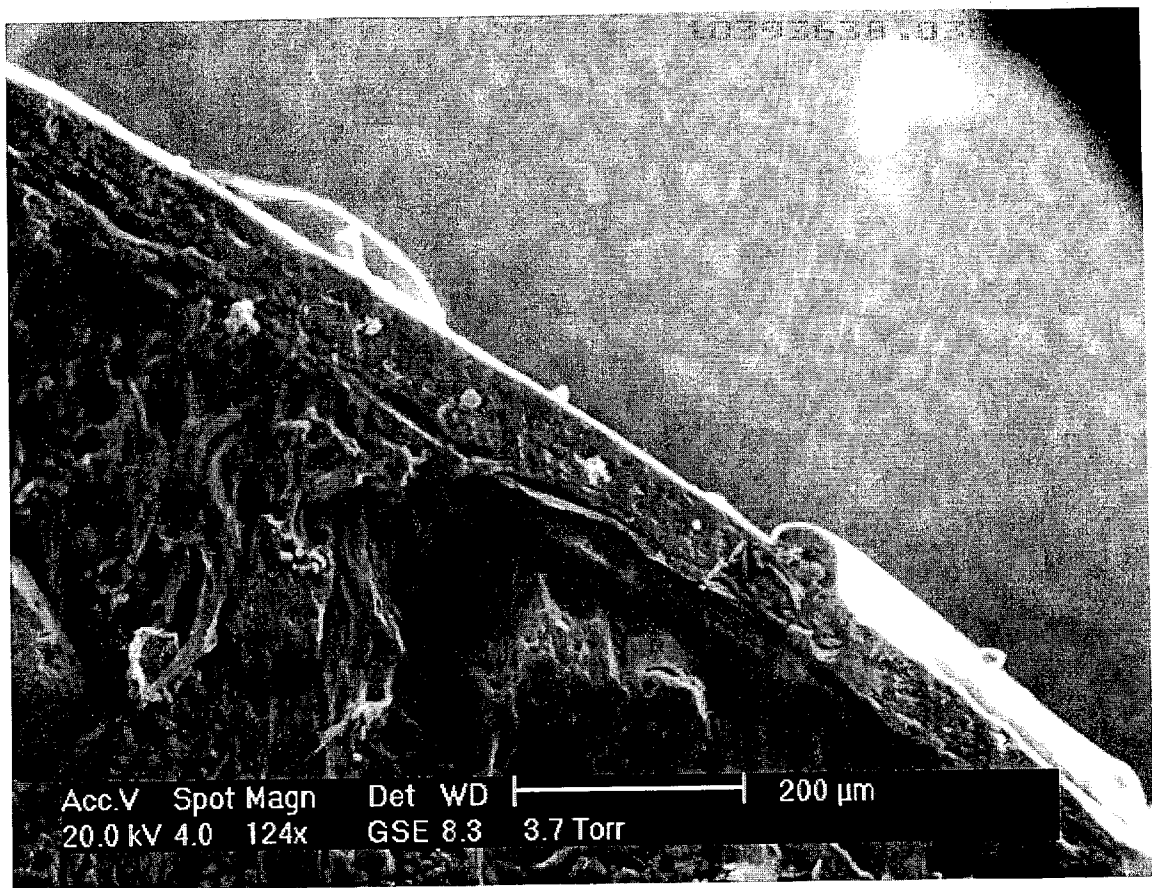


Fig. 8A

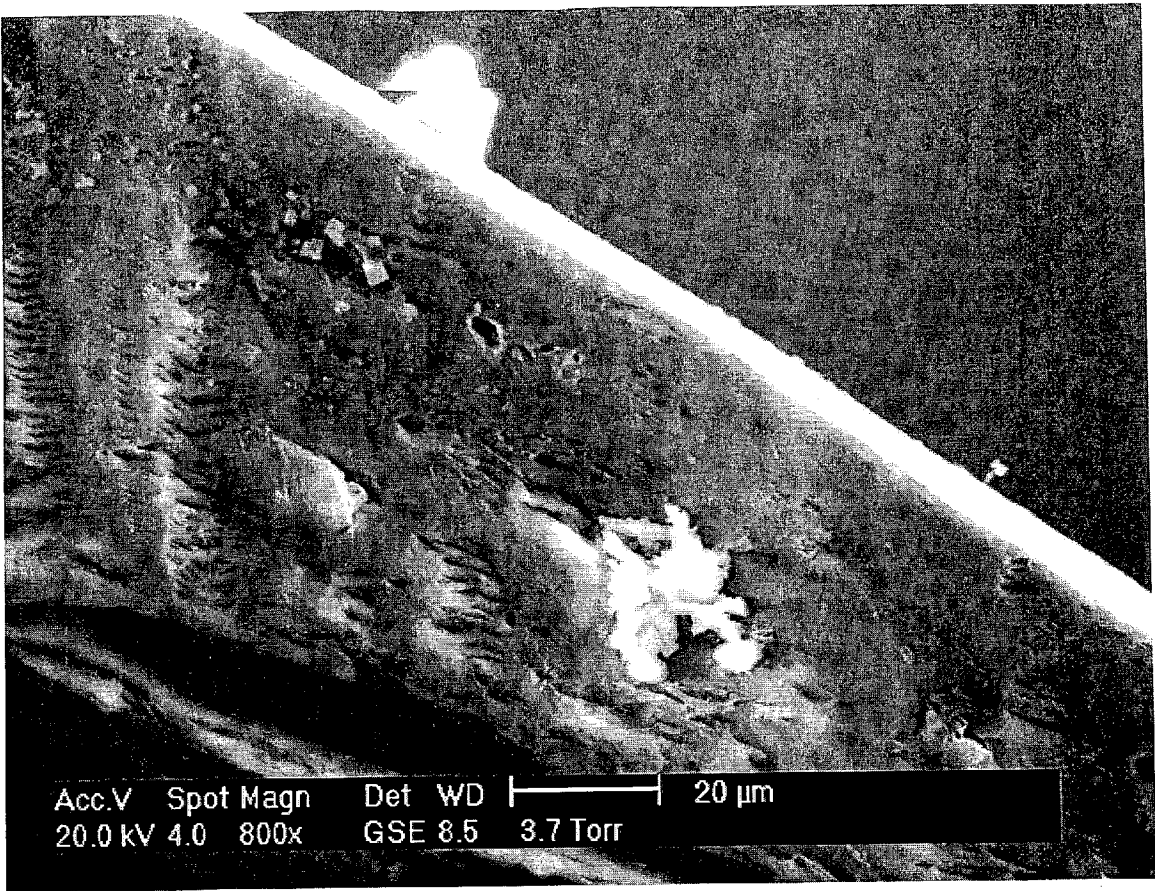
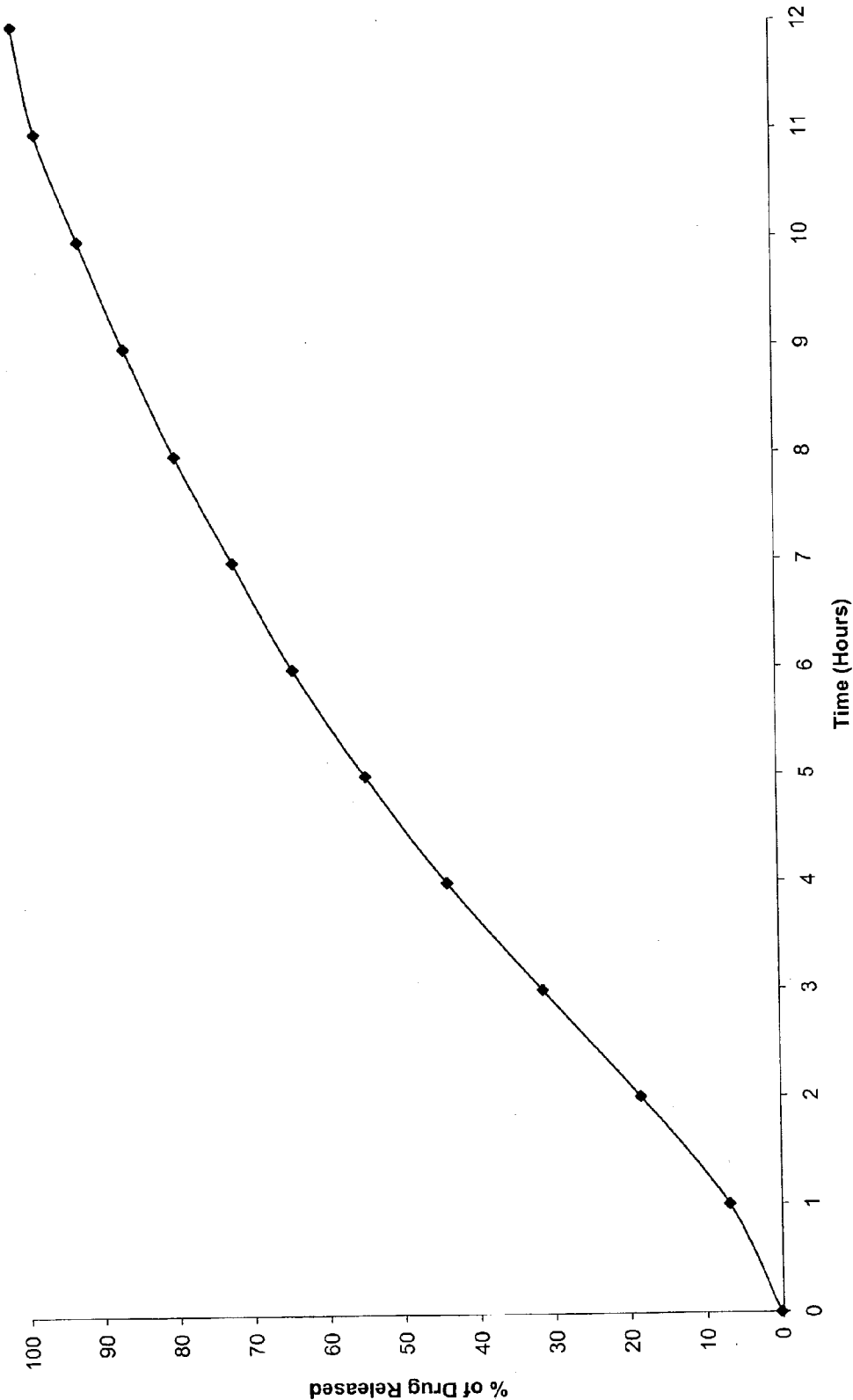


Fig. 8B

Figure 9



MODIFIED RELEASE DOSAGE FORMS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation-in-part of PCT Application Nos. PCT/IUS02/31129, filed Sep. 28, 2002; PCT/US02/31117, filed Sep. 28, 2002; PCT/US02/31062, filed Sep. 28, 2002; PCT/US02/31024, filed Sep. 28, 2002; and PCT/US02/31163, filed Sep. 28, 2002, which are each continuations-in-part of U.S. Ser. No. 09/966,939, filed Sep. 28, 2001; U.S. Ser. No. 09/966,509, filed Sep. 28, 2001; U.S. Ser. No. 09/966,497, filed Sep. 28, 2001; U.S. Ser. No. 09/967,414, filed Sep. 28, 2001; and U.S. Ser. No. 09/966,450, filed September 28, the disclosures of all of the above being incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to modified release dosage forms such as modified release pharmaceutical compositions, and methods of providing predetermined active ingredient concentrations, which may be substantially constant or substantially non-constant, over an extended period of time, using such dosage forms. More particularly, this invention relates to modified release dosage forms for delivering one or more active ingredients in a controlled or delayed manner upon contacting of the dosage form with a liquid medium. The dosage form contains at least one active ingredient, and has a core and a shell. At least a portion of the shell is semipermeable to a liquid medium such as the gastrointestinal (GI) fluids of a patient, such that the liquid medium diffuses through the semipermeable shell or shell portion to the core, for example due to osmosis. The shell or shell portion also provides for delivery of active ingredient to the liquid medium outside of the dosage form after the dosage form is contacted with the liquid medium.

[0004] 2. Background Information

[0005] Modified release pharmaceutical dosage forms have long been used to optimize drug delivery and enhance patient compliance, especially by reducing the number of doses of medicine the patient must take in a day. For this purpose, it is often desirable to modify the rate of release of a drug (one particularly preferred type of active ingredient) from a dosage form into the GI fluids of a patient, especially to slow the release to provide prolonged action of the drug in the body.

[0006] The rate at which an orally delivered pharmaceutical active ingredient reaches its site of action in the body depends on a number of factors, including the rate and extent of drug absorption through the GI mucosa. To be absorbed into the circulatory system (blood), the drug must first be dissolved in the GI fluids. For many drugs, diffusion across the GI membranes is relatively rapid compared to dissolution. In these cases, the dissolution of the active ingredient is the rate limiting step in drug absorption, and controlling the rate of dissolution allows the formulator to control the rate of drug absorption into the circulatory system of a patient.

[0007] An important objective of modified release dosage forms is to provide a desired blood concentration versus time (pharmacokinetic, or PK) profile for the drug. Funda-

mentally, the PK profile for a drug is governed by the rate of absorption of the drug into the blood, and the rate of elimination of the drug from the blood. The type of PK profile desired depends, among other factors, on the particular active ingredient, and physiological condition being treated.

[0008] A particularly desirable PK profile for a number of drugs and conditions is one in which the level of drug in the blood is maintained essentially constant (i.e. the rate of drug absorption is approximately equal to the rate of drug elimination) over a relatively long period of time. Such systems have the benefit of reducing the frequency of dosing, improving patient compliance, as well as minimizing side effects while maintaining full therapeutic efficacy. A dosage form which provides a "zero-order," or constant release rate of the drug is useful for this purpose. Since zero-order release systems are difficult to achieve, systems which approximate a constant release rate, such as for example first-order and square root of time profiles are often used to provide sustained (e.g. prolonged, extended, or retarded) release of a drug.

[0009] Another particularly desirable PK profile is an "ascending blood level" profile. This is achieved when the rate of absorption of drug into the blood (circulation) exceeds its rate of elimination from the blood for a period of time, producing an increasing blood level over the course of the dosing interval or a portion thereof. This type of PK profile is exemplified in PCT Publication No. WO99/62946.

[0010] Another particularly desirable PK profile is achieved by a dosage form that delivers a delayed release dissolution profile, in which the release of one or more doses of drug from the dosage form is delayed for a pre-determined time after contact with a liquid medium, e.g. ingestion by the patient. The delay period ("lag time") can be followed either by prompt release of the active ingredient ("delayed burst"), or by sustained (prolonged, extended, or retarded) release of the active ingredient ("delayed then sustained").

[0011] One particularly desirable type of delayed release PK profile, is a "pulsatile" profile, in which for example, a first dose of a first drug is delivered, followed by a delay period during which there is substantially no release of the first drug from the dosage form, followed by either prompt or sustained release of a subsequent dose of the same drug. In one particularly desirable type of pulsatile drug delivery system, the first dose is released essentially immediately upon contacting of the dosage form with a liquid medium. In another particularly desirable type of pulsatile drug delivery system, the delay period corresponds approximately to the time during which a therapeutic concentration of the first dose is maintained in the blood. Pulsatile delivery systems are particularly useful for applications where a continuous release of drug is not ideal. Examples of this are drugs exhibiting first pass metabolism by the liver, drugs that induce biological tolerance (i.e. the therapeutic effect decreases with continuous presence of the drug at the site of action), and drugs whose efficacy is influenced by circadian rhythms of body functions or diseases.

[0012] It is also particularly desirable for a pharmaceutical dosage form to deliver more than one drug at a modified rate. Because the onset and duration of the therapeutic efficacy of drugs vary widely, as do their absorption, distribution, metabolism, and elimination, it is often desirable to modify

the release of different drugs in different ways, or to have a first active ingredient immediately released from the dosage form, while a second drug is released in a delayed, controlled, sustained, prolonged, extended, or retarded manner.

[0013] Well known mechanisms by which a dosage form (or drug delivery system) can deliver drug at a controlled rate (e.g. sustained, prolonged, extended or retarded/release) include diffusion, erosion, and osmosis.

[0014] One classic diffusion-controlled release system comprises a "reservoir" containing the active ingredient, surrounded by a "membrane" through which the active ingredient must diffuse to be absorbed into the bloodstream of the patient. The rate of drug release, dM/dt depends on the area (A) of the membrane, the diffusional pathlength (l), the concentration gradient (AC) of the drug across the membrane, the partition coefficient (K) of the drug into the membrane, and the diffusion coefficient (D) according to the following equation:

$$dM/dt = \{ADKAC\}/l$$

[0015] Since one or more of the above terms, particularly the diffusional pathlength, and concentration gradient tend to be non-constant, diffusion-controlled systems generally deliver a non-constant release rate. In general, the rate of drug release from diffusion-controlled release systems typically follows first order kinetics.

[0016] Another common type of diffusion-controlled release system comprises active ingredient, distributed throughout an insoluble porous matrix through which the active ingredient must diffuse to be absorbed into the bloodstream of the patient. The amount of drug release (M) at a given time at sink conditions (i.e. drug concentration at the matrix surface is much greater than drug concentration in the bulk solution) depends on the area (A) of the matrix, the diffusion coefficient (D), the porosity (E) and tortuosity (T) of the matrix, the drug solubility (Cs) in the dissolution medium, time (t) and the drug concentration (Cp) in the dosage form according to the following equation:

$$M = A(DE/T(2Cp - ECs)(Cs)t)^{1/2}$$

[0017] It will be noted in the above relationship that the amount of drug released is generally proportional to the square root of time. Assuming factors such as matrix porosity and tortuosity are constant within the dosage form, a plot of amount of drug released versus the square root of time should be linear.

[0018] A commonly used erosion-controlled release system comprises a "matrix" throughout which the drug is distributed. The matrix typically comprises a material which swells at the surface, and slowly dissolves away layer by layer, liberating drug as it dissolves. The rate of drug release (dM/dt) in these systems depends on the rate of erosion (dx/dt) of the matrix, the concentration profile in the matrix, and the surface area (A) of the system according to the following equation:

$$dM/dt = A \{dx/dt\} \{f(C)\}$$

[0019] Again, variation in one or more terms, such as surface area, typically lead to a non-constant release rate of drug. In general, the rate of drug release from erosion-controlled release systems typically follows first order kinetics.

[0020] Another type of erosion controlled delivery system employs materials which swell and dissolve slowly by surface erosion to provide a delayed release of pharmaceutical active ingredient. Delayed release is useful, for example in pulsatile or repeat action delivery systems, in which an immediate release dose is delivered, followed by a pre-determined lag time before a subsequent dose is delivered from the system. In these systems, the lag time (T_1) depends on the thickness (h) of the erodible layer, and the rate of erosion (dx/dt) of the matrix, which in turn depends on the swelling rate and solubility of the matrix components according to the following equation:

$$T_1 = h(dx/dt)$$

[0021] The cumulative amount of drug (M) released from these systems at a given time generally follows the equation:

$$M = (dM/dt)(t - T_1)$$

[0022] where dM/dt is generally described by either the diffusion-controlled or erosion-controlled equations above, and T_1 is the lag time.

[0023] It is often practical to design dosage forms which use a combination of the above mechanisms to achieve a particularly desirable release profile for a particular active ingredient. It will be readily recognized by those skilled in the art that a dosage form construct which offers multiple compartments, such as for example multiple core portions and/or multiple shell portions, is particularly advantageous for its flexibility in providing a number of different mechanisms for controlling the release of one or more active ingredients.

[0024] In various embodiments of this invention, the modified release dosage forms of this invention act as osmotically controlled drug delivery systems. As discussed, for example, in Verma et al., "Osmotically Controlled Oral Drug Delivery," *Drug Development and Industrial Pharmacy*, 26(7), pp. 695-708 (2000), osmotically controlled drug delivery systems offer a number of advantages over conventional controlled release delivery systems. The basic principle of operation of osmotic drug delivery systems employs the difference in osmotic pressure between the exterior and interior of a dosage form which contains active ingredient. For example, as discussed by Verna et al., in an elementary osmotic pump (EOP) system, an active ingredient, together with a suitable osmotic solute is contained within a core such as a compressed tablet, which is coated at least in part with a semipermeable membrane or shell having a small orifice therein. When this dosage form contacts a liquid medium such as the aqueous environment of the GI tract, the active ingredient draws liquid through the semipermeable membrane due to the osmotic pressure gradient and forms a saturated solution of active ingredient within the dosage form. Hydrostatic pressure thus develops within the dosage form, and is relieved by the flow of saturated solution through the orifice and out of the dosage form, thereby delivering the active ingredient to the patient until the pressures inside and outside the dosage form are equal. Such a system is exemplified in U.S. Pat. No. 3,845,770, which discloses (see FIG. 1 of U.S. Pat. No. 3,845,770) a device having a semipermeable wall which surrounds a compartment containing active ingredient. A passageway communicates with the compartment and the exterior of the device. Fluid permeates the wall into the compartment and produces a solution of active ingredient which is released through the passageway.

[0025] Various improvements have also been made in the design of osmotic drug delivery systems. For example, U.S. Pat. No. 3,995,631 discloses a system in which a semipermeable membrane houses a solution of an osmotically effective solute and a flexible bag of relatively impervious material which contains active ingredient. The flexible bag is provided with dispensing means for dispensing active ingredient out of the flexible bag when liquid permeates the membrane and exerts mechanical compressing or deflating force on the bag.

[0026] U.S. Pat. No. 4,111,202 discloses a dosage form having a semipermeable wall which surrounds an active ingredient compartment and an osmagent compartment. The two compartments are separated by a moveable film which is impermeable to the active ingredient and osmagent. The semipermeable wall has a passageway therethrough for delivering active ingredient from its compartment. The system operates by having fluid imbibe through the wall into the osmagent compartment and causing the osmagent compartment to expand in volume and move the film, thereby diminishing the volume of the active ingredient compartment and delivering the active ingredient through the passageway.

[0027] U.S. Pat. No. 4,327,725 discloses a system having a semipermeable outer wall which contains an active agent compartment and a fluid swellable hydrogel compartment. The semipermeable wall has a passageway therethrough for delivering active ingredient in solution from its compartment when the hydrogel absorbs fluid passing through the outer wall and the hydrogel swells. A precipitate forms at the interface of the hydrogel and active ingredient to restrict the passage of active ingredient into the hydrogel, and to act as an in situ formed membrane to apply pressure against the active ingredient in solution.

[0028] U.S. Pat. No. 4,449,983 discloses a system in which a semipermeable wall contains first and second compartments which each contain a different active ingredient. Each of the compartments has an orifice which permits delivery of the active ingredient from each compartment, and the two compartments are separated by a hydrogel partition. The hydrogel absorbs fluid and swells, causing delivery of a solution of active ingredient through the respective compartment orifices.

[0029] U.S. Pat. No. 4,627,971 discloses a device in which a semipermeable wall which surrounds a compartment containing a first layer containing an active ingredient and a second layer containing a hydrogel and means for sealing or closing a passageway by forming a film under the influence of thermo laser energy. A first passageway permits delivery of the active ingredient out of the compartment, and a second passageway formed during the manufacture of the device is adjacent to the hydrogel layer. Upon exposure of the means to thermo laser energy, a film is formed and the second passageway is sealed. The hydrogel absorbs fluid and swells, causing delivery of a solution of active ingredient through the first passageway.

[0030] U.S. Pat. No. 5,830,501 discloses a dosage form having a semipermeable wall which surrounds an internal compartment. The semipermeable wall contains at least one exit means such as a passageway, and the internal compartment contains an active ingredient, a flocculating hydrophilic polymer, a dehydrating agent, a surfactant, a swellable

hydrophilic polymer, a lubricant, and an osmagent. When the dosage form is in a biological environment of use, the flocculating polymer precipitates and forms a floc containing the active ingredient. When fluid permeates the semipermeable wall, the swellable polymer and osmagent act as a push member to deliver the floc through the exit means. The floc lessens the tackiness and/or irritation of the mucosal tissue of the patient.

[0031] U.S. Pat. No. 6,342,249 discloses a dosage form having a semipermeable wall with an exit orifice, in which the wall defines a cavity containing an active ingredient layer adjacent to the orifice and an expandable "push" layer remote from the orifice. The active ingredient layer contains a liquid active ingredient formulation absorbed in porous particles. A placebo layer to delay onset of delivery of the active ingredient may optionally be placed between the active ingredient layer and the exit orifice. When fluid permeates the semipermeable wall, the push layer expands to deliver the placebo (if employed) and particles containing active ingredient through the orifice.

[0032] European Patent Publication No. 0384642 discloses a device for releasing active ingredient in a pulsed manner. The device comprises a water permeable or impermeable capsule containing an active ingredient and a water swellable material, in which the capsule has an opening which is closed by a water permeable plug. When fluid permeates into the capsule, the water swellable material expands to eject the plug and deliver the active ingredient through the opening. If the flux of liquid through the plug is sufficient to achieve the desired pulsed release of active ingredient, the capsule may be made of a water impermeable material.

[0033] The modified release dosage forms of this invention employ a core and a shell, which may optionally comprise multiple portions having different compositions and/or functions. The dosage forms of this invention are prepared by a novel method which enables at least portion of the shell to be semipermeable. In contrast, current core-shell systems are limited by the available methods for manufacturing them, as well as the materials that are suitable for use with the current methods. A shell, or coating, which confers modified release properties is typically applied via conventional methods, such as for example, spray-coating in a coating pan. Pan-coating produces a single shell which essentially surrounds the core. The single shell is inherently limited in its functionality. It is possible via pan-coating to apply multiple concentric shells, each with a different functionality, however such systems are limited in that the outer shell must first dissolve before the functionality conferred by each successive layer can be realized. It is also known, via pan coating, to deliver a first dose of active ingredient from a coating, and a second dose of active ingredient from a core. Dosage forms having sprayed coatings which provide delayed release are described, for example, in Maffione et al., "High-Viscosity HPMC as a Film-Coating Agent," *Drug Development and Industrial Pharmacy* (1993) 19(16), pp. 2043-2053. U.S. Pat. No. 4,576,604, for example, discloses an osmotic device (dosage form) comprising a drug compartment surrounded by a wall (coating) in which the coating may comprise an immediate release dose of drug, and the inner drug compartment may comprise a sustained release dose of drug. The coating compositions that can be applied via spraying are limited by their viscosity. High

viscosity solutions are difficult or impractical to pump and deliver through a spray nozzle. Spray coating methods suffer the further limitations of being time-intensive and costly. Several hours of spraying may be required to spray an effective amount of coating to control the release of an active ingredient. Coating times of 8 to 24 hours are not uncommon.

[0034] It is one object of this invention to provide a modified release dosage form in which at least one active ingredient contained therein exhibits a modified release profile upon contacting of the dosage form with a liquid medium. It is one feature of the dosage form of this invention that it has a semipermeable shell or shell portion. It is another feature of this invention that the semipermeable shell or shell portion allows the liquid medium to diffuse through the shell or shell portion to the core, for example due to osmosis and permeate into the core. It is another feature of this invention that the shell provides for delivery of liquid medium carrying active ingredient out of the dosage form. Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description set forth below.

SUMMARY OF THE INVENTION

[0035] The invention provides a dosage form comprising (a) at least one active ingredient; (b) a core having an outer surface having an outer surface; and (c) a shell which resides upon at least a portion of the core outer surface, wherein at least a portion of the shell is semipermeable, at least about 30% of the cross-sectional area of the semipermeable shell portion is non-striated, and the shell comprises means for providing the active ingredient to a liquid medium outside the shell after contacting of the dosage form with the liquid medium.

[0036] The invention also provides a dosage form comprising (a) at least one active ingredient; (b) a core having an outer surface; and (c) a shell which resides upon at least a portion of the core outer surface, wherein the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and the shell comprises means for providing the active ingredient to a liquid medium outside the shell after contacting of the dosage form with the liquid medium.

[0037] The invention further provides a dosage form comprising: (a) at least one active ingredient; (b) a core having an outer surface, a first core portion, a second core portion, and a third core portion located between the first and second core portions, wherein the third core portion comprises an osmopolymer; (c) and a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and at least one of the first or second shell portions has at least one passageway therein extending to the core outer surface.

[0038] The invention also provides a dosage form comprising (a) at least one active ingredient; (b) a core having an

outer surface; (c) and a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and the shell and core have a continuous cavity therein defining an interior surface, wherein neither the first shell portion nor the second shell portion extend substantially upon the interior surface.

[0039] The invention further provides a dosage form comprising: (a) at least one active ingredient; (b) a core having an outer surface, a first core portion, a second core portion, and a third core portion located between the first and second core portions, wherein the third core portion comprises an osmopolymer; and (c) a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and the shell and core have a continuous cavity therein defining an interior surface, wherein neither the first shell portion nor the second shell portion extend substantially upon the interior surface.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1A depicts a cross-sectional side view of one embodiment of the dosage form of this invention.

[0041] FIG. 1B depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0042] FIG. 2 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0043] FIG. 3 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0044] FIG. 4 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0045] FIG. 5 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0046] FIG. 6 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0047] FIGS. 7A and 7B depict cross-sectional micrographs of a prior art coated composition.

[0048] FIGS. 8A and 8B depict cross-sectional micrographs of an embodiment of this invention.

[0049] FIG. 9 depicts the release profile of active ingredient for the dosage form of this invention described in Example 1 herein.

DETAILED DESCRIPTION OF THE INVENTION

[0050] As used herein, the term "dosage form" applies to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (dose) of a certain ingredient, for example an active ingredient as defined below. Suitable dosage forms include pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, topi-

cal or mucosal delivery, or subcutaneous implants, or other implanted drug delivery systems; or compositions for delivering minerals, vitamins and other nutraceuticals, oral care agents, flavorants, and the like. Preferably the dosage forms of the present invention are considered to be solid, however they may contain liquid or semi-solid components. In a particularly preferred embodiment, the dosage form is an orally administered system for delivering a pharmaceutical active ingredient to the GI tract of a human.

[0051] The dosage forms of this invention exhibit modified release of one or more active ingredients contained therein. The active ingredient or ingredients may be found within the core, the shell, or a portion or combination thereof. As used herein, the term "modified release" shall apply to dosage forms, coatings, shells, cores, portions thereof, or compositions that alter the release of an active ingredient in any manner. The active ingredient or ingredients that are released in a modified manner may be contained within the coating, shell, core, composition, or portion thereof providing the modification. Alternatively the modified release active ingredient may be contained in a different portion of the dosage form from the coating, shell, core, composition, or portion thereof providing the modification; for example the modified release active ingredient may be contained in a core portion, and the modification may be provided by the overlaying shell portion. Types of modified release include controlled, prolonged, sustained, extended, delayed, pulsatile, repeat action, and the like. Suitable mechanisms for achieving these types of modified release include diffusion, erosion, surface area control via geometry and/or impermeable barriers, or other mechanisms known in the art. Moreover, the modified release properties of the dosage form may be achieved through design of the core or a portion thereof, or the shell or portion thereof, or a combination of two or more of these parts of the dosage form.

[0052] The dissolution profile of each active ingredient from the dosage form may be governed by a sum of contributions from the properties of the various portions. Additionally, a single portion, for example a core portion may possess a combination of erosional and diffusional properties. In any case, the dissolution rate of a particular active ingredient from the dosage form will be the sum of the contributions from all the various mechanisms contributed by the various portions of the dosage form which effect the release of that particular active ingredient

[0053] The dosage forms of the present invention are designed to release substantially all (i.e. at least about 80%, or at least about 90%, say at least about 95%) of the active ingredient contained therein, within a specified amount of time. As used herein, the total amount of time required for substantially all of the active ingredient(s) to be released from the dosage form shall be referred to as the "dosing interval." During the dosing interval, the amount of drug released is typically measured at several time points.

[0054] As used herein, the term "time interval" shall refer to periods of time during the dosing interval, over which a periodic rate of release may be measured. The time interval may be the entire dosing interval, or a portion thereof.

[0055] As used herein, a drug "release rate" refers to the quantity of drug released from a dosage form per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug

release rates are calculated under in vitro dosage form dissolution testing conditions known in the art. As used herein, a drug release rate obtained at a specified time "following administration" refers to the in vitro drug release rate obtained at the specified time following implementation of an appropriate dissolution test.

[0056] As used herein, a "periodic release rate" refers to the quantity per unit time of drug released from a dosage form during a specified periodic interval as determined at the end of that specified periodic interval, i.e., at each periodic interval when a determination is made, the quantity per unit time of drug released represents the periodic release rate during that periodic interval. For example, the quantity of drug released per hour (h) determined as the difference in quantity released between $t=0$ and $t=2h$ divided by the time interval of 2 hours represents the periodic release rate during the first two hours following administration, the quantity of drug released per hour as determined from $t=2h$ to $t=4h$ represents the periodic release rate from two to four hours following administration, etc.

[0057] As used herein, a "constant release rate" is obtained over a given time interval when the periodic release rates determined during two or more portions of the time interval are substantially the same, i.e. not more than 6% different. As used herein, "non-constant release rate" shall mean two or more periodic release rates are not the same, i.e. more than 6% different, over the entire duration of the specified interval.

[0058] As used herein, an "ascending release rate" refers to a periodic release rate that is increased over the immediately preceding periodic release rate. For example, when the quantity of drug released from a dosage form is measured at hourly intervals and the quantity of drug released during the fifth hour following administration is greater than the quantity of drug released from the dosage form during the fourth hour following administration, an ascending release rate from the fourth hour to the fifth hour has occurred. It will be appreciated that the first periodic release rate measured, e.g., the periodic release rate at $t=1$ hour (unless equal to 0), will always be greater than the release rate during the preceding period, e.g., the hour before the dosage form was administered, and thus, the first periodic release rate always constitutes an occurrence of an ascending release rate.

[0059] As used herein, "ascending blood level" refers to the PK profile obtained when the rate of release of drug from the dosage form, and also its absorption into the bloodstream, exceeds its rate of elimination from the blood of a mammal for a period of time, producing an increasing blood level over the course of the dosing interval or a portion thereof.

[0060] As used herein, a "burst release" profile refers to a release profile which meets immediate release criteria during a specified interval. The specified interval may optionally follow a pre-determined lag time.

[0061] A first embodiment of this invention is depicted in FIG. 1A, which is a cross-sectional view of a dosage form 2 which comprises a core 4 and a shell 5. In other embodiments of this invention, shell 5 may reside upon a portion of core 4 without surrounding core 4. In this embodiment of the invention, shell 5 is semipermeable to a liquid medium, and

at least about 30% of the cross-sectional area of the semi-permeable shell **5** is non-striated as is discussed further herein. Core **4** contains at least one active ingredient, and shell **5** may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core **4**. In this embodiment of the invention, shell **5** contains passageway **12** which extends from the outer surface of shell **5** to the outer surface of core **4**, as shown. In other embodiments of this invention, a plurality of passageways may be employed. Accordingly, upon contacting of dosage form **2** with a liquid medium, the liquid medium permeates shell **5**, reaches core **4** (where active ingredient, and optionally osmagent or osmopolymer, are contained), and liquid medium containing active ingredient is osmotically "pumped" through passageway **12** and out of dosage form **2** into the surrounding liquid medium.

[0062] Another embodiment of this invention is depicted in FIG. 11B, which is a cross-sectional view of a dosage form **22** which comprises a core **24**, a first shell portion **25** and a second shell portion **26**, which in this embodiment surround core **24**. In other embodiments of this invention, first shell portion **25** or second shell portion **26** may reside upon a portion of core **24** without surrounding core **24**. First shell portion **25** is semipermeable to a liquid medium and second shell portion **26** is compositionally different than first shell portion **25**. In the embodiment depicted in FIG. 1B, second shell portion **26** is diffusible. Core **24** contains at least one active ingredient, and first shell portion **25** and/or second shell portion **26** may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core **24**. Accordingly, upon contacting of dosage form **22** with a liquid medium, the liquid medium permeates first shell portion **25**, reaches core **24** (where active ingredient is contained), and liquid medium containing active ingredient is osmotically "pumped" through diffusible second shell portion **26** and out of dosage form **22** into the surrounding liquid medium. In other embodiments, second shell portion **26** may be erodible, thereby permitting active ingredient to be released from the core **24** as second shell portion **26** erodes to expose core **24** to the liquid medium.

[0063] Another embodiment of this invention is depicted in FIG. 2, which is a cross-sectional side view of a dosage form **202** which comprises a core **204** and a shell **206** having a first shell portion **208** which is semipermeable to the liquid medium, and a second shell portion **210** which is compositionally different than first shell portion **208**. For example, second shell portion **210** may be diffusible, impermeable or erodible. Core **204** contains at least one active ingredient, and shell **206** may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core **204**. In this embodiment of the invention, first shell portion **208** contains passageway **212** which extends from the outer surface of first shell portion **208** to the outer surface of core **204**, as shown. In other embodiments of this invention, first shell portion **208** may contain a plurality of passageways. In this embodiment, first shell portion **208** is semipermeable, and second shell portion **210** is impermeable. Accordingly, upon contacting of dosage form **202** with a liquid medium, the liquid medium permeates first shell portion **208**, reaches core **204** (where active ingredient, and optionally osmagent or osmopolymer are contained), and liquid medium containing active ingredient is osmotically "pumped" through passageway **212** and

out of dosage form **202** into the surrounding liquid medium. In other embodiments of this invention (not shown in FIG. 2), second shell portion **210** may contain at least one passageway which extends from the outer surface of second shell portion **210** to the outer surface of core **204**, or both first shell portion **208** and second shell portion **210** may each contain at least one passageway which extends from the outer surface of first shell portion **208** and second shell portion **210**, respectively, to the outer surface of core **204**.

[0064] Another embodiment of this invention is depicted in FIG. 3, which is a cross-sectional side view of a dosage form **302** which comprises a core **304** having first core portion **303** and second core portion **305**, and shell **306** having a plurality of passageways **312** therein which extend from the outer surface of shell **306** to the outer surfaces of first and second core portions **303** and **305**. In other embodiments of this invention, shell **306** may have a single passageway. Core **304** contains at least one active ingredient, and shell **306** may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core **304**. At least a portion of shell **306** is semipermeable to a liquid medium, and at least about 30% of the cross-sectional area of the semipermeable portion of the shell is non-striated. Upon contacting of dosage form **302** with a liquid medium, the liquid medium permeates shell **306**, reaches first and second core portions **303** and **305**, respectively, (where active ingredient or ingredients, and optionally osmagent or osmopolymer are contained), and liquid medium containing active ingredient or ingredients is osmotically "pumped" through passageways **312** and out of dosage form **302** into the surrounding liquid medium. In one embodiment, first core portion **303** contains a first active ingredient and second core portion **305** contains a second active ingredient which may be the same or different than the first active ingredient. In another preferred embodiment, first and second core portions **303** and **305** each contain a different dose or concentration of first and second active ingredients, which may be the same or different active ingredients. In another embodiment, passageways **312** in shell **306** may expose different surface areas of the underlying core portions **303** and **305**, respectively, thereby permitting either different release rates for the first and second active ingredients, or the same release rate for the first and second active ingredients, if the first and second active ingredients have different solubilities.

[0065] Another embodiment of this invention is depicted in FIG. 4, which is a cross-sectional side view of a dosage form **402** which comprises a core **404** having first core portion **403**, second core portion **405**, and third core portion **407**, and shell **406** comprising first and second shell portions **408** and **410**, respectively. A plurality of passageways **412** extend from the outer surface of shell **406** to the outer surfaces of first and second core portions **403** and **405**. In other embodiments of this invention, shell **406** may have a single passageway located in either first shell portion **408** or second shell portion **410**. In this embodiment, first shell portion **408** and second shell portion **410** are each semipermeable to a liquid medium. Second shell portion **410** may be compositionally different than first shell portion **408**. For example, in other embodiments first shell portion **408** may be semipermeable, and second shell portion **410** may be diffusible, impermeable or erodible. Core **404** contains at least one active ingredient, and shell **406** may optionally contain at least one active ingredient which may be the same

or different than the active ingredient contained within core 404. In the embodiment depicted in FIG. 4, first core portion 403 contains a first active ingredient, second core portion 405 contains a second active ingredient which may be the same or different than the first active ingredient, and third core portion 407 contains an osmopolymer which provides osmotic pressure upon contact with the liquid medium to push the active ingredients through the passageways 412 to the surface of shell 406. In the embodiment depicted in FIG. 4, upon contacting of dosage form 402 with a liquid medium, the liquid medium permeates the first and second shell portions 408 and 410, reaches first and second core portions 403 and 405, respectively (where active ingredient or ingredients are contained), as well as third core portion 407 containing the osmopolymer (which swells and compresses against first and second core portions 403 and 405), and liquid medium containing active ingredient is osmotically "pumped" through passageways 412 and out of dosage form 402 into the surrounding liquid medium. In addition, passageways 412 in first and second shell portions 408 and 410 may expose different surface areas of the underlying core portions 403 and 405, respectively, thereby permitting either different release rates for the first and second active ingredients, or the same release rate for the first and second active ingredients, if the first and second active ingredients have different solubilities.

[0066] Another embodiment of this invention is depicted in FIG. 5, which is a cross-sectional side view of a dosage form 502 which comprises a core 504 and a shell 506 having a first shell portion 508 which is semipermeable to the liquid medium, and a second shell portion 510 which is compositionally different than first shell portion 508. For example, second shell portion 510 may be semipermeable, diffusible, impermeable or erodible, although in this embodiment second shell portion 510 is semipermeable. Core 504 contains at least one active ingredient, and shell 506 may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core 504. As depicted in FIG. 5, cavity 501 extends through core 504, first shell portion 508 and second shell portion 510. The interior surface 513 of core 504 is defined by cavity 501, and neither first shell portion 508 nor second shell portion 510 substantially extend upon interior surface 513, thereby permitting active ingredient contained within core 504 to be released only through interior surface 513. The diameter of the continuous cavity is preferably in the range of about 15 to about 90 percent of the thickness of the dosage form, and the diameter of the continuous cavity is preferably in the range of about 5 to about 30 percent of the core diameter. The length of the continuous cavity is typically about the same as the thickness of the dosage form, and the length of the continuous cavity is preferably about 25 to about 40 percent of the diameter of the dosage form. Upon contacting of dosage form 502 with a liquid medium, the liquid medium permeates interior surface 513, as well as first and second shell portions 508 and 510, reaches core 504 (where active ingredient is contained), and liquid medium containing active ingredient passes through interior surface 513 into central cavity 501 and out of dosage form 502 into the surrounding liquid medium. In this embodiment, the predominant mechanism for drug release is erosion.

[0067] Another embodiment of this invention is depicted in FIG. 6, which is a cross-sectional side view of a dosage form 602 which comprises a core 604 having first core

portion 603, second core portion 605, and third core portion 607, and a shell 606 having a first shell portion 608 which is semipermeable to the liquid medium, and a second shell portion 610 which is compositionally different than first shell portion 608. For example, second shell portion 610 may be semipermeable, diffusible, impermeable or erodible, although in this embodiment second shell portion 610 is semipermeable. Core 604 contains at least one active ingredient, and shell 606 may optionally contain at least one active ingredient which may be the same or different than the active ingredient contained within core 604. As depicted in FIG. 6, cavity 601 extends through core 604, first shell portion 608 and second shell portion 610. The interior surface 613 of core 604 is defined by cavity 601, and neither first shell portion 608 nor second shell portion 610 substantially extend upon interior surface 613, thereby permitting active ingredient contained within core 604 to be released only through interior surface 613. In one embodiment, first core portion 603 contains a first active ingredient, second core portion 605 contains a second active ingredient which may be the same or different than the first active ingredient, and third core portion 607 contains an osmopolymer which provides osmotic pressure upon contact with the liquid medium to push the active ingredients through the interior surface 613 and into the liquid medium. The diameter of the continuous cavity is preferably in the range of about 15 to about 90 percent of the thickness of the dosage form, and the diameter of the continuous cavity is preferably in the range of about 5 to about 30 percent of the core diameter. The length of the continuous cavity is typically about the same as the thickness of the dosage form, and the length of the continuous cavity is preferably about 25 to about 40 percent of the diameter of the dosage form. Upon contacting of dosage form 602 with the liquid medium, the liquid medium permeates interior surface 613, as well as the first and second shell portions 608 and 610, respectively, reaches first core portion and second core portions 603 and 605, respectively, (where active ingredient or ingredients are contained) as well as third core portion 607 containing the osmopolymer (which swells and compresses against first core portion 603 and second core portion 605), and liquid medium containing the active ingredient or ingredients passes through interior surface 613 into central cavity 601 and out of dosage form 602 into the surrounding liquid medium. In this embodiment, the predominant mechanism for drug release is erosion.

[0068] In embodiments of this invention in which the shell comprises at least two shell portions, the inner surface of each shell portion must be substantially in contact with the outer surface of the core, as depicted, for example, in FIGS. 1B, 2, 4, 5 and 6. Accordingly, in such embodiments, the inner surface of any shell portion does not reside upon the outer surface of any other shell portion.

[0069] Suitable active ingredients for use in this invention include for example pharmaceuticals, minerals, vitamins and other nutraceuticals, oral care agents, flavorants and mixtures thereof. Suitable pharmaceuticals include analgesics, anti-inflammatory agents, antiarthritics, anesthetics, antihistamines, antitussives, antibiotics, anti-infective agents, antivirals, anticoagulants, antidepressants, antidiabetic agents, antiemetics, antifatulents, antifungals, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, oral contracep-

tives, diuretics, expectorants, gastrointestinal agents, migraine preparations, motion sickness products, mucolytics, muscle relaxants, osteoporosis preparations, polydimethylsiloxanes, respiratory agents, sleep-aids, urinary tract agents and mixtures thereof.

[0070] Suitable oral care agents include breath fresheners, tooth whiteners, antimicrobial agents, tooth mineralizers, tooth decay inhibitors, topical anesthetics, mucoprotectants, and the like.

[0071] Suitable flavorants include menthol, peppermint, mint flavors, fruit flavors, chocolate, vanilla, bubblegum flavors, coffee flavors, liqueur flavors and combinations and the like.

[0072] Examples of suitable gastrointestinal agents include antacids such as calcium carbonate, magnesium hydroxide, magnesium oxide, magnesium carbonate, aluminum hydroxide, sodium bicarbonate, dihydroxyaluminum sodium carbonate; stimulant laxatives, such as bisacodyl, cascara sagrada, danthron, senna, phenolphthalein, aloe, castor oil, ricinoleic acid, and dehydrocholic acid, and mixtures thereof; H₂ receptor antagonists, such as famotadine, ranitidine, cimetidine, nizatidine; proton pump inhibitors such as omeprazole or lansoprazole; gastrointestinal cytoprotectives, such as sucralfate and misoprostol; gastrointestinal prokinetics, such as prucalopride, antibiotics for *H. pylori*, such as clarithromycin, amoxicillin, tetracycline, and metronidazole; antidiarrheals, such as diphenoxylate and loperamide; glycopyrrolate; antiemetics, such as ondansetron, analgesics, such as mesalamine.

[0073] In one embodiment of the invention, the active ingredient may be selected from bisacodyl, famotadine, ranitidine, cimetidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, antacids, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0074] In another embodiment, the active ingredient is selected from analgesics, anti-inflammatories, and antipyretics, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), including propionic acid derivatives, e.g. ibuprofen, naproxen, ketoprofen and the like; acetic acid derivatives, e.g. indomethacin, diclofenac, sulindac, tolmetin, and the like; fenamic acid derivatives, e.g. mefenamic acid, meclofenamic acid, flufenamic acid, and the like; biphenyl-carboxylic acid derivatives, e.g. diflunisal, flufenisal, and the like; and oxicams, e.g. piroxicam, sudoxicam, isoxicam, meloxicam, and the like. In one particular embodiment, the active ingredient is selected from propionic acid derivative NSAID, e.g. ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, indoprofen, ketoprofen, fluprofen, pirofen, carprofen, oxaprozin, pranoprofen, suprofen, and pharmaceutically acceptable salts, derivatives, and combinations thereof. In another particular embodiment of the invention, the active ingredient may be selected from acetaminophen, acetyl salicylic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, diclofenac, cyclobenzaprine, meloxicam, rofecoxib, celecoxib, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0075] In another embodiment of the invention, the active ingredient may be selected from pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan, diphenhydramine, astemizole, terfenadine, fexofenadine,

loratadine, desloratadine, cetirizine, mixtures thereof and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0076] Examples of suitable polydimethylsiloxanes, which include, but are not limited to dimethicone and simethicone, are those disclosed in U.S. Pat. Nos. 4,906,478, 5,275,822, and 6,103,260, the contents of each is expressly incorporated herein by reference. As used herein, the term "simethicone" refers to the broader class of polydimethylsiloxanes, including but not limited to simethicone and dimethicone.

[0077] The active ingredient is present in the dosage form in a therapeutically effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular active ingredient being administered, the bioavailability characteristics of the active ingredient, the dosing regimen, the age and weight of the patient, and other factors must be considered, as known in the art. Typically, the dosage form comprises about 2 to about 75 weight percent, for example, the dosage form may comprise about 5 to about 50 weight percent, say about 7 to about 25 weight percent of a combination of one or more active ingredients. In one embodiment, the core comprises a total of at least about 25 weight percent, e.g. about 25 to about 75 weight percent (based on the weight of the core) of one or more active ingredients.

[0078] The active ingredient may be present in the dosage form in any form. For example, the active ingredient may be dispersed at the molecular level, e.g. melted or dissolved, within the dosage form, or may be in the form of particles, which in turn may be coated or uncoated. If the active ingredient is in form of particles, the particles (whether coated or uncoated) typically have an average particle size of about 1-2000 microns. In one embodiment, such particles are crystals having an average particle size of about 1-300 microns. In another embodiment, the particles are granules or pellets having an average particle size of about 50-2000 microns, preferably about 50-1000 microns, most preferably about 100-800 microns.

[0079] In embodiments where an active ingredient is contained within the core, at least a portion of the active ingredient may be optionally coated with a release-modifying coating, as known in the art. This advantageously provides an additional tool for modifying the release profile of active ingredient from the dosage form. For example, the core may contain coated particles of one or more active ingredients, in which the particle coating confers a release modifying function, as is well known in the art. Examples of suitable release modifying coatings for particles are described in U.S. Pat. Nos. 4,173,626; 4,863,742; 4,980,170; 4,984,240; 5,286,497; 5,912,013; 6,270,805; and 6,322,819. Commercially available modified release coated active particles may also be employed. Accordingly, all or a portion of one or more active ingredients in the core may be coated with a release-modifying material.

[0080] In embodiments in which it is desired for the active ingredient to be absorbed into the systemic circulation of an animal, the active ingredient or ingredients are preferably capable of dissolution upon contact with a fluid such as water, gastric fluid, intestinal fluid or the like. In one

embodiment, the dissolution characteristics of one or more active ingredients are modified: e.g. controlled, sustained, extended, retarded, prolonged, delayed and the like. In one embodiment in which one or more active ingredients are released in a modified manner, the modified release active ingredient or ingredients are contained in the core. In one particular such embodiment, the dosage form releases one or more active ingredients contained in the core at a substantially constant rate over a specified time interval.

[0081] In one embodiment, the dissolution characteristics of at least one active ingredient meets USP specifications for immediate release tablets containing the active ingredient. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19-20 and 856 (1999). In embodiments in which at least one active ingredient is released immediately, the immediately released active ingredient is preferably contained in the shell or on the surface of the shell, e.g. in a further coating surrounding at least a portion of the shell.

[0082] In certain embodiments, the core or core portions function as an eroding matrix from which dispersed active ingredient is liberated by the dissolution of successive layers of the matrix surface. In these embodiments, the rate of active ingredient release from the core or core portion will depend on the dissolution rate of the matrix material. Particularly useful eroding matrix materials for providing surface erosion include those which first absorb liquid, then swell and/or gel prior to dissolving. In certain such embodiments, the eroding matrix core or core portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, insoluble edible materials, and combinations thereof.

[0083] In certain other embodiments, the core or core portions function as a diffusional matrix. In these embodiments, the core portion preferably comprises active ingredient, distributed throughout an insoluble porous matrix, which contains pores or channels through which fluids can enter the core or core portion, and the active ingredient must diffuse to be released from the dosage form. In these embodiments, the rate of active ingredient release from the core or core portion will depend upon the area (A) of the matrix, the diffusion coefficient (D), the porosity (E) and tortuosity (T) of the matrix, the drug solubility (Cs) in the dissolution medium, and the drug concentration (Cp) in the dosage form. In embodiments in which a core or core portion functions as a diffusional matrix, the release of the active ingredient from the core or core portion may be described as controlled, prolonged, sustained, or extended. In these embodiments, the contribution to active ingredient dissolution from the subject core portion may follow zero-order, first-order, or preferably square-root of time kinetics. In certain such embodiments, the diffusional matrix core or core portion preferably comprises a pore former.

[0084] In embodiments in which the core or core portion functions to modify release of an active ingredient contained

therein, the release of active ingredient may be further modified by the function of the surrounding shell or shell portion, as described above. In such embodiments, the release of the active ingredient from the dosage form will be governed by the sum of all the contributions acting upon it, e.g. from the relevant core or core portion and shell or shell portions, and may be described as controlled, prolonged, sustained, extended, delayed, or pulsatile. In these embodiments, the dissolution of active ingredient from the dosage form may follow zero-order, first-order, or square-root of time kinetics.

[0085] In embodiments in which the core comprises multiple portions, the portions may comprise different materials, or be prepared by different methods, or both. In one particular embodiment a first core portion may be prepared by compression, and a second core portion may be prepared by molding.

[0086] In certain embodiments, the core comprises multiple portions, which comprise different active ingredients or have different release-modifying properties, or both; and the shell comprises a corresponding number of multiple portions, which each cover a specific core portion in order to modify or further modify the release of one or more active ingredients contained within the respective core portion. For such embodiments, it is critical to have a manufacturing process which is capable of maintaining the orientation of the core prior to and during the application of the shell or each shell portion thereon. Advantageously, the orientation of the components of the dosage forms of the present invention can be precisely controlled, when manufactured using the thermal cycle or thermal setting apparatus and described below. In one such particularly preferred embodiment, the dosage form comprises a core comprising a first core portion and a second core portion which are compositionally different, wherein at least one of the first or second core portions comprises an active ingredient; and a shell which surrounds the core and comprises a first shell portion and a second shell portion which are compositionally different, wherein at least one of the first or second shell portions confers a modification to the release of an active ingredient contained in the underlying core portion.

[0087] The core or core portion of the present invention may be prepared by any suitable method, including for example compression and molding, and depending on the method by which it is made, typically comprises active ingredient and a variety of excipients (inactive ingredients which may be useful for conferring desired physical properties to the core).

[0088] In embodiments in which the core, or a portion thereof, is made by compression, suitable excipients include fillers, binders, disintegrants, lubricants, glidants, and the like, as known in the art. In embodiments in which the core is made by compression and additionally confers modified release of an active ingredient contained therein, the core preferably further comprises a release-modifying compressible excipient.

[0089] Suitable fillers for use in making the core, or a portion thereof, by compression include water-soluble compressible carbohydrates such as sugars, which include dextrose, sucrose, maltose, and lactose, sugar-alcohols, which include mannitol, sorbitol, maltitol, xylitol, starch hydrolysates, which include dextrans, and maltodextrins, and the

like, water soluble plastically deforming materials such as microcrystalline cellulose or other cellulosic derivatives, water-insoluble brittle fracture materials such as dicalcium phosphate, tricalcium phosphate and the like and mixtures thereof.

[0090] Suitable binders for making the core, or a portion thereof, by compression include dry binders such as polyvinyl pyrrolidone, hydroxypropylmethylcellulose, and the like; wet binders such as water-soluble polymers, including hydrocolloids such as acacia, alginates, agar, guar gum, locust bean, carrageenan, carboxymethylcellulose, tara, gum arabic, tragacanth, pectin, xanthan, gellan, gelatin, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, inulin, whelan, rhamnan, zooglan, methylan, chitin, cyclodextrin, chitosan, polyvinyl pyrrolidone, celluloses, sucrose, starches, and the like; and derivatives and mixtures thereof.

[0091] Suitable disintegrants for making the core, or a portion thereof, by compression, include sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and the like.

[0092] Suitable lubricants for making the core, or a portion thereof, by compression include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, glycerides and waxes.

[0093] Suitable glidants for making the core, or a portion thereof, by compression, include colloidal silicon dioxide, and the like.

[0094] Suitable release-modifying compressible excipients for making the core, or a portion thereof, by compression include swellable erodible hydrophilic materials, insoluble edible materials, pH-dependent polymers, and the like.

[0095] Suitable swellable erodible hydrophilic materials for use as release-modifying excipients for making the core, or a portion thereof, by compression include: water swellable cellulose derivatives, polyalkylene glycols, thermoplastic polyalkylene oxides, acrylic polymers, hydrocolloids, clays, gelling starches, and swelling cross-linked polymers, and derivatives, copolymers, and combinations thereof. Examples of suitable water swellable cellulose derivatives include sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxyphenylcellulose, hydroxyethylcellulose (HEC), hydroxypentylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose. Examples of suitable polyalkylene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkylene oxides include poly (ethylene oxide). Examples of suitable acrylic polymers include potassium methacrylate-divinylbenzene copolymer, polymethylmethacrylate, CARBOPOL (high-molecular weight cross-linked acrylic acid homopolymers and copolymers), and the like. Examples of suitable hydrocolloids include alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, gelatin, whelan, rhamnan,

zooglan, methylan, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples of suitable gelling starches include acid hydrolyzed starches, swelling starches such as sodium starch glycolate, and derivatives thereof. Examples of suitable swelling cross-linked polymers include cross-linked polyvinyl pyrrolidone, cross-linked agar, and cross-linked carboxymethylcellulose sodium.

[0096] Suitable insoluble edible materials for use as release-modifying excipients for making the core, or a portion thereof, by compression include water-insoluble polymers, and low-melting hydrophobic materials. Examples of suitable water-insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof. Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurylate, glyceryl myristate, GLYCOWAX-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, and phosphatidic acid. Examples of suitable waxes include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[0097] Suitable pH-dependent polymers for use as release-modifying excipients for making the core, or a portion thereof, by compression include enteric cellulose derivatives, for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[0098] Suitable pharmaceutically acceptable adjuvants for making the core, or a portion thereof, by compression include, preservatives; high intensity sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharin; flavorants; colorants; antioxidants; surfactants; wetting agents; and the like and mixtures thereof

[0099] In one embodiment, the core or a portion thereof comprises at least one osmagent, an osmotically effective

solute or osmotically effective compound that can be blended homogeneously or heterogeneously with the core constituents to form a push member, acting as osmotically effective solutes that are soluble in liquid medium imbibed into the core, and exhibit an osmotic pressure gradient across the semipermeable shell or shell portion against an exterior liquid medium. Osmagents useful in the present invention include compounds disclosed at col. 8, lines 18-35 of U.S. Pat. No. 5,830,501, which is incorporated herein by reference.

[0100] In another embodiment, the core or a portion thereof comprises at least one osmopolymer. The osmopolymer, if employed, exhibits fluid absorbing and or fluid imbibing properties. The osmopolymer comprises a hydrophilic polymer that can interact with water and aqueous biological fluids and then swell or expand to an equilibrium state. The osmopolymer exhibits the ability to retain a significant portion of the imbibed or absorbed fluid. Other osmopolymers include poly(hydroxyalkyl methacrylate) having a molecular weight of 20,000 to 5,000,000; poly(vinylpyrrolidone) having a molecular weight of about 10,000 to 360,000; poly(vinylalcohol) having a low acetate content and lightly cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 2,000 to 30,000; poly(ethylene oxide) having a molecular weight from 10,000 to 7,800,000; acidic carboxy polymers known as carboxypolymethylene or as carboxyvinyl polymers, a polymer consisting of acrylic acid lightly cross-linked with polyallylsucrose and sold under the trade name CARBOPOL, acidic carboxy polymer having a molecular weight of 200,000 to 6,000,000, including sodium acidic carboxyvinyl hydrogel and potassium acidic carboxyvinyl hydrogel; CYANAMER polyacrylamide; and the like. Representative polymers, used for the purpose of the present invention, are known to those skilled in the art and described, for example, in Scott & Roff, *Handbook of Common Polymers* (published by the Chemical Company Cleveland, Ohio); Ratner & Hoffman, ACS Symposium Series, No. 31, pp. 1 to 36, (1976) (published by the American Chemical Society); and Schacht, *Recent Advances in Drug Delivery Systems*, pp. 259 to 278 (published by Plenum Press, N.Y.).

[0101] In embodiments in which the core or core portion is prepared by compression, a dry blending (i.e. direct compression), or wet granulation process may be employed. In a dry blending (direct compression) method, the active ingredient or ingredients, together with the excipients, are blended in a suitable blender, then transferred directly to a compression machine for pressing into tablets. In a wet granulation method, the active ingredient or ingredients, appropriate excipients, and a solution or dispersion of a wet binder (e.g. an aqueous cooked starch paste, or solution of polyvinyl pyrrolidone) are mixed and granulated. Alternatively a dry binder may be included among the excipients, and the mixture may be granulated with water or other suitable solvent. Suitable equipment for wet granulation are known in the art, including low shear, e.g. planetary mixers; high shear mixers; and fluid beds, including rotary fluid beds. The resulting granulated material is dried, and optionally dry-blended with further ingredients, e.g. adjuvants and/or excipients such as for example lubricants, colorants, and the like. The final dry blend is then suitable for compression. Methods for direct compression and wet granulation processes are known in the art, and are described in

detail in, for example, Lachman, et al., *The Theory and Practice of Industrial Pharmacy*, Chapter 11 (3rd ed. 1986).

[0102] The dry-blended, or wet granulated, powder mixture is typically compacted into tablets using a rotary compression machine as known in the art, such as for example those commercially available from Fette America Inc. (Rockaway, N.J.), or Manesty Machines LTD (Liverpool, UK). In a rotary compression machine, a metered volume of powder is filled into a die cavity, which rotates as part of a "die table" from the filling position to a compaction position where the powder is compacted between an upper and a lower punch to an ejection position, where the resulting tablet is pushed from the die cavity by the lower punch and guided to an ejection chute by a stationary "take-off" bar.

[0103] In one particular optional embodiment, the core or core portion may be prepared by the compression methods and apparatus described in copending U.S. patent application Ser. No. 09/966,509, pages 16-27, the disclosure of which is incorporated herein by reference. Specifically, the core is made using a rotary compression module comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus having a double row die construction as shown in FIG. 6 of U.S. patent application Ser. No. 09/966,509. The dies of the compression module are preferably filled using the assistance of a vacuum, with filters located in or near each die. The purge zone of the compression module includes an optional powder recovery system to recover excess powder from the filters and return the powder to the dies.

[0104] In certain preferred embodiments of this invention, the core, or the shell, or a portion thereof, is prepared by molding. In particular, the core, the shell or a portion of either one may be made by solvent-based or solvent-free molding. In such embodiments, the core, or the shell, or a portion thereof, is made from a flowable material optionally comprising an active ingredient. The flowable material may be any edible material that is flowable at a temperature between about 37° C. and 250° C., and that is solid, semi-solid, or can form a gel at a temperature between about -10° C. and about 35° C. When it is in the fluid or flowable state, the flowable material may comprise a dispersed, dissolved, or molten component, and optionally a solvent such as for example water or organic solvents, or combinations thereof. The solvent may be partially or substantially removed by drying.

[0105] In one embodiment, solvent-based or solvent-free molding is performed via thermal setting molding using the method and apparatus described in copending U.S. patent application Ser. No. 09/966,450, pages 57-63, the disclosure of which is incorporated herein by reference. In this embodiment, a core, shell, or portion thereof is formed by injecting flowable form into a molding chamber. The flowable material preferably comprises a thermal setting material at a temperature above its melting point but below the decomposition temperature of any active ingredient contained therein. The flowable material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[0106] According to this method, the flowable material may comprise solid particles suspended in a molten matrix, for example a polymer matrix. The flowable material may be

completely molten or in the form of a paste. The flowable material may comprise an active ingredient dissolved in a molten material in the case of solvent-based molding. Alternatively, the flowable material may be made by dissolving a solid in a solvent, which solvent is then evaporated after the molding step in the case of solvent-based molding.

[0107] In another embodiment, solvent-based or solvent-free molding is performed by thermal cycle molding using the method and apparatus described in copending U.S. patent application Ser. No. 09/966,497, pages 27-51, the disclosure of which is incorporated herein by reference. Thermal cycle molding is performed by injecting a flowable material into a heated molding chamber. The flowable material may comprise active ingredient and a thermoplastic material at a temperature above the set temperature of the thermoplastic material but below the decomposition temperature of active ingredient. The flowable material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[0108] In the thermal cycle molding method and apparatus of U.S. patent application Ser. No. 09/966,497 a thermal cycle molding module having the general configuration shown in **FIG. 3** therein is employed. The thermal cycle molding module **200** comprises a rotor **202** around which a plurality of mold units **204** are disposed. The thermal cycle molding module includes a reservoir **206** (see **FIG. 4**) for holding flowable material to make the core. In addition, the thermal cycle molding module is provided with a temperature control system for rapidly heating and cooling the mold units. **FIGS. 55 and 56** depict the temperature control system **600**.

[0109] The mold units may comprise center mold assemblies **212**, upper mold assemblies **214**, and lower mold assemblies **210**, as shown in **FIGS. 26-28**, which mate to form mold cavities having a desired shape, for instance of a core or a shell surrounding a core. As rotor **202** rotates, opposing center and upper mold assemblies or opposing center and lower mold assemblies close. Flowable material, which is heated to a flowable state in reservoir **206**, is injected into the resulting mold cavities. The temperature of the flowable material is then decreased, hardening the flowable material. The mold assemblies open and eject the finished product.

[0110] In a particularly preferred embodiment of the invention, the shell is applied to the dosage form using a thermal cycle molding apparatus of the general type shown in **FIGS. 28A-C** of copending U.S. application Ser. No. 09/966,497 comprising rotatable center mold assemblies **212**, lower mold assemblies **210** and upper mold assemblies **214**. Cores are continuously fed to the mold assemblies. Shell flowable material, which is heated to a flowable state in reservoir **206**, is injected into the mold cavities created by the closed mold assemblies holding the cores. The temperature of the shell flowable material is then decreased, hardening it around the cores. The mold assemblies open and eject the finished dosage forms. Shell coating is performed in two steps, each half of the dosage forms being coated separately as shown in the flow diagram of **FIG. 28B** of copending U.S. application Ser. No. 09/966,939 via rotation of the center mold assembly.

[0111] A preferred method for making the shell or a shell portion by solvent-based molding comprises: (a) preparing a

flowable dispersion of the film former, release-modifying excipient, and other shell materials in a suitable solvent, e.g. water, organic solvents such as alcohols or acetone, or combinations of water and organic solvents, such as acetone; (b) injecting the flowable dispersion (which may be heated in a heated feed tank) into a mold cavity (at room temp or below) containing a core such that the flowable dispersion surrounds a first portion of the core within the mold cavity; (c) rapidly changing the temperature of the mold cavity to induce thermal setting of the flowable dispersion around at first portion of the core; (d) opening the mold cavity and rotating the portion of the mold containing the core to expose a second portion of the core; (e) closing the mold cavity; (f) injecting heated, flowable dispersion into the mold cavity such that the flowable dispersion surrounds the second portion of the core within the mold cavity; (g) rapidly changing the temperature of the mold cavity to induce thermal setting of the flowable dispersion surrounding the second portion of the core; (h) removing the coated core from the mold cavity; and (i) drying the coated core to remove residual solvent. The mold may be optionally heated to remove solvent, then cooled to set the shell materials. This is preferred if organic solvents are used, but is not required if the solvent used is water.

[0112] A preferred method for making the shell or a shell portion by solvent-free molding comprises: (a) melting a thermal reversible carrier, adding and mixing a release-modifying excipient and any other desired ingredients for the shell into the thermal reversible carrier to form a flowable shell material; (b) injecting the flowable shell material (which is heated in a heated feed tank) into a mold cavity (heated to allow the flowable shell material to flow) containing a core such that the flowable shell material surrounds a first portion of the core within the mold cavity; (c) rapidly lowering the temperature of the mold cavity to induce thermal setting of the flowable shell material surrounding the first portion of the core; (d) opening the mold cavity and rotating the portion of the mold containing the core to expose a second portion of the core; (e) closing the mold cavity; (f) injecting heated, flowable shell material into the mold cavity (also heated) such that the flowable shell material surrounds the second portion of the core within the mold cavity; (g) rapidly lowering the temperature of the mold cavity to induce thermal setting of the flowable shell material surrounding the second portion of the core; (h) removing the coated core from the mold cavity. The mold may be optionally rapidly heated or cooled to facilitate removal of dosage form.

[0113] In one embodiment, the compression module of copending U.S. patent application Ser. No. 09/966,509, pp. 16-27 may be employed to make cores. The shell may be made applied to these cores using a thermal cycle molding module as described above. A transfer device as described in U.S. patent application Ser. No. 09/966,414, pp. 51-57, the disclosure of which is incorporated herein by reference, may be used to transfer the cores from the compression module to the thermal cycle molding module. Such a transfer device may have the structure shown as **300** in **FIG. 3** of copending U.S. application Ser. No. 09/966,939. It comprises a plurality of transfer units **304** attached in cantilever fashion to a belt **312** as shown in **FIGS. 68 and 69** of copending U.S. application Ser. No. 09/966,939. The transfer device rotates and operates in sync with the compression module and the thermal cycle molding module to which it is coupled.

Transfer units **304** comprise retainers **330** for holding cores as they travel around the transfer device.

[0114] Suitable materials for use in or as the flowable material include those comprising thermoplastic materials; film formers; thickeners such as gelling polymers or hydrocolloids; low melting hydrophobic materials such as fats and waxes; non-crystallizable carbohydrates; and the like. Suitable molten components of the flowable material include thermoplastic materials, low melting hydrophobic materials, and the like. Suitable dissolved components for the flowable material include film formers, thickeners such as gelling polymers or hydrocolloids, non-crystallizable carbohydrates, and the like. Suitable dispersed components include insoluble edible materials.

[0115] Suitable thermoplastic materials can be molded and shaped when heated, and include both water soluble and water insoluble polymers that are generally linear, not crosslinked, nor strongly hydrogen bonded to adjacent polymer chains. Examples of suitable thermoplastic materials include: thermoplastic water swellable cellulose derivatives, thermoplastic water insoluble cellulose derivatives, thermoplastic vinyl polymers, thermoplastic starches, thermoplastic polyalkylene glycols, thermoplastic polyalkylene oxides, and amorphous sugar-glass, and the like, and derivatives, copolymers, and combinations thereof. Examples of suitable thermoplastic water swellable cellulose derivatives include hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC). Examples of suitable water insoluble cellulose derivatives include cellulose acetate (CA), ethyl cellulose (EC), cellulose acetate butyrate (CAB), cellulose propionate. Examples of suitable thermoplastic vinyl polymers include polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP). Examples of suitable thermoplastic starches are disclosed for example in U.S. Pat. No. 5,427,614. Examples of suitable thermoplastic polyalkylene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkylene oxides include polyethylene oxide having a molecular weight from about 100,000 to about 900,000 Daltons. Other suitable thermoplastic materials include sugar in the form of an amorphous glass such as that used to make hard candy forms.

[0116] Any film former known in the art is suitable for use in the flowable material of the present invention. Examples of suitable film formers include, but are not limited to, film-forming water soluble polymers, film-forming proteins, film-forming water insoluble polymers, and film-forming pH-dependent polymers. In one embodiment, the film-former for making the core or shell or portion thereof by molding may be selected from cellulose acetate, ammonio methacrylate copolymer type B, shellac, hydroxypropylmethylcellulose, and polyethylene oxide, and combinations thereof.

[0117] Suitable film-forming water soluble polymers include water soluble vinyl polymers such as polyvinylalcohol (PVA); water soluble polycarbohydrates such as hydroxypropyl starch, hydroxyethyl starch, pullulan, methylethyl starch, carboxymethyl starch, pre-gelatinized starches, and film-forming modified starches; water swellable cellulose derivatives such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), hydroxyethylmethylcellulose (HEMC), hydroxybutylmethylcellulose (HBMC), hydroxy-

ethylethylcellulose (HEEC), and hydroxyethylhydroxypropylmethyl cellulose (HEMPMC); water soluble copolymers such as methacrylic acid and methacrylate ester copolymers, polyvinyl alcohol and polyethylene glycol copolymers, polyethylene oxide and polyvinylpyrrolidone copolymers; and derivatives and combinations thereof.

[0118] Suitable film-forming proteins may be natural or chemically modified, and include gelatin, whey protein, myofibrillar proteins, coagulatable proteins such as albumin, casein, caseinates and casein isolates, soy protein and soy protein isolates, zein; and polymers, derivatives and mixtures thereof.

[0119] Suitable film-forming water insoluble polymers, include for example ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof.

[0120] Suitable film-forming pH-dependent polymers include enteric cellulose derivatives, such as for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins, such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename, EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename, EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[0121] One suitable hydroxypropylmethylcellulose compound for use as a thermoplastic film-forming water soluble polymer is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about 30% methoxyl groups and from about 7% to about 12% hydroxypropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename METHOCEL E. METHOCEL E5, which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20° C. in a 2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, METHOCEL E6 which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20° C. in a 2% aqueous solution as determined by a Ubbelohde viscometer. METHOCEL E15, which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20° C. in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to a anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

[0122] One suitable polyvinyl alcohol and polyethylene glycol copolymer is commercially available from BASF Corporation under the tradename KOLLICOAT IR.

[0123] As used herein, “modified starches” include starches that have been modified by crosslinking, chemically modified for improved stability or optimized performance, or physically modified for improved solubility properties or optimized performance. Examples of chemically-modified starches are well known in the art and typically include those starches that have been chemically treated to cause replacement of some of its hydroxyl groups with either ester or ether groups. Crosslinking, as used herein, may occur in modified starches when two hydroxyl groups on neighboring starch molecules are chemically linked. As used herein, “pre-gelatinized starches” or “instantized starches” refers to modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A. E. Staley Manufacturing Company, and National Starch & Chemical Company. One suitable film forming modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames PURITY GUM and FILMSET, and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100% to about 88% of amylopectin.

[0124] Another suitable film forming modified starch includes the hydroxypropylated starches, in which some of the hydroxyl groups of the starch have been etherified with hydroxypropyl groups, usually via treatment with propylene oxide. One example of a suitable hydroxypropyl starch that possesses film-forming properties is available from Grain Processing Company under the tradename, PURE-COTE B790.

[0125] Suitable tapioca dextrins for use as film formers include those available from National Starch & Chemical Company under the tradenames CRYSTAL GUM or K-4484, and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename PURITY GUM 40, and copolymers and mixtures thereof.

[0126] Any thickener known in the art is suitable for use in the flowable material of the present invention. Examples of such thickeners include but are not limited to hydrocolloids (also referred to herein as gelling polymers), clays, gelling starches, and crystallizable carbohydrates, and derivatives, copolymers and mixtures thereof.

[0127] Examples of suitable hydrocolloids (also referred to herein as gelling polymers) such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pushtulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples of suitable gelling starches include acid hydrolyzed starches, and derivatives and mixtures thereof. Additional suitable thickening hydrocolloids include low-moisture polymer solutions such as mixtures of gelatin and other hydrocolloids at water contents up to about 30%, such as for example those used to make “gummi” confection forms.

[0128] Additional suitable thickeners include crystallizable carbohydrates, and the like, and derivatives and combinations thereof. Suitable crystallizable carbohydrates include the monosaccharides and the oligosaccharides. Of the monosaccharides, the aldohexoses e.g., the D and L isomers of allose, altrose, glucose, mannose, gulose, idose, galactose, talose, and the ketohexoses e.g., the D and L isomers of fructose and sorbose along with their hydrogenated analogs: e.g., glucitol (sorbitol), and mannitol are preferred. Of the oligosaccharides, the 1,2-disaccharides sucrose and trehalose, the 1,4-disaccharides maltose, lactose, and cellobiose, and the 1,6-disaccharides gentiobiose and melibiose, as well as the trisaccharide raffinose are preferred along with the isomerized form of sucrose known as isomaltulose and its hydrogenated analog isomalt. Other hydrogenated forms of reducing disaccharides (such as maltose and lactose), for example, maltitol and lactitol are also preferred. Additionally, the hydrogenated forms of the aldopentoses: e.g., D and L ribose, arabinose, xylose, and lyxose and the hydrogenated forms of the aldotetroses: e.g., D and L erythrose and threose are preferred and are exemplified by xylitol and erythritol, respectively.

[0129] In one embodiment of the invention, the flowable material comprises gelatin as a gelling polymer. Gelatin is a natural, thermogelling polymer. It is a tasteless and colorless mixture of derived proteins of the albuminous class which is ordinarily soluble in warm water. Two types of gelatin—Type A and Type B—are commonly used. Type A gelatin is a derivative of acid-treated raw materials. Type B gelatin is a derivative of alkali-treated raw materials. The moisture content of gelatin, as well as its Bloom strength, composition and original gelatin processing conditions, determine its transition temperature between liquid and solid. Bloom is a standard measure of the strength of a gelatin gel, and is roughly correlated with molecular weight. Bloom is defined as the weight in grams required to move a half-inch diameter plastic plunger 4 mm into a 6.67% gelatin gel that has been held at 10° C. for 17 hours. In a preferred embodiment, the flowable material is an aqueous solution comprising 20% 275 Bloom pork skin gelatin, 20% 250 Bloom Bone Gelatin, and approximately 60% water.

[0130] Suitable xanthan gums include those available from C. P. Kelco Company under the tradenames KELTROL 1000, XANTROL 180, or K9B310

[0131] Suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof.

[0132] “Acid-hydrolyzed starch,” as used herein, is one type of modified starch that results from treating a starch suspension with dilute acid at a temperature below the gelatinization point of the starch. During the acid hydrolysis, the granular form of the starch is maintained in the starch suspension, and the hydrolysis reaction is ended by neutralization, filtration and drying once the desired degree of hydrolysis is reached. As a result, the average molecular size of the starch polymers is reduced. Acid-hydrolyzed starches (also known as “thin boiling starches”) tend to have a much lower hot viscosity than the same native starch as well as a strong tendency to gel when cooled.

[0133] “Gelling starches,” as used herein, include those starches that, when combined with water and heated to a

temperature sufficient to form a solution, thereafter form a gel upon cooling to a temperature below the gelation point of the starch. Examples of gelling starches include, but are not limited to, acid hydrolyzed starches such as that available from Grain Processing Corporation under the tradename PURE-SET B950; hydroxypropyl distarch phosphate such as that available from Grain Processing Corporation under the tradename, PURE-GEL B990, and mixtures thereof.

[0134] Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurate, glyceryl myristate, GLYCOWAX-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, and phosphatidic acid. Examples of suitable waxes include candelilla wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[0135] Suitable non-crystallizable carbohydrates include non-crystallizable sugars such as polydextrose, and starch hydrolysates, e.g. glucose syrup, corn syrup, and high fructose corn syrup; and non-crystallizable sugar-alcohols such as maltitol syrup.

[0136] Suitable solvents for optional use as components of the flowable material for making the core, or the shell, or a portion thereof by molding include water; polar organic solvents such as methanol, ethanol, isopropanol, acetone, and the like; and non-polar organic solvents such as methylene chloride, and the like; and mixtures thereof.

[0137] The flowable material for making the core or the shell or a portion thereof by molding may optionally comprise adjuvants or excipients, which may comprise up to about 30% by weight of the flowable material. Examples of suitable adjuvants or excipients include plasticizers, detackifiers, humectants, surfactants, anti-foaming agents, colorants, flavorants, sweeteners, opacifiers, and the like. Suitable plasticizers for making the core, the shell, or a portion thereof, by molding include, but not be limited to polyethylene glycol; propylene glycol; glycerin; sorbitol; triethyl citrate; tributyl citrate; dibutyl sebacate; vegetable oils such as castor oil, rape oil, olive oil, and sesame oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctylsodium sulfosuccinates; mono acetate of glycerol; diacetate of glycerol; triacetate of glycerol; natural gums; triacetin; acetyltributyl citrate; diethylxalate; diethylmalate; diethyl fumarate; diethylmalonate; dioctylphthalate; dibutylsuccinate; glyceroltributyrate; hydrogenated castor oil; fatty acids; substituted triglycerides and glycerides; and the like and/or mixtures thereof. In one embodiment, the plasticizer is triethyl citrate. In certain embodiments, the shell is substantially free of plasticizers, i.e. contains less than about 1%, say less than about 0.01% of plasticizers.

[0138] In one preferred embodiment, the flowable material comprises less than 5% humectants, or alternately is sub-

stantially free of humectants, such as glycerin, sorbitol, maltitol, xylitol, or propylene glycol. Humectants have traditionally been included in pre-formed films employed in enrobing processes, such as that disclosed in U.S. Pat. Nos. 5,146,730 and 5,459,983, assigned to Banner Gelatin Products Corp., to ensure adequate flexibility or plasticity and bondability of the film during processing. Humectants function by binding water and retaining it in the film. Pre-formed films used in enrobing processes can typically comprise up to 45% water. Disadvantageously, the presence of humectant prolongs the drying process, and can adversely affect the stability of the finished dosage form.

[0139] In certain embodiments in which the core, the shell, or portions thereof are prepared using solvent-free molding, the core, shell, or portions thereof may comprise active ingredient contained within an excipient matrix. The matrix, or the core, or the shell, or portions thereof typically comprises at least about 30 percent, e.g. at least about 45 weight percent of a thermal-reversible carrier, and optionally up to about 30 weight percent of various adjuvants such as for example plasticizers, gelling agents, strengthening agents, colorants, stabilizers, preservatives, and the like as known in the art. The matrix or the core, or the shell, or portions thereof may optionally further comprise up to about 55 weight percent of one or more release-modifying moldable excipients as described below. Solvent-free molding may be used to obtain semipermeable, impermeable, or diffusible shells or shell portions.

[0140] The core may be in a variety of different shapes. For example, the core may be shaped as a polyhedron, such as a cube, pyramid, prism, or the like; or may have the geometry of a space figure with some non-flat faces, such as a cone, truncated cone, cylinder, sphere, torus, or the like. In certain embodiments, the core has one or more major faces. For example in embodiments wherein the core is a compressed tablet, the core surface typically has two opposing major faces formed by contact with the upper and lower punch faces in the compression machine. In such embodiments the core surface typically further comprises a "belly-band" located between the two major faces, and formed by contact with the die walls in the compression machine. Exemplary core shapes which may be employed include tablet shapes formed from compression tooling shapes described by "The Elizabeth Companies Tablet Design Training Manual" (Elizabeth Carbide Die Co., Inc., p. 7 (McKeesport, Pa.) (incorporated herein by reference) as follows (the tablet shape corresponds inversely to the shape of the compression tooling):

- [0141]** 1. Shallow Concave.
- [0142]** 2. Standard Concave.
- [0143]** 3. Deep Concave.
- [0144]** 4. Extra Deep Concave.
- [0145]** 5. Modified Ball Concave.
- [0146]** 6. Standard Concave Bisect.
- [0147]** 7. Standard Concave Double Bisect.
- [0148]** 8. Standard Concave European Bisect.
- [0149]** 9. Standard Concave Partial Bisect.
- [0150]** 10. Double Radius.

- [0151] 11. Bevel & Concave.
- [0152] 12. Flat Plain.
- [0153] 13. Flat-Faced-Beveled Edge (F.F.B.E.).
- [0154] 14. F.F.B.E. Bisect.
- [0155] 15. F.F.B.E. Double Bisect.
- [0156] 16. Ring.
- [0157] 17. Dimple.
- [0158] 18. Ellipse.
- [0159] 19. Oval.
- [0160] 20. Capsule.
- [0161] 21. Rectangle.
- [0162] 22. Square.
- [0163] 23. Triangle.
- [0164] 24. Hexagon.
- [0165] 25. Pentagon.
- [0166] 26. Octagon.
- [0167] 27. Diamond.
- [0168] 28. Arrowhead.
- [0169] 29. Bullet.
- [0170] 30. Shallow Concave.
- [0171] 31. Standard Concave.
- [0172] 32. Deep Concave.
- [0173] 33. Extra Deep Concave.
- [0174] 34. Modified Ball Concave.
- [0175] 35. Standard Concave Bisect.
- [0176] 36. Standard Concave Double Bisect.
- [0177] 37. Standard Concave European Bisect.
- [0178] 38. Standard Concave Partial Bisect.
- [0179] 39. Double Radius.
- [0180] 40. Bevel & Concave.
- [0181] 41. Flat Plain.
- [0182] 42. Flat-Faced-Beveled Edge (F.F.B.E.).
- [0183] 43. F.F.B.E. Bisect.
- [0184] 44. F.F.B.E. Double Bisect.
- [0185] 45. Ring.
- [0186] 46. Dimple.
- [0187] 47. Ellipse.
- [0188] 48. Oval.
- [0189] 49. Capsule.
- [0190] 50. Rectangle.
- [0191] 51. Square.
- [0192] 52. Triangle.
- [0193] 53. Hexagon.

- [0194] 54. Pentagon.
- [0195] 55. Octagon.
- [0196] 56. Diamond.
- [0197] 57. Arrowhead.
- [0198] 58. Bullet.
- [0199] 59. Barrel.
- [0200] 60. Half Moon.
- [0201] 61. Shield.
- [0202] 62. Heart.
- [0203] 63. Almond.
- [0204] 64. House/Home Plate.
- [0205] 65. Parallelogram.
- [0206] 66. Trapezoid.
- [0207] 67. **FIG. 8**/Bar Bell.
- [0208] 68. Bow Tie.
- [0209] 69. Uneven Triangle.

[0210] In one embodiment of the invention, the core comprises multiple portions, for example a first portion and a second portion. The portions may be prepared by the same or different methods, such as the thermal cycle molding or thermal setting molding methods described herein, and mated using various techniques. For example, the first and second portions may both be made by compression, or both may be made by molding. Or one portion may be made by compression and the other by molding. The same or different active ingredient may be present in the first and second portions of the core. Alternately, one or more core portions may be substantially free of active ingredients.

[0211] In another embodiment of this invention, the core comprises first, second and third portions, each comprising the same or different active ingredient. In another embodiment, the core comprises first, second and third portions, and the third portion (located between the first and second portions) has a higher concentration of active ingredient, thereby causing a particularly desired release profile for at least one active ingredient from the dosage form. In this embodiment, release of at least one active ingredient from the dosage form may have a substantially constant release rate, substantially non-constant release rate, or an ascending release rate. In another embodiment the core comprises first, second, and third portions, and the third portion (located between the first and second portions) is substantially free of active ingredient, and may contain osmagent or osmopolymer, or may serve as a barrier to the passage of active ingredient between the first and second core portions.

[0212] In certain embodiments of the invention, the core or a portion thereof may function to confer modified release properties to at least one active ingredient contained therein. In such embodiments, wherein the core or core portion is made by compression, as previously noted, the core preferably comprises a release-modifying compressible excipient. In such embodiments, wherein the core or core portion is made by molding, as previously noted, the core preferably comprises a release-modifying moldable excipient. In embodiments in which one or more core portions function as

an eroding matrix from which dispersed active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic agents, pH-dependent polymers, and combinations thereof.

[0213] In embodiments in which one or more core portions function as a diffusional matrix through which active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore formers. Alternately, in such embodiments in which the core portion is prepared by molding, a thermal-reversible carrier may be included in the core portion and may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[0214] As described herein, at least a portion of the shell is semipermeable to a liquid medium. As used herein, the term "semipermeable" means permeable to the passage of water but not permeable to the passage of active ingredient therethrough. The semipermeable shell or shell portion allows water to be absorbed therethrough and into the core of the dosage form from the environment, such as the dissolution media or gastro-intestinal fluids. The semipermeable shell portion functions as a barrier to the passage of active ingredient from the underlying core portion, forcing the active ingredient to be released from the dosage form via a different avenue, such as an orifice or passageway, or through a diffusible shell portion. The semipermeable shell or shell portions are non-erodible, and they are insoluble in fluids.

[0215] In one embodiment of this invention, the semipermeable shell or shell portion is made using a flowable material. Suitable dissolved or molten components for the flowable material for forming the semi-permeable shell or shell portion may include thermoplastic film-formers selected from cellulose esters, cellulose ethers, and cellulose ester-ethers. These cellulosic polymers have a degree of substitution (D.S.) on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By "degree of substitution" as used herein it is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include those selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di-, and tricellulose alkanylates, nono-, di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32 to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3, such as cellulose trivalerate, cellulose trilaurate,

cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6, such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose, such as cellulose acetate butyrate and cellulose acetate propionate.

[0216] Additional polymers useful for manufacturing the semipermeable shell or shell portion include ethyl cellulose of various degree of etherification with ethoxy content of from about 40 to 55%, acetaldehyde demethylcellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 4,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked poly(sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm²/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to those skilled in the art, as set forth in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020.

[0217] In one embodiment, wherein the semipermeable shell or shell portion functions to slow or delay the rate of passage of a fluid, such as water or a biological fluid therethrough, the dissolved or molten components for the flowable material for forming the semi-permeable shell or shell portion comprise a polymer exhibiting a 8,500 to 4,000,000 molecular weight, and is present in the shell portion at a level from about 15 to about 85 weight percent of the shell portion. Polymeric materials, which may be used include non-ionic water-soluble polymers, cellulose ether nonionic with its solutions unaffected by cations, hydroxyalkylcellulose, hydroxyalkylalkylcellulose, hydroxypropylcellulose, phenylcellulose, benzylcellulose, nonionic cellulose ester with its solutions unaffected by cations, benzhydrylcellulose, hydroxyethyloctylcellulose, diphenylmethylcellulose, hydroxyethylcellulose, tritylcellulose and polymercompositions that delay water flux up to 7.0 hours, and more preferably, up to 4.5 hours.

[0218] In one embodiment, at least about 30% of the cross-sectional area of the semipermeable shell or semipermeable shell portion used in dosage forms of this invention is non-striated. In other embodiments, at least about 50% of the cross-sectional area of the semipermeable shell or semipermeable shell portion is non-striated. In yet other embodiments, at least about 80% of the cross-sectional area of the semipermeable shell or semipermeable shell portion is non-striated. As used herein, "non-striated" means homogeneous with respect to appearance, and with respect to the internal structure of the shell or shell portion when viewed under any magnification and lighting conditions. For example a cross-section of the shell or shell portion is free of striations, and uniform with respect to refractive properties when observed utilizing a light microscope at a magnification of about 50 to about 400 times.

[0219] The costly and lengthy prior art method for building up a semi-permeable coating on tablets and pharmaceu-

tical dosage forms by spray-coating techniques gives rise to a characteristic striated pattern, which is visible in the cross section of such dosage forms or their semi-permeable coatings (see for example **FIGS. 7A and 7B**). These characteristic striations are indicative of the spray-coating process consisting of multiple repetitions of the steps consisting of: (a) application via spraying of coating solution; followed by (b) warm air drying, to a tumbling bed of dosage forms in a revolving coating pan such that numerous layers of coating material are built up as each application of coating material dries to form a layer. The thickness of typical sprayed semi-permeable coatings is about 60 to about 150 microns. The thickness of an individual layer is typically in the range of about 10 microns to about 13 microns.

[0220] In contrast, the shell or shell portion of the present invention may advantageously be applied to a core directly by a molding process, yielding a uniform and homogeneous layer in 5 minutes or less, e.g. 60 seconds or less, or 30 seconds or less, or 10 seconds or less, and in certain embodiments, say 1 second or less. As such, at least about 30% of the cross-sectional area of the shell or shell portion in certain embodiments of the present invention is non-striated.

[0221] **FIGS. 7A and 7B** show prior art spray coated compositions having striations which are thus distinguishable from certain embodiments of the present invention. **FIG. 7A** is a micrographic cross-section (121× magnification) of a prior art PROCARDIA XL tablet (commercially available from Pfizer Labs) and **FIG. 7B** is a micrographic cross-section (800× magnification) of the same tablet. This prior art product clearly had striations. In contrast, **FIGS. 8A and 8B** show a dosage form of this invention (at 124× and 800× magnifications, respectively). As shown, this embodiment of the invention had no striations.

[0222] The shell or shell portion of the present invention has a cross-sectional area in the range of about 1 to 900 sq. mm, preferably about 25 to 600 sq. mm, most preferably about 50 to about 500 sq. mm.

[0223] In one particular embodiment, the shell comprises two parts that abut one another, thereby forming a shell that completely surrounds the core.

[0224] In certain embodiments of this invention, a portion of the shell contains active ingredient which is released essentially immediately upon ingestion of the dosage form. In these embodiments, the shell or shell portion preferably comprises materials which exhibit rapid dissolution in gastro-intestinal fluids.

[0225] The shell or shell portion employed in this invention also provides for delivery of active ingredient from the core or core portion to the liquid medium outside the dosage form after the dosage form is contacted with the liquid medium. In one embodiment, this is accomplished by having at least one aperture or passageway within the shell or shell portion to permit liquid medium containing active ingredient within the dosage form to pass through the shell or shell portion and out of the dosage form. In another embodiment, the shell comprises a diffusible shell or shell portion, and active ingredient diffuses therethrough to the liquid medium outside of the dosage form. In yet another embodiment, the shell or shell portion has at least a portion which is extremely thin (e.g. less than about 50 microns), and internal

pressure within the shell or shell portion causes a breach or mechanical failure of the thin shell portion, thereby delivering active ingredient from the core to the liquid medium outside of the dosage form. In yet another embodiment, the shell or shell portion has a seam, and internal pressure within the shell or shell portion causes a breach or mechanical failure of the seam, thereby delivering active ingredient from the core to the liquid medium outside of the dosage form.

[0226] In certain other embodiments, a portion of the shell functions as a diffusional membrane which contains pores through which liquid medium containing active ingredient within the dosage form can be released through the diffusible shell portion in a sustained, extended, prolonged or retarded manner. In these embodiments, the rate of release of active ingredient from the underlying core or core portion will depend upon the total pore area in the shell or shell portion, the pathlength of the pores, and the solubility and diffusivity of the active ingredient (in addition to its rate of release from the core or core portion itself). In preferred embodiments in which the shell or shell portion functions as a diffusional membrane, the release of the active ingredient from the dosage form may be described as controlled, prolonged, sustained or extended. In these embodiments, the contribution to active ingredient dissolution from the shell or shell portion may follow zero-order, first-order, or square-root of time kinetics. In certain such embodiments, the diffusional membrane shell or shell portion preferably comprises a release-modifying excipient such as a combination of a pore former and an insoluble edible material such as for example a film forming water insoluble polymer. Alternately, in such embodiments in which the shell or shell portion is prepared by solvent-free molding using a thermal reversible carrier, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[0227] In certain other embodiments, a portion of the shell functions as an eroding matrix from which active ingredient dispersed in the shell portion is liberated by the dissolution of successive layers of the shell or shell portion surface. In these embodiments, the rate of active ingredient release will depend on the dissolution rate of the matrix material in the shell or shell portion. Particularly useful matrix materials for providing surface erosion include those which first absorb liquid, then swell and/or gel prior to dissolving. In certain such embodiments, the eroding matrix shell or shell portion preferably comprises a swellable erodible hydrophilic material.

[0228] In certain other embodiments, one or more shell portions function as a barrier to prevent release therethrough of an active ingredient contained in the underlying core or core portion. In such embodiments, active ingredient is typically released from a portion of the core which is not covered by the barrier shell portion. Typically, this is achieved by having at least one passageway in the shell or shell portion to permit active ingredient to reach the liquid medium outside the dosage form. Such embodiments advantageously allow for control of the surface area for release of the active ingredient. In certain particular embodiments, for example, the surface area for release of active ingredient can be maintained substantially constant over time. In a particularly preferred embodiment, the release of at least one active ingredient follows substantially zero-order kinetics. In cer-

tain such embodiments, the barrier shell portion preferably comprises a water insoluble material such as for example a water insoluble polymer.

[0229] In certain other embodiments, the shell or portion thereof functions as a delayed release coating to delay release of an active ingredient which is contained in the core or a portion thereof. In these embodiments, the lag-time for onset of active ingredient release may be governed by erosion of the coating or diffusion through the coating or a combination thereof. In certain such embodiments, the eroding matrix shell or shell portion preferably comprises a swellable erodible hydrophilic material.

[0230] In embodiments in which the shell or portion thereof functions to modify the release of an active ingredient which is contained in the core or the subject shell or shell portion, the thickness of the shell or shell portion is critical to the release properties of the dosage form. Advantageously the dosage forms of the invention can be made with precise control over shell thickness. In a preferred embodiment in which the shell or one or more shell portions function to modify the release of an active ingredient which is contained in the core or the subject shell or shell portion, the shell or shell portion is made by the thermal cycle or thermal setting molding methods and apparatus described below.

[0231] In certain other embodiments of the invention, a further degree of flexibility in designing the dosage forms of the present invention can be achieved through the use of an additional outer coating overlaying the shell or one or more portions thereof. The additional outer coating may be applied for example by compression, or by molding. In such embodiments, the dosage form of the invention comprises at least one active ingredient; a core; a shell or shell portion which resides upon at least a portion of the core; and an outer coating which covers at least a portion of the shell or shell portion. The outer coating may for example cover a portion of the first shell portion, or the second shell portion, or both, or may surround the entire shell. In one particularly preferred embodiment, the outer coating comprises an active ingredient, which is released immediately (i.e. the dissolution of the active ingredient from the outer coating conforms to USP specifications for immediate release dosage forms of the particular active ingredient employed). In one such particularly preferred embodiment, the dosage form is a pulsatile drug delivery system, in which one or more shell portions provides for delayed release of a second dose of active ingredient, which is contained in an underlying core portion.

[0232] In one embodiment of the present invention, in which the shell comprises first and second shell portions, the first and second shell portions may comprise different levels of the same ingredients, e.g. colorants, opacifiers, film-formers, etc. In one such embodiment, the first and second shell portions may be visually distinct from one another, for example the visually distinct portions may be of different colors, hues, glosses, reflective qualities, brightness, depth, shades, chroma, opacity, etc. For example, the shell may have a red portion and a yellow portion, or a flat finish portion and a glossy portion, or an opaque portion and a translucent portion. Alternatively, the first and second shell portions may have different thickness. The first and second shell portions may have different functionalities. For

example, the first and second shell portions may confer different release properties to an active ingredient contained in either the subject shell portion, or in a corresponding underlying core portion. In one particular embodiment, the first shell portion may function as a diffusional membrane which contains pores through which fluids can enter the dosage form, and dissolved active ingredient can be released from an underlying core portion; and the second shell portion, may function as an eroding matrix from which active ingredient dispersed in the second shell portion is liberated by the dissolution of successive layers of the shell portion surface.

[0233] In embodiments in which the shell or shell portion or portions are prepared using a solvent-free molding process, the shell or shell portions will typically comprise at least about 30 percent, e.g. at least about 45 percent by weight of a thermal-reversible carrier. The shell or shell portion or portions may optionally further comprise up to about 55 weight percent of a release-modifying excipient. The shell or shell portion or portions may optionally further comprise up to about 30 weight percent total of various plasticizers, adjuvants and excipients. In certain embodiments in which the shell or shell portions are prepared by solvent-free molding, and function to delay the release of one or more active ingredients from an underlying core or core portion, the release modifying excipient is preferably selected from swellable, erodible hydrophilic materials.

[0234] In embodiments in which the shell or shell portion or portions are prepared using a solvent-based molding process, the shell or shell portion or portions will typically comprise at least about 10 weight percent, e.g. at least about 12 weight percent or at least about 15 weight percent or at least about 20 weight percent or at least about 25 weight percent of a film-former. Here, the solvent-molded shell or shell portion or portions may optionally further comprise up to about 55 weight percent of a release-modifying excipient. The solvent-molded shell or shell portion or portions may again also optionally further comprise up to about 30 weight percent total of various plasticizers, adjuvants, and excipients.

[0235] In one embodiment of this invention, the shell or shell portion or portions of the present invention, whether prepared by a solvent-free molding process, or by a solvent-based molding process, are substantially free of pores having a diameter of 0.5-5.0 microns. As used herein, "substantially free" means that the shell or shell portion or portions have a pore volume of less than about 0.02 cc/g, preferably less than about 0.01 cc/g, more preferably less than about 0.005 cc/g in the pore diameter range of 0.5 to 5.0 microns. In contrast, typical compressed materials have pore volumes of more than about 0.02 cc/g in this diameter range. In another embodiment of this invention, the core is a molded core and the core or core portions are substantially free of pores having a diameter of 0.5-5.0 microns.

[0236] Shell or shell portions may be tested for surface gloss using an instrument available from TriCor Systems Inc. (Elgin, IL) under the tradename TRI-COR MODEL 805A/806H SURFACE ANALYSIS SYSTEM and generally in accordance with the procedure described in "TriCor Systems WGLOSS 3.4 Model 805A/806H Surface Analysis System Reference Manual" (1996), which is incorporated by reference herein, except as modified below.

[0237] This instrument uses a CCD camera detector, a flat diffuse light source, compares tablet samples to a reference standard, and determines average gloss values at a 60 degree incident angle. During its operation, the instrument generates a gray-scale image, wherein the occurrence of brighter pixels indicates the presence of more gloss at that given location.

[0238] The instrument also incorporates software that uses a grouping method to quantify gloss: i.e., pixels with similar brightness which are grouped together for averaging purposes.

[0239] The "percent full scale" or "percent ideal" setting (also referred to as the "percent sample group" setting), is specified by the user to designate the portion of the brightest pixels above the threshold that will be considered as one group and averaged within that group. "Threshold," as used herein, is defined as the maximum gloss value that will not be included in the average gloss value calculation. Thus, the background, or the non-glossy areas of a sample are excluded from the average gloss value calculations. The method disclosed in K. Fegley and C. Vesey, "The Effect of Tablet Shape on the Perception of High Gloss Film Coating Systems," which is available at www.colorcon.com as of Mar. 18, 2002 and incorporated by reference herein, is used to minimize the effects resulting from different tablet shapes, and to report a metric that was comparable across the industry. (The 50% sample group setting is selected as the setting which best approximates analogous data from tablet surface roughness measurements.)

[0240] After initially calibrating the instrument using a calibration reference plate (190-228; 294 degree standard; no mask, rotation 0, depth 0), a standard surface gloss measurement is created. For example, a standard surface gloss was obtained using gel-coated caplets available from McNEIL-PPC, Inc. under the tradename, EXTRA STRENGTH TYLENOL GELCAPS. The average gloss value for a sample of 112 of such gel-coated caplets was then determined, while employing the 25 mm full view mask (190-280), and configuring the instrument to the following settings:

[0241] Rotation: 0

[0242] Depth: 0.25 inches

[0243] Gloss Threshold: 95

[0244] % Full Scale: 50%

[0245] Index of Refraction: 1.57

[0246] The average surface gloss value for the reference standard was determined to be 269.

[0247] The total weight of the shell or shell portion or portions is preferably about 20 percent to about 400 percent of the weight of the core. In embodiments wherein the shell or shell portion or portions prepared by a solvent-free molding process, the total weight of the shell or shell portion or portions is typically from about 50 percent to about 400 percent, e.g. from about 75 percent to about 400 percent, or

about 100 percent to about 200 percent of the weight of the core. In embodiments wherein the shell portion or portions are prepared by a solvent-based molding process, the total weight of the shell or shell portion or portions is typically from about 20 percent to about 100 percent of the weight of the core.

[0248] Typical shell or shell portion thicknesses which may be employed in this invention are about 10 to about 1000 microns. In certain preferred embodiments, the shell or shell portion has a thickness of less than 800 microns. In embodiments wherein the shell or shell portion is prepared by a solvent-free molding process, the shell or shell portion typically has a thickness of about 500 to about 4000 microns, e.g. about 500 to about 2000 microns, say about 500 to about 800 microns, or about 800 to about 1200 microns. In embodiments wherein the shell or shell portion is prepared by a solvent-based molding process, the shell or shell portion typically has a thickness of less than about 800 microns, e.g. about 20 to about 600 microns, say about 40 to about 200 microns. The semi-permeable shell or shell portion typically has a thickness from about 20 to about 400 microns, e.g. about 20 to about 200 microns, say about 40 to about 100 microns.

[0249] In those embodiments in which solvent-free molding is employed, the flowable material may comprise a thermal-reversible carrier. Suitable thermal-reversible carriers are thermoplastic materials typically having a melting point below about 110° C., more preferably between about 20 and about 100° C. Examples of suitable thermal-reversible carriers for solvent-free molding include thermoplastic polyalkylene glycols, thermoplastic polyalkylene oxides, low melting hydrophobic materials, thermoplastic polymers, thermoplastic starches, and the like. Preferred thermal-reversible carriers include polyethylene glycol and polyethylene oxide. Suitable thermoplastic polyalkylene glycols for use as thermal-reversible carriers include polyethylene glycol having molecular weight from about 100 to about 20,000, e.g. from about 100 to about 8,000 Daltons. Suitable thermoplastic polyalkylene oxides include polyethylene oxide having a molecular weight from about 100,000 to about 900,000 Daltons. Suitable low-melting hydrophobic materials for use as thermal-reversible carriers include fats, fatty acid esters, phospholipids, and waxes which are solid at room temperature, fat-containing mixtures such as chocolate; and the like. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl trilaurate, glyceryl myristate, GLYCOWAX-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, and phosphatidic acid. Examples of suitable waxes which are solid at room temperature include carnauba wax, spermaceti

wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax. Suitable thermoplastic polymers for use as thermal-reversible carriers include thermoplastic water swellable cellulose derivatives, thermoplastic water insoluble polymers, thermoplastic vinyl polymers, thermoplastic starches, and thermoplastic resins, and combinations thereof. Suitable thermoplastic water swellable cellulose derivatives include hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), carboxymethylcellulose (CMC), cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxybutylcellulose (HBC), hydroxyethylcellulose (HEC), hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose, and salts, derivatives, copolymers, and combinations thereof. Suitable thermoplastic water insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers, and the like and derivatives, copolymers, and combinations thereof. Suitable thermoplastic vinyl polymers include polyvinylacetate, polyvinyl alcohol, and polyvinyl pyrrolidone (PVP). Examples of suitable thermoplastic starches for use as thermal-reversible carriers are disclosed for example in U.S. Pat. No. 5,427,614. Examples of suitable thermoplastic resins for use as thermal-reversible carriers include dammars, mastic, rosin, shellac, sandarac, and glycerol ester of rosin. In one embodiment, the thermal-reversible carrier for making the core, or a portion thereof, by molding is selected from polyalkylene glycols, polyalkaline oxides, and combinations thereof.

[0250] Suitable release-modifying excipients for making the core, or the shell, or a portion thereof, by solvent free or solvent based molding include but are not limited to swellable erodible hydrophilic materials, pH-dependent polymers, pore formers, and insoluble edible materials. In one embodiment, suitable release-modifying excipients for making the core, or the shell, or a portion thereof, by molding include hydroxypropylmethylcellulose, polyethylene oxide, ammonio methacrylate copolymer type B, and shellac, and combinations thereof.

[0251] Suitable swellable erodible hydrophilic materials for use as release-modifying excipients for making the core, or the shell, or a portion thereof by a solvent-free molding process include water swellable cellulose derivatives, polyalkylene glycols, thermoplastic polyalkylene oxides, acrylic polymers, hydrocolloids, clays, gelling starches, and swelling cross-linked polymers, and derivatives, copolymers, and combinations thereof. Examples of suitable water swellable cellulose derivatives include sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxyphenylcellulose, hydroxyethylcellulose (HEC), hydroxypentylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose. Examples of suitable polyalkylene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkylene oxides include poly (ethylene oxide). Examples of suitable acrylic

polymers include potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, CARBOPOL (high-molecular weight cross-linked acrylic acid homopolymers and copolymers), and the like. Examples of suitable hydrocolloids include alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, gelatin, whey, rhamnan, zooglan, methyl, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples of suitable gelling starches include acid hydrolyzed starches, swelling starches such as sodium starch glycolate, and derivatives thereof. Examples of suitable swelling cross-linked polymers include cross-linked polyvinyl pyrrolidone, cross-linked agar, and cross-linked carboxymethylcellulose sodium.

[0252] Suitable pH-dependent polymers for use as release-modifying moldable excipients for making the molded core or molded shell or a portion thereof by molding include enteric cellulose derivatives, for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[0253] Suitable insoluble edible materials for use as release-modifying excipients making the core, or the shell, or a portion thereof by molding, include water-insoluble polymers, and low-melting hydrophobic materials. Examples of suitable water-insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof. Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl trioleate, glyceryl myristate, GLYCOWAX-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids

include phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, and phosphatidic acid. Examples of suitable waxes include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[0254] Suitable pore formers for use as release-modifying excipients for making the molded core, the shell, or a portion thereof by molding include water-soluble organic and inorganic materials. In one embodiment the pore former is hydroxypropylmethylcellulose. Examples of suitable water-soluble organic materials include water soluble polymers including water soluble cellulose derivatives such as hydroxypropylmethylcellulose, and hydroxypropylcellulose; water soluble carbohydrates such as sugars, and starches; water soluble polymers such as polyvinylpyrrolidone and polyethylene glycol, and insoluble swelling polymers such as microcrystalline cellulose. Examples of suitable water soluble inorganic materials include salts such as sodium chloride and potassium chloride and the like and/or mixtures thereof.

[0255] In embodiments in which the shell or portions thereof comprise an active ingredient intended to have immediate release from the dosage form, the shell or shell portion is preferably prepared via the solvent-free molding method described above. In such embodiments the thermal-reversible carrier is preferably selected from polyethylene glycol with weight average molecular weight from about 1450 to about 20000, polyethylene oxide with weight average molecular weight from about 100,000 to about 900,000, and the like.

[0256] In embodiments in which the shell or shell portion functions to confer modified release properties to at least one active ingredient contained within the dosage form, in the core, the shell or both, the shell or shell portion typically comprises at least one release modifying agent as described above.

[0257] In embodiments of the invention in which the core or portion thereof and shell or portion thereof each comprise a dose of active ingredient, the dosage form may function for example as a multi-compartment, e.g. a four-compartment pulsatile release delivery system. In one such embodiment, each of the compartments may comprise a dose of the same active ingredient, to be release at a desired time or rate. In another such embodiment, the corresponding first core portion and first shell portions may comprise a dose of the same first active ingredient to be released at a desired time or rate, while the second core portion and second shell portion may comprise a dose of the same second active ingredient to be released at a desired time or rate. In such embodiments, each compartment comprises inactive materials which enable the desired functionality of that particular core portion or shell portion.

[0258] In certain such embodiments, the dosage form may further comprise a water-impermeable barrier layer between the first and second core portions. The water-impermeable

barrier layer may be made by any method, for example compression or molding, and preferably comprises at least one water-insoluble material selected from water-insoluble polymers, insoluble edible materials, pH-dependent polymers, and mixtures thereof.

[0259] In one particular embodiment of this invention, at least one active ingredient contained within the dosage form exhibits a non-constant release rate.

[0260] In another particular embodiment of this invention, at least one active ingredient contained within the dosage form exhibits a delayed burst release profile. By “delayed burst release profile” it is meant that the release of that particular active ingredient from the dosage form is delayed for a pre-determined time after ingestion by the patient, and the delay period (“lag time”) is followed by prompt (immediate) release of that active ingredient. At least one shell portion of the present invention provides for the delay period and is preferably substantially free of the active ingredient to be released in a delayed burst manner. In such embodiments, the delayed burst active ingredient is typically contained within the corresponding underlying core portion. In these embodiments, the core portion may be prepared by compression or molding, and is formulated for immediate release, as is known in the art, so that the core portion is readily soluble upon contact with the dissolution medium. In such embodiments the core portion preferably comprises a disintegrant, and optionally comprises additional excipients such as fillers or thermoplastic materials selected from water-soluble or low-melting materials, and surfactants or wetting agents. In these embodiments, the dissolution of the burst release active ingredient, after the delay period, meets USP specifications for immediate release tablets containing that active ingredient. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. (See USP 24, 2000 Version, 19-20 and 856 (1999)).

[0261] In another particular embodiment of this invention at least one active ingredient contained within the dosage form exhibits a delayed and sustained release profile. By “delayed then sustained release profile” it is meant that the release of that particular active ingredient from the dosage form is delayed for a pre-determined time after ingestion by the patient, and the delay period (“lag time”) is followed by sustained (prolonged, extended, or retarded) release of that active ingredient. At least one shell portion of the present invention provides for the delay period, and is preferably substantially free of the active ingredient to be released in a delayed then sustained manner. In such embodiments, the delayed then sustained release active ingredient is preferably contained within the corresponding underlying core portion. In such embodiments the core portion may function for

example as an eroding matrix or a diffusional matrix, or an osmotic pump. In embodiments in which the core portion functions as a diffusional matrix through which active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore-formers. Alternately, in such embodiments in which the core portion is prepared by molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated. In embodiments in which the core portion functions as an eroding matrix from which dispersed active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, and combinations thereof.

[0262] In embodiments in which one or more core portions function as a diffusional matrix through which active ingredient contained therein is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore formers. Alternately, in such embodiments in which the core portion is prepared by solvent-free molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[0263] In embodiments in which a shell or shell portion functions by an erosion-based mechanism to provide a time delay for the release of an active ingredient from an underlying core portion, the release-delaying shell or shell portion preferably comprises a release modifying excipient selected from swellable erodible hydrophilic materials, insoluble edible materials, and combinations thereof.

[0264] In embodiments in which a shell or shell portion functions as an eroding matrix from which active ingredient dispersed therein is liberated in a sustained, extended, prolonged, or retarded manner, the shell or shell portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, insoluble edible materials, and combinations thereof.

[0265] In embodiments of the invention in which a shell or shell portion functions to confer a delay to the release of one or more active ingredients contained in an underlying core portion, the release-delaying shell or shell portion preferably provides a delay of greater than one hour, for example at least about 3 hours, or at least about 4 hours, or at least about 6 hours, or at least about 12 hours to the onset of dissolution of the active ingredient upon contacting of the dosage form with a liquid medium such as water, gastrointestinal fluid or the like. The delay period is typically controlled by the shell or shell portion thickness, composition, or a combination thereof. In one embodiment the delay period is independent of the pH of the dissolution media or fluid environment. For

example, the average lag-time for dissolution of active ingredient in 0.1 N HCl is not substantially different (i.e. within about 30 minutes, preferably within about 15 minutes) from the average lag-time for the dissolution of active ingredient in pH 5.6 buffer system. In certain such embodiments, the release-delaying shell or shell portion preferably comprises a release modifying excipient selected from swellable erodible hydrophilic materials, insoluble edible materials, and combinations thereof.

[0266] In embodiments in which the shell or portions thereof contain active ingredient which is released essentially immediately upon ingestion of the dosage form, the shell or shell portion preferably comprises materials which exhibit rapid dissolution in gastro-intestinal fluids. For example the immediate release shell or shell portion or portions may comprise readily soluble materials selected from water soluble or water swellable thermoplastic film formers, water soluble or water swellable thickeners, crystallizable and non-crystallizable carbohydrates. In certain such embodiments, suitable water soluble or water swellable thermoplastic film formers may be selected from water swellable cellulose derivatives, thermoplastic starches, polyalkalene glycols, polyalkalene oxides, and amorphous sugar glass, and combinations thereof. In certain other such embodiments, suitable film formers may be selected from film forming water soluble polymers such as for example water soluble vinyl polymers, water soluble polycarbohydrates, water swellable cellulose derivatives, and water soluble copolymers; film-forming proteins, and combinations thereof. In certain other such embodiments, suitable thickeners may be selected from gelling polymers or hydrocolloids; gelling starches, and crystallizable carbohydrates. In certain other such embodiments, suitable non-crystallizable carbohydrates may be selected from polydextrose, starch hydrolysates, and non-crystallizable sugar alcohols. In such embodiments, the immediate release shell or shell portion will preferably be breached or dissolved within 30 minutes in 900 ml water or 0.1 N HCl, or phosphate buffer solution at 37° C. with stirring by a USP type 2 (Paddle method) at 50 or 100 rpm.

[0267] In one embodiment of this invention, the shell or portion thereof additionally comprises at least one active ingredient which may be the same or different than the active ingredient contained in the core.

[0268] In embodiments in which the shell or portion thereof confers sustained, extended, or retarded release of an active ingredient contained in an underlying core or core portion, the release-modifying agent in the shell or shell portion preferably comprises a pore-former, and optionally a film-former. In a particularly preferred embodiment, the shell or shell portion functions as a diffusional membrane. In some such embodiments, the dissolution of the active ingredient may follow "diffusion-controlled" release kinetics, as described for example in Example 1 of U.S. Pat. No. 5,286,497. Shells or shell portions which confer sustained, extended, or retarded release and/or function as diffusional membranes can be prepared by a solvent-free method, or a solvent-based method, as described above.

[0269] In embodiments in which the shell or portion thereof confers sustained, extended, or retarded release of an active ingredient contained in the shell or first or second shell portion, the release-modifying agent in the shell or shell portion preferably comprises a swellable erodible hydrophilic material, and may optionally comprise a secondary gelling agent such as for example cross-linked carboxymethylcellulose, cross-linked polyvinylpyrrolidone, or sodium starch glycolate.

[0270] In embodiments in which the shell or portion thereof confers a delayed release to an active ingredient contained in an underlying core or core portion, the release-modifying agent is preferably selected from swellable erodible hydrophilic materials. The shell or shell portions which confer delayed release can be prepared by a solvent-free method, or a solvent-based method, as described above.

[0271] In embodiments in which the shell or portion thereof provides a barrier to prevent release therethrough of an active ingredient contained in the underlying core or core portion, the shell or shell portion is preferably prepared via a solvent-free molding method, as described above. In such embodiments, the thermal-reversible carrier is preferably selected from waxes, such as for example camuba wax,

preferably selected from water insoluble polymers such as cellulose acetate, acrylates, acrylic acid copolymers, cellulose acetate, cellulose acetate propionate, cellulose acetate propionate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, ethylcellulose, methacrylates, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, and the like, and mixtures thereof. In such embodiments, the shell or shell portion may optionally further comprise a liquid carrier such as for example mineral oil, propylene glycol, low molecular weight polyethylene glycol, glycerin, and the like.

[0272] This invention will be illustrated by the following examples, which are not meant to limit the invention in any way.

EXAMPLE 1

[0273] Dosage forms according to the invention comprising a core having a first core portion and a second core portion within a shell having a first shell portion and a second shell portion were prepared as follows.

[0274] The following ingredients were used to make the first core portion (Osmotic layer):

Ingredient	Trade Name	Manufacturer	Mg/Dosage	
			Weight %	Form
Polyethylene Oxide (MW = 7,000,000)	Polyox ® WSR 303	Union Carbide Corporation, Danbury, CT	69	128.3
Sodium Chloride		Sigma Chemical Co. St Louis, MO	25	46.5
Hydroxypropyl Methylcellulose	Methocel E5	Dow Chemical Company, Midland, MI	5.8	10.8
Magnesium Stearate		Mallinckrodt Inc., St. Louis, MO	0.2	0.4
FD&C Yellow #6			Trace	
			Amount	
Ethanol Anhydrous (dried as solvent)				

spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; hydrogenated vegetable oils such as for example cocoa butter, hydrogenated castor oil; other waxy materials such as for example glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl trilaurylate, glyceryl myristate; thermal-reversible polymers such as for example polycaprolactones and polyvinyl acetate. In certain embodiments, an impermeable barrier can be formed which consists essentially of the thermal reversible carrier. In such embodiments, an additional release-modifying agent is not necessary. In certain other embodiments, the release-modifying agent is

[0275] Sodium chloride, hydroxypropyl methylcellulose, polyethylene oxide (PEO) (MW=7,000,000), and FD&C yellow # 6 were mixed in a plastic bag for 5 minutes. This powder mixture was added into a 5 qt. bowl of a planetary mixer (available from Hobart Corp., Dayton, Ohio). The alcohol was added to the powder mixture while mixing at low speed. The ingredients were mixed for 3 minutes. The resulting granulation was removed from the bowl and dried at room temperature for 12 to 16 hours to remove all residual solvent. The granulation was screened through a #20 mesh screen and put into a plastic bag. Magnesium stearate was added to the dry granules, followed by mixing for 5 minutes to form the first core portion.

[0276] The following ingredients were used to make the second core portion:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Pseudoephedrine HCl Crystal		BASF PharmaChemikalien GmbH & Co.	15.0	65.1
Polyethylene Oxide (MW = 300,000)	Polyox ® WSR N-750	Union Carbide Corporation, Danbury, CT	75.0	325.5
Hydroxypropyl Methylcellulose	Methocel ES	Dow Chemical Company, Midland, MI	8.5	36.9
Magnesium Stearate		Mallinckrodt Inc., St. Louis, MO	1.5	6.5
Alcohol USP (dried as solvent)				

[0277] The pseudoephedrine HCl crystal, hydroxypropyl methylcellulose, and PEO (MW=300,000) were first mixed in a plastic bag for 1-2 minutes. This powder mixture was added into the 5 qt. bowl of a planetary mixer (available from Hobart Corp., Dayton, Ohio). The alcohol was added to the powder mixture while mixing at low speed. The ingredients were mixed for 10 minutes. The resulting granulation was removed from the bowl and dried at room temperature for 12 to 16 hours to remove all residual solvent. The granulation was screened through a #20 mesh screen and put into a plastic bag. Magnesium stearate was added to the dry granules, followed by mixing for 3 minutes to form the second core portion.

[0278] Cores were made from two different portions (by weight) of the first and second core portions as follows. A model M hydraulic Carver Laboratory Press (available from Fred S. Carver, Inc., Hydraulic Equipment, Summit, N.J.) was employed. A round, concave punch and die unit having a 0.4375" diameter was used for compression. The osmotic layer granulation (186 mg) for the first core portion was fed into the cavity mold of the press and was gently tapped. Then the pseudoephedrine HCl granulation (434 mg) for the second core portion was fed into the cavity overlying the osmotic granulation. The granulations were pressed into a solid two-portion core using 1600 lb/sq. in. of compression force.

[0279] The shell portion was made using the following ingredients:

[0280] The cellulose acetate was added to a beaker containing acetone and mixed using a mixer until all powder was dissolved. An agitating speed of 500 rpm was used. PEO, which was screened through a #40 mesh screen, was added to the cellulose acetate solution, which was again mixed until all powder was dispersed. The shell portion material was provided in flowable form.

[0281] A laboratory scale thermal cycle molding unit was used to apply the first and second shell portions to the core, and comprised a single mold assembly made from an upper mold assembly portion comprising an upper mold cavity, and a lower mold assembly portion comprising a lower mold cavity. The lower mold assembly portion was first cycled to a cold stage at 5° C. for 30 seconds. The shell portion material was added to the lower mold cavity. A two-portion core as described above was inserted into the lower mold cavity such that the first core portion, containing osmotic layer granules, was inserted into the lower mold cavity. A blank upper mold assembly portion was mated the lower mold assembly portion. The mold assembly was then cycled to a hot stage at 85° C. for 2 minutes. Next, the assembly was cycled to a cold stage at 5° C. for 1 minute to harden the first shell portion. The blank upper mold assembly portion was then removed from the lower mold assembly portion.

[0282] The upper mold assembly portion was next cycled to a cold stage at 5° C. for 30 seconds. The shell portion material was added to the upper mold cavity. The half-coated core, with the first shell portion, was inserted into the upper mold cavity such that the uncoated core portion containing pseudoephedrine HCl sustained release granules rested within the upper mold cavity. The lower mold assem-

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Cellulose Acetate 398-10		Eastman Chemical Company, Kingsport, TN	80.0	27.4
Polyethylene Oxide (MW = 200,000)	Polyox ® WSR N-80	Union Carbide Corporation, Danbury, CT	20.0	6.8
Acetone (dried as solvent)				

bly portion, which had been maintained at 5° C., was then mated with the upper mold assembly portion. The upper mold assembly portion was then cycled to a hot stage at 85° C. for 2 minutes, followed by a cold stage at 5° C. for 1 minute to harden the second shell portion. The lower mold assembly portion was removed and the finished dosage form, a two-portion core coated with the same shell portion, was ejected from the upper mold cavity. The weight gain due to the shell portion, i.e. the difference in weights of the finished dosage form and the uncoated core, was recorded. The finished dosage form was dried at room temperature for 12 hours to remove all residual solvent. A 0.55 mm aperture was manually drilled on the pseudoephedrine HCl layer side of the dosage form by using a pin of diameter of 0.55 mm.

[0283] The release profile for the active ingredient contained in the dosage form of this example is given as follow. The results are shown in **FIG. 9**, which depicts the percent release of active ingredient versus hours for the dosage form of Example 1. The curve depicts the dissolution profile of the pseudoephedrine HCl contained in the second core portion of the finished dosage form of this example.

[0284] All curves were obtained using the following dissolution apparatus: USP Type II apparatus (paddles, 50 RPM). Media: pH 6.8 phosphate buffer at 37° C. Time points: Samples were removed at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours to be analyzed for pseudoephedrine HCl. Dissolution samples were analyzed for pseudoephedrine HCl versus a standard prepared at the theoretical concentration for 100% released of the compound. Samples were assayed spectrophotometrically using a Cary 50 UV-Visible spectrophotometer at 257 nm for pseudoephedrine HCl content.

[0285] Although this invention has been illustrated by reference to specific embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made which clearly fall within the scope of the invention.

The invention claimed is:

1. A dosage form comprising:
 - (a) at least one active ingredient;
 - (b) a core having an outer surface; and
 - (c) a shell which resides upon at least a portion of the core outer surface, wherein at least a portion of the shell is semipermeable, at least about 30% of the cross-sectional area of the semipermeable shell portion is non-striated, and the shell comprises means for providing the active ingredient to a liquid medium outside the shell after contacting of the dosage form with the liquid medium.
2. The dosage form of claim 1, in which substantially all of the shell is semipermeable, and the shell additionally comprises at least one passageway therein extending to the core outer surface.
3. The dosage form of claim 1, in which at least about 50% of the cross sectional area of the shell is non-striated.
4. The dosage form of claim 1, in which at least about 80% of the cross sectional area of the shell is non-striated.
5. The dosage form of claim 1, in which the core comprises at least one active ingredient.
6. The dosage form of claim 1, in which the shell comprises at least one active ingredient.

7. The dosage form of claim 1, in which the core and the shell each comprise at least one active ingredient.

8. The dosage form of claim 1, in which the core comprises an osmagent.

9. The dosage form of claim 1, in which the core comprises a first core portion and a second core portion.

10. The dosage form of claim 9, in which the shell comprises a plurality of passageways therein extending to the core.

11. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core having an outer surface; and
- (c) a shell which resides upon at least a portion of the core outer surface,

wherein the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and the shell comprises means for providing the active ingredient to a liquid medium outside the shell after contacting of the dosage form with the liquid medium.

12. The dosage form of claim 11, in which at least one of the first or second shell portions has at least one passageway therein extending to the core outer surface.

13. The dosage form of claim 11, in which the second shell portion is diffusible.

14. The dosage form of claim 11, in which the first shell portion has at least one passageway therein extending to the core, and the second shell portion is impermeable to the liquid medium.

15. The dosage form of claim 11, in which the second shell portion has at least one passageway therein extending to the core.

16. The dosage form of claim 11, in which the core comprises at least one active ingredient.

17. The dosage form of claim 11, in which the first shell portion comprises at least one active ingredient.

18. The dosage form of claim 11, in which the second shell portion comprises at least one active ingredient.

19. The dosage form of claim 11, in which the core, the first shell portion and the second shell portion each comprises at least one active ingredient.

20. The dosage form of claim 11, in which the first shell portion has a first thickness, and the second shell portion has a second thickness which is different than the first shell portion thickness.

21. The dosage form of claim 11, in which the first shell portion has a first thickness, and the second shell portion has a second thickness which is substantially the same as the first shell portion thickness.

22. The dosage form of claim 11, in which the core comprises a first core portion and a second core portion.

23. The dosage form of claim 22, in which at least one of the first or second core portions comprises at least one active ingredient.

24. The dosage form of claim 22, in which the first core portion comprises a first active ingredient and the second core portion comprises a second active ingredient which may be the same or different than the first active ingredient.

25. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core having an outer surface, a first core portion, a second core portion, and a third core portion located between the first and second core portions, wherein the third core portion comprises an osmopolymer; and
- (c) a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and at least one of the first or second shell portions has at least one passageway therein extending to the core outer surface.

26. The dosage form of claim 25, in which at least one of the first or second core portions comprises at least one active ingredient.

27. The dosage form of claim 25, in which the first core portion comprises a first active ingredient and the second core portion comprises a second active ingredient which may be the same or different than the first active ingredient.

28. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core having an outer surface; and
- (c) a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the core outer surface, and the shell and core have a continuous cavity therein defining an interior surface, wherein neither the first shell portion nor the second shell portion extend substantially upon the interior surface.

29. The dosage form of claim 28, in which the core comprises at least one active ingredient.

30. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core having an outer surface, a first core portion, a second core portion, and a third core portion located between the first and second core portions, wherein the third core portion comprises an osmopolymer; and
- (c) a shell which resides upon at least a portion of the core outer surface, in which the shell comprises a first shell portion which is semipermeable to the liquid medium, and a second shell portion which is compositionally different than the first shell portion, the first and second shell portions each are substantially in contact with the

core outer surface, and the shell and core have a continuous cavity therein defining an interior surface, wherein neither the first shell portion nor the second shell portion extend substantially upon the interior surface.

31. The dosage form of claim 30, in which at least one of the first or second core portions comprises at least one active ingredient.

32. The dosage form of claim 30, in which the first core portion comprises a first active ingredient and the second core portion comprises a second active ingredient which may be the same or different than the first active ingredient.

33. The dosage form of claims 28 or 30, in which the core erodes upon contacting of the interior surface with a liquid medium.

34. The dosage form of claims 28 or 30, in which the diameter of the continuous cavity is in the range of about 15 to about 90 percent of the thickness of the dosage form.

35. The dosage form of any of claims 1, 11, 25, 28 or 30, wherein the providing of at least one active ingredient follows substantially zero-order kinetics over a specified time interval.

36. The dosage form of any of claims 1, 11, 25, 28 or 30, wherein the providing of at least one active ingredient follows square-root-of-time kinetics over a specified time interval.

37. The dosage form of any of claims 1, 11, 25, 28 or 30, wherein the providing of at least one active ingredient follows substantially first-order kinetics over a specified time interval.

38. The dosage form of any of claims 9, 22, 25 or 30, wherein at least one of the first or second core portions functions as an eroding matrix.

39. The dosage form of claim 38, wherein the eroding matrix core portion comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic agents, pH-dependent polymers, and combinations thereof.

40. The dosage form of any of claims 1, 11, 25, 28 or 30, in which the release rate of at least one active ingredient is non-constant.

41. The dosage form of any of claims 1, 11, 25, 28 or 30, in which the release of at least one dose of at least one active ingredient is a burst release.

42. The dosage form of any of claims 1, 11, 25, 28 or 30, in which the release rate of at least one active ingredient is an ascending release rate.

43. The dosage form of any of claim 1, 11, 25, 28, or 30, which provides an ascending blood level PK profile for at least one active ingredient after administration to a mammal.

44. The dosage form of any of claims 1, 11, 25, 28 or 30, in which the shell contains greater than 90 mg of at least one active ingredient.

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