COMPOSITE DOSAGE FORMS

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Abstract

A composite dosage form comprises at least one active ingredient, a first portion comprising a first molded material, and a second portion comprising a second material which is compositionally different from the first material. The first and second portions are joined at an interface, and a surface of the first portion at the interface resides substantially conformally upon a surface of the second portion of the interface. Either the first portion, the second portion, or a combination thereof may contain at least one active ingredient. The first portion, second portion or both may also each comprise an insert which may contain at least one active ingredient. The dosage form may also comprise a third portion which is located between the first and second portions.
FIG. 1A

FIG. 2A

FIG. 1B

FIG. 2B
BACKGROUND OF THE INVENTION

This invention relates to composite dosage forms such as pharmaceutical compositions. More particularly, this invention relates to composite dosage forms comprising at least one active ingredient and having a first portion comprising a first molded material and a second portion comprising a second material, in which the second material is compositionally different than the first material, surfaces of the first and second portions are joined at an interface, and the first portion surface at the interface resides substantially conformally upon the second portion surface at the interface.

Dosage forms having two or more distinct portions are useful in the pharmaceutical arts for overcoming a number of commonly encountered challenges, including the separation of incompatible active ingredients, achieving acceptable content uniformity of a low-dose/high potency active ingredient, delivering one or more active ingredients in a pulsatile manner, and providing unique aesthetic characteristics for dosage form identification. Known methods for achieving a multi-portion pharmaceutical dosage form include particle coating, multi-layer tablets, compression-coating, and spray coating techniques. It is also known for example in the household products industry to assemble solid forms from two or more different parts for the purpose of separating active ingredients, or delivering different active ingredients at different times.

Dosage forms comprising coated particles are described for example in U.S. Pat. No. 5,593,696, which describes oral dosage forms for treating of gastric disorders. The dosage forms contain, as active ingredients, famotidine and sucralfate. In the dosage form, the famotidine is present in the composition in particulate (granulate) form, and the particulate famotidine is provided with a protective barrier layer which prevents interaction between the famotidine and the sucralfate in the composition. The barrier layer is preferably a polymeric coat which dissolves partially in vivo in the stomach environs to release the coated famotidine. U.S. Pat. No. 5,980,944 describes a solid oral dosage form for the treatment of gastrointestinal disorders comprising a therapeutically effective amount of a pharmaceutical suitable for the treatment of gastric disorders selected from the group consisting of granules of diphenoxylate, loperamide, loperamide-N-oxide, pharmaceutically acceptable salts thereof and combinations thereof, and a therapeutically effective amount of simethicone wherein the pharmaceutical and simethicone are separated by a barrier coat on the granules which is substantially impermeable to simethicone.

Multi-layer tablets are described, for example, in U.S. Pat. No. 5,200,193, which describes multi-layered pharmaceutical active tablets comprising an immediate release layer and a homogenous compressed supported release layer comprising an erosion promoter, which upon administration results in a long-lasting, slow and relatively regular incremental release of the pharmaceutical active ingredient. U.S. Pat. No. 6,372,252 describes a pharmaceutical sustained release formulation capable of providing therapeutically effective bioavailability of guaifenesin for at least twelve hours after dosing in a human subject. The modified release guaifenesin bi-layer tablet disclosed has a first portion comprising an immediate release formulation of guaifenesin and a second portion comprising a sustained release formulation of guaifenesin. U.S. Pat. No. 4,999,226 discloses a multi-layered tablet containing an ibuprofen layer, a piperidino-alkanol antihistamine layer, and a layer or layers containing conventional pharmaceutical excipients which is interspersed between the ibuprofen and piperidino-alkanol layer and serves to physically separate them. This multi-layered tablet solves the problems associated with the physical and chemical incompatibilities between ibuprofen and the piperidinoalkanol antihistamines. U.S. Pat. No. 4,198,390 describes a tablet containing at least two separate and discrete volume portions, one of which contains simethicone and the other of which contains antacid. A barrier separates the two volume portions to maintain the simethicone out of contact with the antacid and to prevent migration of the simethicone from its volume portion of the tablet into the volume portion containing the antacid, and vice versa. U.S. Pat. No. 5,133,692 describes a multi-layer detergent tablet containing an outer layer, a barrier layer and an inner layer. The tablet sequentially releases ingredients contained in the outer layer and ingredients contained in the inner layer. The time interval between the release of the outer layer ingredients and the release of the inner layer ingredients is controlled by the particular choice of an ingredient for the barrier layer and the relative thicknesses of the inner layer, the barrier layer and the outer layer. The tablet is able to separate in time the dissolution of incompatible ingredients such as an enzyme and a chlorine bleach. The tablet also provides sequential release of a dishwashing composition and a rinse aid composition such that cleaning is accomplished prior to the release of the rinse aid.

Compression-coated tablets are useful for separation of incompatible active ingredients, and for pulsatile release of one or more active ingredients. Compressed coatings may have shapes which are substantially independent of the shape of the core, as disclosed for example in WO 00/18447. Commerically available compression coating machines are available for example from Korsch America Inc., a subsidiary of Korsch AG, and described in WO 09/15968. Modified release dosage forms prepared via compression are exemplified in U.S. Pat. Nos. 5,738,874 and 6,294,200, and WO 99/5209. It is possible, via compression-coating, to produce a 2-portion shell, which may function as a barrier, or release delaying coating; however compression-coated systems are limited by the shell thickness and shell composition as well as processing costs. Günsel et al., “Compression-Coated and Layer Tablets” in Pharmaceutical Dosage Forms—Tablets, edited by H. A. Lieberman, L. Lachman, J. B. Schwartz (2nd ed., rev. and expanded Marcel Dekker, Inc.) pp. 247-284, for example, discloses the thickness of compression coated shells is typically between 800 and 1200 microns. Additionally these authors note that “the advent of film coating dissipated much of the advantage of dry coating since larger quantities of tablets can be coated in a short time with film-formers dissolved in organic or aqueous solvents.” Typically, compressed coatings must contain a substantial amount of a compressible material. The compressed shell of WO 00/18447, for example, employs microcrystalline cellulose at a level of about 30%.
One method for addressing the challenge of low-dose/high potency actives is described for example in U.S. Pat. No. 4,322,449 and U.S. RE 31764, which disclose a method for the preparation of pharmaceuticals which comprises using a piezoelectric dosing system to dot liquid, dissolved or suspended active substance onto a pharmaceutical carrier. The disclosed method enables precise dosing of active pharmaceutical ingredients onto pharmaceutical carriers. The dotting is effected by, for example, use of tubular or plate-shaped piezoelectric dosing systems. However, the liquid, dissolved or suspended active substance can also be divided into discrete droplets of specific volume after application of a high pressure during passage through a narrow nozzle, whereby the individual droplets are successively charged electrically and are intermittently deflected electrostatically towards the pharmaceutical carriers.

The incorporation of molded portions into delivery systems has been used in the household products industry to achieve an additional degree of versatility. Assembled forms comprising a mixture of compressed and molded portions are known for example for delivery of detergents. WO 01/49815 describes a composition for use in a dishwasher characterized by a base composition in the form of a tablet which becomes active substantially during the main wash cycle, and at least one separate zone in or on the tablet is provided with a substance that becomes active substantially during the rinse cycle of the dishwasher. One example of such assembled forms comprises a compressed tablet portion having a hemispherical indentation in a major face, and a molded spherical portion fit into and adhered to the indentation in the compressed portion. One limitation of such assemblies is the propensity for the two portions to become detached due to inadequate adherence and minimal surface area of contact between them. In such assemblies, the molded portion may be smaller than the indentation in the compressed portion, e.g. the diameter of the molded portion is at least about 20 microns less that the diameter of the opening in the compressed portion. Alternatively, similar forms may be assembled by press-fitting. In these forms the dimensions of the molded portion and the opening in the compressed portion may be similar. Such assemblies are additionally limited in the types of geometries that are possible at the interface. In press-fit assemblies, the width of the molded portion at the deepest part of the interface may not be substantially larger than the width of the opening through which it must be fit. In other words the draft angle between the outer and inner surfaces of the compressed portion may not be negative. Moreover, the interface or area of contact between the two portions may not form an interlock.

Another significant opportunity in designing pharmaceutical dosage forms is that of product identification and differentiation. It is useful, both from a consumer safety perspective, and a commercial perspective, to have a dosage form with a unique appearance that is readily recognizable and identifiable.

Current techniques for providing unique dosage form identification include the use of intagulations. Intagulations are impressed marks typically achieved by engraving or impressing of a graphical representation, for example a figure, mark, character, symbol such as a letter, a name, a logo, a pictorial representation, and the like, or any combination thereof, in a tablet or other solid dosage form, preferably by a punching procedure. U.S. Pat. No. 5,827, 535, for example, describes soft gelatin capsules having an external surface having defined thereon an impressed graphical representation. U.S. Pat. No. 5,405,642 discloses a method of highlighting intagulations in white or colored coated tablets by spraying onto said tablets a suspension comprising a filling material having a different color, a waxy material and a solvent, and removing the solvent and the excess of filling material and waxy material. The suspension of U.S. Pat. No. 5,405,642 comprises a waxy material and a filling material in a critical weight ratio from about 1:3 to about 1:12. Too little waxy material will lead to insufficient bonding of the filling material; too much waxy material the filling material will bond too strongly to the tablet surface and consequently will be difficult to remove afterwards. Suitable solvents for the suspension of U.S. Pat. No. 5,405, 642 are those solvents wherein the filling material and, if present, the dye, do not dissolve. For example, non-dyed starches and celluloses may be suspended in alcohols, e.g. ethanol, isopropanol and the like, halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like. EP 060,023 discloses a method of emphasizing intagulations in colored (i.e. not white) solid articles, in particular tablets, by coating the tablet surface and filling up the intagulations with a coating film comprising an optically anisotropic substance. An optical contrast between the tablet surface and the intagulations is obtained, presumably due to the different orientation of the optically anisotropic substance on the tablet surface and in the intagulations. The technique is limited to colored articles and only allows the use of optically anisotropic filling materials. The optical effect merely being based on a different contrast is not particularly clear.

EP 088,556 relates to a method of highlighting intagulations in white or colored tablets by contacting said tablets with a dry, powdery material having a different color than the tablet surface and then removing the excess powdery material not deposited in the intagulations. The powdery material is thought to adhere better to the intagulations of coated tablets than to those of uncoated tablets. Adherence can further be increased by using a mixture of a wax and a powdery material as the deposition material and heating the filled tablets to 40°C-90°C to melt the wax. Finally, an outer coating may be applied to the filled tablets. However, the method disclosed in EP 088,556 has several problems. First, it has been found that the adhesion of the powdery material to the intagulations is not satisfactory as the material shows a tendency to loosen and fall out. This problem arises particularly when an outer coating film is applied to the filled tablet and the loosened material becomes fixed in the outer coating film, thus yielding speckled tablets. Addition of a wax to the powdery material to improve adhesion, on the other hand, adversely affects the distribution of the powdery material in that more of it sticks to the surface of the tablet and is difficult to remove. Several other drawbacks are associated with the use of a wax in the dry powdery material. In particular the necessity to heat the tablets filled with a wax and a powdery material to melt the wax poses a barely acceptable risk since many medicines are thermolabile and might deteriorate significantly in the process. Further, it is difficult to evenly dye a dry mixture of a wax and a powdery material, which in turn puts a limitation on the effectively possible color combinations.
U.S. Pat. No. 4,139,589 describes a process for the manufacture of an inlaid tablet, comprising the steps of incorporating into a plastic chewing gum mass a sustained-release active ingredient; incorporating into a non-plastic tablet mass a substantially immediate-release pharmaceutically active ingredient; and respectively converting the chewing gum mass and the tablet mass into the core and the outer layer of the inlaid tablet. A preferred embodiment includes converting the tablet mass into a recessed preformed element, converting the chewing gum mass into the core, inserting the core into the recess of the preformed element, introducing the preformed element and the core into a tablet mold, and subjecting the preformed element and the core in the mold to pressure.

All of the methods described above for producing a dosage form having one or more separate portions are relatively costly, complex, and time-intensive. Additionally, known methods for producing filled-in intagulations are limited in terms of suitable materials and the obtainable surface configurations and appearance of the resultant dosage form. Besides the above-mentioned limitations on the fill material itself, the tablet subcoating must be non-adhesive enough for the fill-in material to rub off upon tumbling in a hot coating pan. These methods cannot produce filled-in intagulations having the fill material raised above the tablet surface, or even perfectly flush with the tablet surface. The prior art product can only have a fill-in material surface that is slightly depressed, abraded, or concave with respect to the tablet surface.

Another significant challenge in the pharmaceutical industry is the opportunity to minimize manufacturing and packaging costs through standardization. Many drugs are available in several different strength tablets for convenience of dosing different patients with varying needs. Typically, higher strength tablets have greater weight and larger size than tablets having lower amounts of active ingredient. Handling and packaging costs could be reduced by having a dosage form design with the versatility to accommodate multiple different dosage amounts of medication in the same size tablet, yet be readily identifiable to patients and healthcare professionals in terms of identity and strength.

All of the prior art methods for forming a shell on a core share the common limitation of having the shape of the shell depend upon and generally conform to the shape of the core. Other limitations shared by conventional encapsulation and enrobing processes include high cost and complexity, limitations on the thickness of the coating or shell, and the creation of raised seams between capsule halves and/or coatings.

In addition, the separation of incompatible ingredients in pharmaceutical dosage forms presents a significant challenge to the formulator. This challenge has primarily been addressed in the art through the use of relatively costly and time-intensive methods of coated particles, multiple layer compressed tablets, or compression coating.

Another significant challenge in the formulation of pharmaceutical dosage forms is that of providing multiple release profiles for multiple active ingredients. This challenge has primarily been addressed in the art through the use of coated particles, or sprayed or compressed tablet coatings, all of which add cost and complexity to the manufacturing process.

The incorporation of molded portions into delivery systems, has been used in the household products industry to achieve an additional degree of versatility. Assembled forms comprising a mixture of compressed and molded portions are known, for example, for delivery of detergents. WO 01/49815 describes a composition for use in a dishwasher characterized by a base composition in the form of a tablet which becomes active substantially during the main wash cycle, and at least one separate zone in or on the tablet is provided with a substance that becomes active substantially during the rinse cycle of the dishwasher. One example of such assembled forms comprises a compressed tablet portion having a hemispherical indentation in a major face, and a molded spherical portion fit into and adhered to the indentation in the compressed portion. However, a limitation of such assemblies is the propensity for the two portions to become detached due to inadequate adherence and minimal surface area of contact therebetween. In such assemblies, the molded portion may be smaller than the indentation in the compressed portion, e.g. the diameter of the molded portion is at least about 20 microns less than the diameter of the opening in the compressed portion. Alternatively, similar forms may be assembled by press-fitting. In these forms the dimensions of the molded portion and the opening in the compressed portion may be similar. Such assemblies are additionally limited in the types of geometries that are possible at the interface. In press-fit assemblies, the width of the molded portion at the deepest part of the interface may not be substantially larger than the width of the opening through which it must be fit. In other words, the “draft angle” between the outer and inner surfaces of the compressed portion may not be negative. Moreover, the interface or area of contact between the two portions may not form an interlock.

Accordingly, it is one object of this invention to provide a dosage form comprising at least one active ingredient and a first portion comprising a first molded material and a second portion comprising a second material, in which the second material is compositionally different than the first material, the first and second material are joined at an interface, and a surface of the first portion at the interface resides substantially conformally upon a surface of the second portion of the interface.

It is another object of this invention to provide a dosage form comprising at least one active ingredient, a first portion comprising a first molded material, a second portion comprising a second material which is compositionally different from the first material, and a third portion which is located between the first and second portions.

Dosage forms of the present invention advantageously have enhanced versatility for a number of applications, including dosage forms to deliver pharmaceuticals, nutritional products and/or confections, which may offer benefits of improved swallowing ability for irregularly shaped substrate, or unique and pleasant aesthetic qualities that are valuable in the marketplace.

The dosage form of the present invention also advantageously provides a cost-effective means for ensuring acceptable content uniformity, and improved safety of handling for low-dose/high potency active ingredients. Low dose active ingredients can be homogeneously dispersed in the molded portion when it is in a flowable state. This
eliminates problems associated with powder segregation in blends for tabletting, and minimizes exposure of workers to potential inhalation of dust containing the high potency active ingredient.

[0024] Other objects, features and advantages of this invention will be apparent to those skilled in the art from the detailed description of the invention provided herein.

SUMMARY OF THE INVENTION

[0025] The dosage form of this invention comprises at least one active ingredient, a first portion comprising a first molded material and a second portion comprising a second material which is compositionally different than the first material. For example, the second material may be a compressed material such as a compressed powder. Surfaces of the first and second portions are joined at an interface, such that the surface of the first portion resides substantially conformally upon the surface of the second portion at the interface.

[0026] In one embodiment, the first portion comprises a thermoplastic material.

[0027] In another embodiment, the first molded material is substantially free of pores having a diameter of 0.5 to 5.0 microns.

[0028] In another embodiment, the first portion comprises a foam.

[0029] In another embodiment, the first portion comprises an aerated material.

[0030] In another embodiment, the active ingredient is coated with a release-modifying coating.

[0031] In another embodiment, the first and second portions are in substantial contact at the interface.

[0032] In another embodiment, the interface is in the form of an abutment.

[0033] In another embodiment, the first and second portions overlap at the interface.

[0034] In another embodiment, the first and second portions interlock at the interface.

[0035] In another embodiment, the first and second portions dissociate upon immersion in aqueous media.

[0036] In another embodiment, the dosage form further comprises a third portion, which is located between the first and second portions.

[0037] In another embodiment, the third portion comprises a chemical reaction product of the first and second materials.

[0038] In another embodiment, the third portion is impermeable to one or more active ingredients contained in the dosage form.

[0039] In another embodiment, the third portion is impermeable to water.

[0040] In another embodiment, the third portion acts as a barrier to the passage there through of one or more active ingredients contained in the first or second portions.

[0041] In another embodiment, the third portion functions to control the passage of one or more active ingredients contained in the first or second portions.

[0042] In another embodiment, the third portion comprises openings which allow the passage of one or more active ingredients therethrough.

[0043] In another embodiment, the third portion comprises a microelectronic device.

[0044] In another embodiment, the first and second portions have different colors.

[0045] In another embodiment, the first and second portions have different opacities.

[0046] In another embodiment, the first and second portions have different solubilities in acidic, alkaline, or neutral aqueous media.

[0047] In another embodiment, the first and second portions have different dissolution rates in acidic, alkaline, or neutral aqueous media.

[0048] In another embodiment, the first and second portions have different disintegration times in acidic, alkaline, or neutral aqueous media.

[0049] In another embodiment, the first and second portions have different hydrophilicities.

[0050] In another embodiment, the first and second portions have different topographies.

[0051] In another embodiment, the first and second portions have different plasticities.

[0052] In another embodiment, the first and second portions have different plasticities.

[0053] In another embodiment, the first and second portions have different tensile strengths.

[0054] In another embodiment, the first and second portions have different crystallinities.

[0055] In another embodiment, the first and second portions each comprise at least one active ingredient, and release active ingredient at different rates.

[0056] In another embodiment, the first portion is obtained by injection molding.

[0057] In another embodiment, the second portion is a substrate, and the first portion is formed directly upon the first portion.

[0058] In another embodiment, the first portion comprises at least one active ingredient.

[0059] In another embodiment, the second portion comprises at least one active ingredient.

[0060] In another embodiment, the first and the second portion each comprise at least one active ingredient which may be the same or different.

[0061] In another embodiment, the first portion further comprises an insert.

[0062] In another embodiment, the second portion further comprises an insert.

[0063] In another embodiment, the insert is molded.
In another embodiment, the first portion is contained within the second portion.

In another embodiment, at least one active ingredient is capable of dissolution, and dissolution of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient.

In another embodiment, the second material is a compressed material.

In another embodiment, either the first portion, the second portion or both comprise a microelectronic device.

In another embodiment, a shell resides upon the outer surfaces of the first and second portions.

In another embodiment, the surface of the first portion at the interface has indentations and protrusions corresponding substantially inversely to indentations and protrusions on the surface of the second portion at the interface.

In another embodiment, wherein the indentations and protrusions have a length, width, height or depth greater than 10 microns.

In another embodiment, the area of the interface surfaces is at least 50% of the area of a major face of either the first or second portion.

In another embodiment, an entire face of the first portion is in substantial contact with the second portion.

In another embodiment, an entire face of the second portion is in substantial contact with the first portion.

In another embodiment, a side or face of the second portion comprises a cavity, and the first portion is in contact with the entire surface of the cavity.

In another embodiment, at least one exterior surface of the first portion is flush with at least one exterior surface of the second portion.

FIGS. 1A and 1B are top and side views of an embodiment of this invention.

FIGS. 2A and 2B are top and side views of another embodiment of this invention.

FIGS. 3A and 3B are top and side views of another embodiment of this invention.

FIGS. 4A and 4B are top and side views of another embodiment of this invention.

FIGS. 5A and 5B are top and side views of another embodiment of this invention.

FIGS. 6A and 6B are top and side views of another embodiment of this invention.

FIGS. 7A-7C are top, side and exploded views of another embodiment of this invention.

FIGS. 8A-8C side views of other embodiments of this invention.

FIGS. 9A and 9B are top and side views of another embodiment of this invention.

FIG. 10 is a side view of another embodiment of this invention.

DETAILED DESCRIPTION OF THE INVENTION

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 (i.e. dose) of a certain ingredient, for example an active ingredient as defined below. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, topical, transdermal, 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 gastrointestinal tract of a human. In another preferred embodiment, the dosage form is an orally administered “placebo” system containing pharmaceutically inactive ingredients, and the dosage form is designed to have the same appearance as a particular pharmaceutically active dosage form, such as may be used for control purposes in clinical studies to test, for example, the safety and efficacy of a particular pharmaceutically active ingredient.

Suitable active ingredients for use in the dosage form of 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, anti flatulents, antifungal s, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, 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.

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

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

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, dantrol, senna, phenolphthalein, aloes, castor oil, ricinoleic acid, and dehydrocholic acid, and mixtures thereof; H2 receptor antagonists, such as famotidine, ranitidine, cimetidine, nizatidine; proton pump inhibi-
tors such as omeprazole or lansoprazole; gastrointestinal cytoprotectives, such as sucralafate and misoprostol; gastrointestinal prokinetics, such as prucalopride, antibiotics for *H. pylori*, such as clarithromycin, amoxicillin, tetracycline, and metronidazole; antiarrheals, such as diphenoxylate and loperamide; glycopyrrolate; antiemetics, such as ondansetron, analgesics, such as mesalamine.

[0091] In one embodiment of the invention, the active agent may be selected from bisacodyl, famotidine, ranitidine, cetirizine, omeprazole, naproxen, ketoprofen and the like; acetic acid derivatives, e.g. indomethacin, diclofenac, sulindac, temelin, and the like; benzoic acid derivatives, e.g. mefenamic acid, meclofenamic acid, flufenamic acid, and the like; biphenylicarboxylic acid derivatives, e.g. diethylamiino, fluorene, and the like; and oxicams, e.g. piroxicam, sulindac, isoxicam, meloxicam, and the like. In a particularly preferred embodiment, the active agent is selected from propionic acid derivative NSAIeS, e.g. ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, indoprofen, ketoprofen, flufenoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, suprofen, and pharmaceutically acceptable salts, derivatives, and combinations thereof.

[0092] In another embodiment, the active agent is selected from analgesics, anti-inflammatory, and antipyretics, e.g. non-steroidal anti-inflammatory drugs (NSAIeS), including propionic acid derivatives, e.g. ibuprofen, naproxen, ketoprofen and the like; acetic acid derivatives, e.g. indomethacin, diclofenac, sulindac, temelin, and the like; benzoic acid derivatives, e.g. mefenamic acid, meclofenamic acid, flufenamic acid, and the like; biphenylicarboxylic acid derivatives, e.g. diethylamiino, fluorene, and the like; and oxicams, e.g. piroxicam, sulindac, isoxicam, meloxicam, and the like. In a particularly preferred embodiment, the active agent is selected from propionic acid derivative NSAIDs, e.g. ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, indoprofen, ketoprofen, flufenoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, suprofen, and pharmaceutically acceptable salts, derivatives, and combinations thereof.

[0093] In another embodiment of the invention, the active agent 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.

[0094] In another embodiment of the invention, the active agent may be selected from pseudoehepridine, phenylpropanolamine, chlorpheniramine, dexamethasone, diphenhydramine, astemizole, terfenadine, fexofenadine, loratadine, desloratadine, doxilamine, norastemizole, cetirizine, mixtures thereof and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0095] Examples of suitable polydimethylsiloxanes, which include, but are not limited to dimethicone and dimethicone, 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 “dimethicone” refers to the broader class of polydimethylsiloxanes, including but not limited to dimethicone and dimethicone.

[0096] The active ingredient or ingredients are 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 dose regime, the age and weight of the patient, and other factors must be considered, as known in the art. In one particular embodiment, the first or second portion comprises at least about 85 weight percent of the active ingredient.

[0097] If the active ingredient has an objectionable taste, and the dosage form is intended to be chewed or disinte-grated in the mouth prior to swallowing, the active ingredient may be coated with a taste masking coating, as known in the art. Examples of suitable taste masking coatings are described in U.S. Pat. No. 4,851,226, U.S. Pat. No. 5,075,114, and U.S. Pat. No. 5,489,436. Commercially available taste masked active ingredients may also be employed. For example, acetaminophen particles which are encapsulated with ethylcellulose or other polymers by a coacervation process may be used in the present invention. Coacervation-encapsulated acetaminophen may be purchased commercially from Eurland America, Inc. (Vandalia, Ohio) or from Circir Inc., Dayton (Ohio).

[0098] In embodiments where an active ingredient is contained within the first or second portion of the dosage form, 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 the dosage form. Examples of suitable release modifying coatings are described, for example, 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 may be coated with a release-modifying material.

[0099] The active ingredient or ingredients 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 preferred embodiment, such particles are crystals having an average particle size of about 1-300 microns. In another preferred 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.

[0100] The first portion of the dosage form is prepared by molding. The first portion may have any shape that can be molded, and has an area of its surface that is in contact with the second portion of the dosage form. Preferably, a substantial proportion of the surface area of one entire face of the first molded portion has a shape which is defined by the shape of the second portion.

[0101] The second portion of the dosage form may be prepared by any suitable method, for example it may be molded or compressed. In one embodiment, the second portion has one or more major faces. If the second portion is molded, it may have any shape that can be molded.

[0102] Molded shapes which may be used for the first portion or second portion (if molded) include a truncated cone; a polyhedron, such as a cube, pyramid, prism, or the like; or a shape having the geometry of a space figure with some non-flat faces, such as a cone, cylinder, sphere, torus, or the like.

[0103] If the second portion is compressed, it may have any shape that can be compressed. Suitable shapes for compressed dosage forms include tablet shapes formed from compression tooling shapes described by "The Elizabeth
[0108] 5. Modified Ball Concave.
[0135] 32. Shield.
[0137] 34. Almond.
[0140] 37. Trapezoid.
[0141] 38. FIG. 8/Bar Bell.

[0144] The surface of one or more faces of the second portion may be substantially smooth, i.e. may have indentations or protrusions only at the microscopic level on the order of less than about 20 microns in width, depth, or height. Alternately the surface of one or more faces the second portion may be textured, i.e. having indentations or protrusions greater than about 20 microns, e.g. greater than about 50 microns, or greater than about 100 microns, or from about 1000 microns to about 30,000 microns in width, depth, or height. In embodiments wherein the surface of one or more faces the second portion is textured, the surface may contain an embossed (raised) or debossed (indent) design. For example, the surface of one or more faces the second portion may contain indentations, intagulations, letters, symbols or a pattern such as a graphic or logo. Alternatively, one or more faces of the second portion may contain one or more depressions covering a substantial proportion of its surface area, for example at least about 10%, or at least about 20% or at least about 50% of the surface area of the face. One type of compressed tablets with indentations in a major face are described for example in WO 01/85437, which describes a process for the production of tablets with a cavity using a press. WO 99/6157 describes tablets, compressed from a particulate material, having cavities to receive an additional ingredient or mix of ingredients.

[0145] In one embodiment of the invention, a surface of the first molded portion resides substantially conformally upon a surface of the second portion. As used herein, “substantially conformally” means that a surface of the first molded portion substantially conforms inversely to the shape and texture of a surface of the second portion, such that the first and second portions are in substantial contact at the interface between them. As used herein, “substantial contact” means that a major portion of the surface area of at least one surface of the first portion is in contact with a major portion of the surface area of at least one surface of the second portion.

[0146] The dosage form of the invention may also incorporate pharmaceutically acceptable adjuvants, including, for example, preservatives, sweeteners such as aspartame, acesulfame potassium, saccharin, flavors, antioxidants, surfactants, and coloring agents.

[0147] In one embodiment, the dissolution characteristics of at least one active ingredient meets USP specifications for immediate release tablets containing the active ingredient. 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. 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 another embodiment, the dissolution characteristics of at least one active ingredient are modified, e.g. controlled, sustained, extended, retarded, prolonged, delayed, and the like. In one particular
embodiment, one portion of the dosage form provides for immediate release of a first dose of an active ingredient therefrom, and the other portion of the dosage form provides for modified release of a second dose of either the same or a different active ingredient contained therein.

[0148] The first portion of the dosage form of this invention comprises a molded material. In a preferred embodiment, the molded material may be obtained from flowable material. 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 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 dissolved or molten component, and a solvent such as for example water. The solvent may be partially or substantially removed by drying. Suitable flowable materials include those comprising film forming polymers, gelling polymers, hydrocolloids, low melting hydrophilic materials such as fats and waxes, non-crystallizable carbohydrates, and the like.

[0149] In one embodiment of the invention, the flowable material comprises gelatin. 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.

[0150] Other preferred flowable materials may comprise sucrose-fatty acid esters; fats such as cocoa butter, hydrogenated vegetable oil such as palm kernel oil, cottonseed oil, sunflower oil, and soybean oil; mono- and di- and triglycerides, phospholipids, waxes such as carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; sugar in the form on an amorphous glass such as that used to make hard candy forms, crystallized sugar in a supersaturated solution such as that used to make fondant forms; carbohydrates such as sugar-alcohols (for example, sorbitol, maltitol, mannitol, xylitol), or thermoplastic starch; and 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.

[0151] In one embodiment of the invention, the flowable material may comprise a film former such as a cellulose ether, e.g. hydroxypropylmethylecellulose or a modified starch, e.g. waxy maize starch; optionally an extender, such as polyhydroxyethyl starch, e.g. polyethylene glycol, propylene glycol, vegetable oils such as castor oil, glycerin, and mixtures thereof. Any film former known in the art is suitable for use in the flowable shell material of the present invention. Examples of suitable film formers include, but are not limited to, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxypropyl starch, hydroxyethyl starch, pullulan, methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPMC), hydroxybutylcellulose (HBMC), hydroxyethylcellulose (HEC), hydroxyethylhydroxypropylmethyl cellulose (HEPMC), methacrylic acid and methacrylate ester copolymers, polyethylene oxide and polyvinylpyrrolidone copolymers, gelatin, proteins such as whey protein, coagglutinable proteins such as albumin, casein, and other casein isolates, soy protein and soy protein isolates, pre-gelatinized starches, and polymers and derivatives and mixtures thereof.

[0153] One suitable hydroxypropylmethylcellulose compound 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 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 millipsal-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 millipsal-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 millipsal-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 an hydroxylglucose ring, and “hydroxypropyl molar substitution” shall mean the number of moles of hydroxypropyl per mole hydroxylglucose.

[0154] As used herein, “modified starches” include starches that have been modified by crosslinking, chemically modified for improved stability, or physically modified for improved solubility properties. 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 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 FILMSEAL, 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.

[0155] Suitable tapioca dextrins include those available from National Starch & Chemical Company under the
tradename 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.

[0156] Any thicker known in the art is suitable for use in the film forming composition of the present invention. Examples of such thickeners include but are not limited to 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, pssstulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamson, zooglan, methylglc, chitin, cyclodextrin, chitosan, and derivatives and mixtures thereof. Additional suitable thickeners include crystallizable sugars, such as glucose (dextrose), fructose, and the like, and derivatives and combinations thereof.

[0157] Suitable xanthan gums include those available from C. P. Kelco Company under the tradename, KELTROL 1000, XANTROL 180, or K93630.

[0158] Any plasticizer known in the pharmaceutical art is suitable for use in the present invention, and may include, but not be limited to polyethylene glycol; glycercin; sorbitol; triethyl citrate; tributyl citrate; dibutyl sebacate; vegetable oils such as castor oil; surfactants such as polysorbates, sodium lauryl sulfates, and diocetyl-sodium sulfosucinate; propylene glycol; mono acetate of glycerol; diacetate of glycerol; trisacetate of glycerol; natural gums and mixtures thereof. In solutions containing a cellulose ether film former, an optional plasticizer may be present in an amount based upon the total weight of the solution, from about 0% to about 40%.

[0159] The flowable material may optionally comprise adjuvants or excipients, in which may comprise up to about 20% by weight of the flowable material. Examples of suitable adjuvants or excipients include detergent (s), humectants, surfactants, anti-foaming agents, colorants, flavorings, sweeteners, opacifiers, and the like. In one preferred embodiment, the flowable material comprises less than 5% humectants, or alternately is substantially free of humectants, such as glycercin, 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, 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.

[0160] In a preferred embodiment of the invention, the molded material comprises at least about 80%; e.g. at least about 90% of a material selected from film formers, gelling polymers (hydrocolloids), low-melting hydrophobic materials, non-crystallizable carbohydrates, and mixtures thereof. The molded material may be formed by injection molding, advantageously minimizing or eliminating the need for direct-compression filler-binders such as microcrystalline cellulose, spray-dried lactose, mineral salts such as calcium phosphate, crystalline sugars such as sucrose, dextrose, and the like. These materials would disadvantageously detract from the clarity and stability of the molded material. Preferably the molded material comprises less than about 10%, e.g. less than about 1%, or less than about 0.1% of direct-compression filler-binders.

[0161] In another embodiment, the molded material is prepared by thermal setting molding using the method and apparatus described in copending U.S. patent application Ser. No. 9/66,450, pages 57-63, the disclosure of which is incorporated herein by reference. In this embodiment, the molded material is formed by injecting a starting material in flowable form into a molding chamber. The starting material preferably comprises an active ingredient and a thermal setting material at a temperature above the melting point of the thermal setting material but below the decomposition temperature of the active ingredient. The starting material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[0162] In another embodiment, the molded material is prepared by thermal cycle molding using the method and apparatus described in copending U.S. patent application Ser. No. 9/66,497, pages 27-51, the disclosure of which is incorporated herein by reference. In this embodiment, the molded material is formed by injecting a starting material in flowable form into a heated molding chamber. The starting material preferably comprises an active ingredient and a thermoplastic material at a temperature above the set temperature of the thermoplastic material but below the decomposition temperature of the active ingredient. The starting material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[0163] According to this method, the starting material must be in flowable form. For example, it may comprise solid particles suspended in a molten matrix, for example a polymer matrix. The starting material may be completely molten or in the form of a paste. The starting material may comprise an active ingredient dissolved in a molten material. Alternatively, the starting material may be made by dissolving a solid in a solvent, which solvent is then evaporated from the starting material after it has been molded.

[0164] The starting material may comprise any edible material which is desirably to incorporate into a shaped form, including active ingredients such as those active ingredients described herein, nutritional, vitamins, minerals, flavors, sweeteners, and the like. Preferably, the starting material comprises an active ingredient and a thermal setting material. The thermal setting material may be any edible material that is flowable at a temperature between about 37 to about 250°C, and that is a solid at a temperature between about 0 to about -10°C. Preferred thermal setting materials include water-soluble polymers such as polyalkylene glycols, polyethylene oxides and derivatives, and sucrose esters; fats such as cocoa butter, hydrogenated vegetable oil such as palm kernel oil, cottonseed oil, sunflower oil, and soybean oil; mono- di- and triglycerides, phospholipids, waxes such as carnuba wax, spermactan wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; sugar in the form on an amorphous glass such as that used to make hard candy forms, crystallized carbohydrates in a supersaturated solution such as that used to make fondant forms; low-moisture polymer solutions such as mixtures of gelatin and other hydrocolloids at water contents up to about 30%
such as those used to make “gummi” confection forms. In a particularly preferred embodiment, the thermal setting material is a water-soluble polymer such as polyethylene glycol.

[0165] The first portion may be made in any shape or size. For instance, irregularly shaped first portions may be made; i.e. shapes having no more than one axis of symmetry. Cylindrically shaped first portions may also be made. The molded material may be prepared by any molding method, such as injection molding. In a preferred embodiment, the molded material may be made using the thermal setting method and apparatus described herein. In another preferred embodiment of the invention, the molded material is prepared by thermal cycle molding as described herein.

[0166] The first molded material and second material of the dosage form of this invention are compositionally different. As used herein, the term “compositionally different” means having features that are readily distinguishable by qualitative or quantitative chemical analysis, physical testing, or visual observation. For example, the first and second materials may contain different ingredients, or different levels of the same ingredients, or the first and second materials may have different physical or chemical properties, different functional properties, or be visually distinct. Examples of physical or chemical properties that may be different include hydrophobicity, hygroscopicity, elasticity, plasticity, tensile strength, crystallinity, and density. Examples of functional properties which may be different include rate and/or extent of dissolution of the material itself or of an active ingredient therefrom, rate of disintegration of the material, permeability to active ingredients, permeability to water or aqueous media, and the like. Examples of visual distinctions include size, shape, topography, or other geometric features, color, hue, opacity, and gloss.

[0167] In one embodiment, the second portion of the dosage form of this invention comprises a compressed material. In one preferred embodiment of this invention, the second portion is obtained by compressing a powder. The powder may preferably comprise an active ingredient and optionally contain various excipients, such as binders, disintegrants, lubricants, fillers, glidants and the like, as is conventional, or other particulate material of a medicinal or non-medicinal nature, such as inactive placebo blends for tabletting, confectionery blends, and the like. In one embodiment, the compressed second portion comprises active ingredient, powdered wax (such as shellac wax, microcrystalline wax, polyethylene glycol, and the like), and optionally disintegrants and lubricants as are well known to those skilled in the art.

[0168] In one embodiment of the invention, the second portion is obtained from a blend of powders having an average particle size of about 50 to about 500 microns. In one embodiment, the active ingredient has an average particle size of about 50 to about 500 microns. In another embodiment, at least one excipient has an average particle size of about 50 to about 500 microns. In one such embodiment, a major excipient, i.e. and excipient comprising at least 50% by weight of the core, has an average particle size of about 50 to about 500 microns. Particles in this size range are particularly useful for direct compression processes.

[0169] In another embodiment of the invention, the second portion is a directly compressed tablet, made from a powder which is substantially free of water soluble polymeric binders and hydrated polymers. This composition is advantageous for maintaining an immediate release dissolution profile, minimizing processing and material costs, and providing for optimal physical and chemical stability of the dosage form.

[0170] Suitable excipients for use in a compressed portion include fillers, binders, disintegrants, lubricants, glidants, and the like.

[0171] Suitable fillers 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 dextrins, and maltodextrins, and the like, water insoluble plastically deforming materials such as microcrystalline cellulose or other cellulose derivatives, water insoluble brittle fracture materials such as dicalcium phosphate, tricalcium phosphate and the like and mixtures thereof.

[0172] Suitable binders include dry binders such as polyvinyl pyrrolidone, hydroxypropylmethylcellulose, and the like; wet binders such as water-soluble polymers, including hydrocolloids such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamsan, zeoglan, methyl, chitin, cycloextrin, chitosan, polyvinyl pyrrolidone, cellulosics, starches, and the like; and derivatives and mixtures thereof.

[0173] Suitable disintegrants include sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and the like.

[0174] Suitable lubricants include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, and waxes.

[0175] Suitable glidants include colloidal silicon dioxide, and the like.

[0176] In a preferred embodiment, the second portion is prepared by the compression methods and apparatus described in copending U.S. application Ser. No. 09/966,509, pages 16-27, the disclosure of which is incorporated herein by reference. Specifically, the second portion 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. 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 fillers and return excess powder to the dies.

[0177] In another embodiment of the invention, the first or second portions, or both, may contain at least in part one or more inserts. The inserts can be made in any shape or size. For instance, irregularly shaped inserts can be made; i.e. shapes having no more than one axis of symmetry. Cylindrically shaped inserts may also be made. The insert may be prepared using conventional techniques such as panning,
compression, or molding. In one embodiment, the insert is prepared using the thermal setting method and apparatus as described herein.

[0178] In one embodiment of the invention, the insert or inserts may have an average diameter from about 100 to about 1000 microns. In another embodiment of this invention, the insert(s) may have an average diameter or thickness from about 10% to about 90% of the diameter or thickness of the dosage form, or portion thereof. In yet another embodiment of this invention, the first or second dosage form portion may comprise a plurality of inserts.

[0179] In another embodiment of the invention, the first portion, second portion, or both may comprise a microelectronic device (e.g., an electronic “chip”) which may be used as an active component or to control, for example, the rate of release of active ingredients contained within the first and/or second portions or insert in response to an input signal. Examples of such microelectronic devices are as follows:

[0180] (1) Integrated, self-regulating responsive therapeutic devices including biosensors, electronic feedback and drug/countermeasure release devices which are fully integrated. Such devices eliminate the need for telemetry and human intervention, and are disclosed, for example, at www.chiprx.com/products.html, which is incorporated herein by reference;

[0181] (2) Miniaturized diagnostic imaging systems which comprise a swallowable capsule containing a video camera, and are disclosed, for example, at www.givenimaging.com/usa/default.asp, which is incorporated herein by reference;

[0182] (3) Subcutaneous glucose monitors which comprise implantable or insertable sensor devices which detect changes in glucose concentration within intestinal fluid, and communicate to an external detector and data storage device. Such devices are disclosed, for example, at www.applied-medical.co.uk/glucosse.htm, which is incorporated herein by reference;

[0183] (4) Microdisplay vision aid devices encapsulated in an artificial intraocular lens. Such devices include a receiver for power supply, data and clock recovery, and a miniature LED array flip-chip bonded to a silicon CMOS driver circuit and micro optics, and are disclosed, for example, at http://ios.oe.uni-duisberg.de/c/, which is incorporated herein by reference. The microdisplay device receives a bit-stream energy wireless signal from a high dynamic range CMOS camera placed outside the eye which generates a digital black & white picture which is converted by a digital signal processing unit (DSP) into a serial bit-stream with a data rate of approximately 1 Mbit/s. The image is projected onto the retina;

[0184] (5) Microchips used to stimulate damaged retinal cells, allowing them to send visual signals to the brain for patients with macular degeneration or other retinal disorders. The chip is 2 mm x 25 microns, and contains approximately 5,000 microscopic solar cells (“microphotodiodes”), each with its own stimulating electrode. These microphotodiodes convert the light energy from images into electrical chemical impulses that simulate the remaining functional cells of the retina in patients with AMD and RP. Such microchips are disclosed, for example, at www.optobionics.com/artificialretina.htm, which is incorporated herein by reference;

[0185] (6) Disposable “smart needles” for breast biopsies which display results in real time. The device fits into a 20 to 21 gauge disposable needle that is connected to a computer, as the needle is inserted into the suspicious lesion. The device measures oxygen partial pressure, electrical impedance, temperature, and light scattering and absorption properties including deoxygenated hemoglobin, vascularization, and tissue density. Because of the accuracy benefits from the six simultaneous measurements, and real-time nature of the device, it is expected to exceed the accuracy levels achieved by the core needle biopsy procedure and approach the high level of accuracy associated with surgical biopsies. Further, if cancer is found, the device can be configured to deliver various therapies such as cancer markers, laser heat, cryogenics, drugs, and radio-active seeds. Such devices are disclosed, for example, at www.bioluminate.com/description.html, which is incorporated herein by reference; and

[0186] (7) Personal UV-B recorders, which are instrument grade devices for measuring and recording UVB exposure and fit into a wrist-waist belt. They may also be worn as a patch.

[0187] In one preferred embodiment, the invention provides a dosage form comprising a thermal cycle molded first portion and a compressed powder second portion.

[0188] In another preferred embodiment, the invention provides a dosage form comprising an injection molded first portion and a compressed powder second portion.

[0189] In one embodiment of the invention, only the first portion comprises one or more active ingredients. In another embodiment of this invention, only the second portion comprises one or more active ingredients. In yet another embodiment of this invention, both the first and second portions comprise one or more active ingredients. In yet another embodiment of this invention, one or more of the first portion, second portion or the insert or inserts comprise one or more of the active ingredients. 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.

[0190] In embodiments wherein one portion of the dosage form comprises active ingredients, and another portion of the dosage form is substantially free of active ingredients, the invention advantageously enables a system of dosage form design with the versatility to accomodate multiple different dosage amounts of medication in the same size tablet, yet be readily identifiable to patients and healthcare professionals in terms of its identity and strength. For example, a particular medication may be commercially available in several different strength dosage forms. It is
possible to design, using the present invention, a series of dosage forms in which the second portion comprises active ingredient, and varies in size according to the amount of active ingredient contained therein. The molded first portion of the dosage form may be substantially free of active ingredient, and may vary in size inversely according the the size of the first portion, such that the overall size of the dosage form remains constant for the different strengths of active ingredient contained therein. In one such embodiment, the two portions of the dosage forms may be visually distinct. For example, the second portion of the dosage form may be colored and/or opaque, and the first portion of the dosage form may be colorless, transparent, semi-transparent or translucent, thus providing visual reinforcement to both healthcare professionals and patients as to the varying strengths of the available dosage forms.

[0191] An overall understanding of the dosage form of this invention may be obtained by reference to FIGS. 1A and 1B. In FIGS. 1A and 1B, a dosage form 2 is depicted which comprises a first portion 8 comprising a molded material 10 and a second portion 4 comprising a compressed material 6. Material 10 and material 6 are compositionally different. It will be understood that the shapes of the first and second portions in FIGS. 1A and 1B are merely illustrative, and are not meant to limit this invention in any way.

[0192] Another embodiment of the invention is depicted in FIGS. 2A and 2B, in which a dosage form 22 is depicted which comprises a first portion 24 comprising a first molded material 26 and a second molded material 27, and a second portion 28 comprising a compressed material 30. Materials 26 and 27 are each are compositionally different from material 30. It will be understood that the shapes of the first and second portions in FIGS. 2A and 2B are merely illustrative, and are not meant to limit this invention in any way.

[0193] Another embodiment of the invention is depicted in FIGS. 3A and 3B, in which dosage form 32 is depicted which comprises a first portion 34 comprising a molded material 36, and a second portion 38 (shown in dashed outline in FIG. 3A) comprising a compressed material 40. Material 36 is compositionally different from material 40. It will be understood that the shapes of the first and second portions in FIGS. 3A and 3B are merely illustrative, and are not meant to limit this invention in any way.

[0194] Another embodiment of the invention is depicted in FIGS. 4A and 4B, in which dosage form 42 is depicted which comprises a first portion 44 comprising a first molded material 46, and a second portion 48 which is a molded insert which comprises a second molded material 50. Material 46 is compositionally different from material 50. It will be understood that the shapes of the first and second portions in FIGS. 4A and 4B are merely illustrative, and are not meant to limit this invention in any way.

[0195] Another embodiment of the invention is depicted in FIGS. 5A and 5B, in which dosage form 52 is depicted which comprises a first portion 54 comprising a molded material 56, and a second portion 58 comprising a compressed material 60. Material 56 is compositionally different from material 60. It will be understood that the shapes of the first and second portions in FIGS. 5A and 5B are merely illustrative, and are not meant to limit this invention in any way.

[0196] Another embodiment of the invention is depicted in FIGS. 6A and 6B, in which dosage form 62 is depicted which comprises a first portion 64 comprising a molded material 66, and a second portion 68 comprising a compressed material 70. Material 66 is compositionally different from material 70. It will be understood that the shapes of the first and second portions in FIGS. 6A and 6B are merely illustrative, and are not meant to limit this invention in any way.

[0197] Another embodiment of the invention is depicted in FIGS. 7A-7C, in which dosage form 72 is depicted which comprises a first portion 74 comprising a molded material 76, and a second portion 78 comprising a compressed material 80. Material 76 is compositionally different from material 70. As shown in FIGS. 7B and 7C, first portion 74 has projections 75 on one face thereof. It will be understood that the shapes of the first and second portions in FIGS. 7A-7C are merely illustrative, and are not meant to limit this invention in any way.

[0198] Other embodiments of the invention are depicted in FIGS. 8A-8C. In FIG. 8A, dosage form 82 is depicted which comprises a first portion 84 comprising a molded material 86, and a second portion 88 comprising a compressed material 90. Material 86 is compositionally different from material 90. In FIG. 8B, dosage form 182 is depicted which comprises a first portion 184 comprising a molded material 186, and a second portion 188 comprising a compressed material 190. Material 186 is compositionally different from material 190. As shown in FIG. 8B, first portion 184 has a tonge shaped portion 183 which interfaces with groove shaped portion 185 of second portion 188. In FIG. 8C, dosage form 282 is depicted which comprises a first portion 284 comprising a molded material 286, and a second portion 288 comprising a compressed material 290. Material 286 is compositionally different from material 290. It will be understood that the shapes of the first and second portions in FIGS. 8A-8C are merely illustrative, and are not meant to limit this invention in any way.

[0199] Another embodiment of the invention is depicted in FIGS. 9A and 9B, in which dosage form 92 is depicted which comprises a first portion 94 comprising a molded material 96, and a second portion 98 comprising a compressed material 100. Material 96 is compositionally different from material 100. It will be understood that the shapes of the first and second portions in FIGS. 9A and 9B are merely illustrative, and are not meant to limit this invention in any way.

[0200] Another embodiment of this invention is depicted in FIG. 10, in which dosage form 102 is depicted which comprises a first portion 104 comprising a molded material 106, a second portion 108 comprising a compressed material 105, and a third portion 107 which may comprise a molded or compressed material 109, preferably a molded material. Material 106 is compositionally different from material 105. Material 109 may be compositionally the same or different than materials 106 or 105, although in the embodiment depicted in FIG. 10 each of materials 106, 105 and 109 is compositionally different from each other. In this embodiment, either first portion 104 or second portion 108 or both contain an active ingredient. Third portion 107 may act as a barrier to prevent the passage there through of either or both the active ingredients contained in first portion 104 or
second portion 108. It will be understood that the shapes of the first, second and third portions in FIG. 10 are merely illustrative, and are not meant to limit this invention in any way.

[0201] In one embodiment, the third portion has one or more major faces. The third portion may be prepared by any suitable method, for example it may be molded or compressed. The third portion may have a variety of molded shapes, as described above with respect to the first and second portions.

[0202] In one particular embodiment, the invention is a bi-layer tablet in which the second portion is a compressed layer, the first portion is a molded layer, and the interface between the compressed and molded portions is a major tablet face.

[0203] The first molded material is substantially free of pores having a diameter of 0.5-5.0 microns. As used herein, “substantially free” means that the first molded material has 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. Typical compressed materials have pore volumes of more than about 0.02 cc/g in this pore diameter range. In embodiments of this invention in which the second or third portions comprise a molded material, the molded material contained in the second or third portion likewise is substantially free of pores having a diameter of 0.5 to 5.0 microns. Pore volume, pore diameter and density may be determined using a Quantachrome Instruments PoreMaster 60 mercury intrusion porosimeter and associated computer software program known as “Porowin.” The procedure is documented in the Quantachrome Instruments PoreMaster Operation Manual. The PoreMaster determines both pore volume and pore diameter of a solid or powder by forced intrusion of a non-wetting liquid (mercury), which involves evacuation of the sample in a sample cell (penetrometer), filling the cell with mercury to surround the sample with mercury, applying pressure to the sample cell by: (i) compressed air (up to 50 psi maximum); and (ii) a hydraulic (oil) pressure generator (up to 60000 psi maximum). Intruded volume is measured by a change in the capacitance as mercury moves from outside the sample into its pores under applied pressure. The corresponding pore size diameter (d) at which the intrusion takes place is calculated directly from the so-called “Washburn Equation”: \( d = 4\gamma \cos \theta / P \) where \( \gamma \) is the surface tension of liquid mercury, \( \theta \) is the contact angle between mercury and the sample surface, and \( P \) is the applied pressure.

[0204] Equipment used for pore volume measurements:

1. Quantachrome Instruments PoreMaster 60.

[0205] 2. Analytical Balance capable of weighing to 0.0001 g.


[0208] Reagents used for measurements:

1. High purity nitrogen.

[0210] 2. Triply distilled mercury.

[0211] 3. High pressure fluid (Dila AX, available from Shell Chemical Co.).

[0212] 4. Liquid nitrogen (for Hg vapor cold trap).

[0213] 5. Isopropanol or methanol for cleaning sample cells.


[0215] Procedure:

[0216] The samples remain in sealed packages or as received in the dessicator until analysis. The vacuum pump is switched on, the mercury vapor cold trap is filled with liquid nitrogen, the compressed gas supply is regulated at 55 psi, and the instrument is turned on and allowed a warm up time of at least 30 minutes. The empty penetrometer cell is assembled as described in the instrument manual and its weight is recorded. The cell is installed in the low pressure station and “evacuation and fill only” is selected from the analysis menu, and the following settings are employed:

[0217] Fine Evacuation time: 1 min.

[0218] Fine Evacuation rate: 10

[0219] Coarse Evacuation time: 5 min.

[0220] The cell (filled with mercury) is then removed and weighed. The cell is then emptied into the mercury reservoir, and two tablets from each sample are placed in the cell and the cell is reassembled. The weight of the cell and sample are then recorded. The cell is then installed in the low-pressure station, the low-pressure option is selected from the menu, and the following parameters are set:

[0221] Mode: [Low pressure]

[0222] Fine evacuation rate: 10

[0223] Fine evacuation until: 200% Hg

[0224] Coarse evacuation time: 10 min.

[0225] Fill pressure: Contact 40.1

[0226] Maximum pressure: 50

[0227] Direction: Intrusion And Extrusion

[0228] Repeat: 0

[0229] Mercury contact angle; 140

[0230] Mercury surface tension: 480

[0231] Data acquisition is then begun. The pressure vs. cumulative volume-intruded plot is displayed on the screen. After low-pressure analysis is complete, the cell is removed from the low-pressure station and reweighed. The space above the mercury is filled with hydraulic oil, and the cell is assembled and installed in the high-pressure cavity. The following settings are used:

[0232] Mode: Fixed rate

[0233] Motor speed: 5

[0234] Start pressure: 20

[0235] End pressure: 60,000

[0236] Direction: Intrusion and extrusion

[0237] Repeat: 0

[0238] Oil fill length: 5

[0239] Mercury contact angle: 140

[0240] Mercury surface tension: 480
Data acquisition is then begun and graphic plot pressure vs. intruded volume is displayed on the screen. After the high pressure run is complete, the low-and high-pressure data files of the same sample are merged.

In another embodiment of this invention, the composite dosage form of the present invention may be coated with an overcoating or shell.

In another embodiment of this invention, at least part of the first portion extends below or penetrates through a surface of the second portion to define a penetrated surface area of the second portion. The area of the interface surfaces is substantially the same, preferably at least 90%, of the penetrated surface area.

In another embodiment of this invention, the area of the interface surfaces is at least 10%, preferably 25%, more preferably at least 50%, say greater than 90% of the area of a major face of either the first or second portions.

In another embodiment of this invention, one face or side of the second portion comprises a cavity, and the first portion is in contact with the entire surface of the cavity.

A particular advantage of the present invention is that either the first molded portion or second portion may be larger in cross-section (in at least one location) than the opening to the cavity within the second portion or first molded portion, respectively, which receives the first portion or second portion. In contrast, in the prior art an insert must be no larger in cross-section than the opening of the cavity which receives the insert. In a preferred embodiment of this invention, the first molded portion or a portion thereof is received by a cavity located within the second portion. Thus, the first molded portion forms a “tongue” which interlocks with the cavity or “groove” within the second portion. This may also be expressed in terms of the “draft angle” of the second portion. As used herein, the term “draft angle” refers to the angle defined by the side wall of the cavity and a line perpendicular to the face of the inserted (e.g. first) portion, as described for example in Rosato et al., Injection Molding Handbook, pp. 601-04, (2d ed. 1995), the disclosure of which is incorporated herein by reference. In the present invention, the draft angle of the second portion may have a value less than zero. However, in the prior art compositions, the draft angle must have a zero or positive value.

In another embodiment of this invention, at least one exterior surface of the first portion is flush with at least one exterior surface of the second portion.

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

**EXAMPLE 1**

Dosage forms of the invention are made in a continuous process using an apparatus comprising a thermal cycle molding module and a compression module linked in series via a transfer device as described at pages 14-16 of copending U.S. application Ser. No. 09/966,939, the disclosure of which is incorporated herein by reference. The dosage forms have the structure shown in FIGS. 1A and 1B and comprise a first portion comprising a first molded material and a second portion comprising a second material that is compressed.

The first portions are made of a flowable material comprising the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Tablet Trade Name</th>
<th>Manufacturer</th>
<th>Weight %</th>
<th>Mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene</td>
<td>Carbowax®</td>
<td>Union Carbide</td>
<td>60.3</td>
<td>90</td>
</tr>
<tr>
<td>Glycol 335®</td>
<td></td>
<td>Corporation, Danbury, CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose</td>
<td>Ac-Di-Sol®</td>
<td>FMC Corporation, Newark, DE</td>
<td>30.1</td>
<td>95</td>
</tr>
<tr>
<td>Sodium Pseudoephedrine Hydrochloride Crystal</td>
<td></td>
<td>BASF PharmaChemikalien GmbH &amp; Co., Ludwigshafen/Rhein</td>
<td>9.5</td>
<td>30</td>
</tr>
</tbody>
</table>

The second portions are made of a dry blend comprising the following ingredients: acetaminophen USP (590 mg/tablet), synthetic wax X-2068 T20 (53 mg/tablet), sodium starch glycolate (EXPLOTAB) (13.9 mg/tablet), silicon dioxide (0.6 mg/tablet), and magnesium stearate NF (2.4 mg/tablet). The dry blend is compressed into second portions on a compression module as described in copending U.S. application Ser. No. 09/966,509 at pages 16-27 (incorporated herein by reference). The compression module is a double row, rotary apparatus, comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone as shown in FIG. 6 of U.S. application Ser. No. 09/966,509. The dies of the compression module are filled using vacuum assistance, with mesh screen filters located in die wall ports of each die.

Second portions are transferred from the compression module to the thermal cycle molding module via a transfer device. The transfer device has the structure shown as 300 in FIG. 3 of copending U.S. application Ser. No. 09/966,414, described at pages 51-57, incorporated herein by reference. 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. 09/966,414. The transfer device rotates and operates in sync with the thermal cycle molding module and compression module to which it is coupled. Transfer units 304 comprise retainers 330 for holding the second portions as they travel around the transfer device.

Next, first portions are produced and joined to the second portions in the thermal cycle molding module, which has the general structure shown in FIG. 3 of copending U.S. application Ser. No. 09/966,497. 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 of pending U.S. application Ser. No. 09/966,497) for holding the material for making the first portions in flowable form. 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 of U.S. application Ser. No. 09/966,497 depict the temperature control system 600.

The thermal cycle molding module has the specific configuration shown in FIG. 26A of copending U.S. application Ser. No. 09/966,497. The thermal cycle molding module comprises center mold assemblies 212 and upper mold assemblies 214 as shown in FIG. 26C of copending
U.S. application Ser. No. 09/966,497, which mate to form mold cavities. As rotor 202 rotates, second portions are loaded into the center mold assemblies, and the opposing center and upper mold assemblies close. Flowable material for making the first portions, which is heated to a flowable state in reservoir 206, is injected into the resulting mold cavities, which contain an empty space adjacent to the second portions. First portions form in the empty space. The temperature of the flowable material is then decreased, hardening the flowable material into first portions joined to the compressed second portions. The mold assemblies open and eject the dosage forms.

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 this invention.

1. A dosage form comprising at least one active ingredient, a first portion comprising a first molded material, and a second portion comprising a second material which is compositionally different from the first material, wherein the first and second portions are joined at an interface, and a surface of the first portion at the interface resides substantially conformally upon a surface of the second portion at the interface.

2. The dosage form of claim 1, wherein the first portion comprises a thermoplastic material.

3. The dosage form of claim 1, wherein the first molded material is substantially free of pores having a diameter of 0.5 to 5.0 microns.

4. The dosage form of claim 1, wherein the first portion comprises a foam.

5. The dosage form of claim 1, wherein the first portion comprises an aerated material.

6. The dosage form of claim 1, in which the active ingredient is coated with a release-modifying coating.

7. The dosage form of claim 1, in which the first and second portions are in substantial contact at the interface.

8. The dosage form of claim 1, in which the interface is in the form of an abutment.

9. The dosage form of claim 1, in which the first and second portions overlap at the interface.

10. The dosage form of claim 1, in which the first and second portions interlock at the interface.

11. The dosage form of claim 1, in which the first and second portions dissipate upon immersion in aqueous media.

12. The dosage form of claim 1, further comprising a third portion, which is located between the first and second portions.

13. The dosage form of claim 12, in which the third portion comprises a chemical reaction product of the first and second materials.

14. The dosage form of claim 12, in which the third portion is impermeable to one or more active ingredients contained in the dosage form.

15. The dosage form of claim 12, in which the third portion is impermeable to water.

16. The dosage form of claim 12, in which the third portion acts as a barrier to the passage therethrough of one or more active ingredients contained in the first or second portions.

17. The dosage form of claim 12, in which the third portion functions to control the passage of one or more active ingredients contained in the first or second portions.

18. The dosage form of claim 12, in which the third portion comprises openings which allow the passage of one or more active ingredients therethrough.

19. The dosage form of claim 12, in which the third portion comprises a microelectronic device.

20. The dosage form of claim 1, in which the first and second portions have different colors.

21. The dosage form of claim 1, in which the first and second portions have different opacities.

22. The dosage form of claim 1, in which the first and second portions have different solubilities in acidic, alkaline or neutral aqueous media.

23. The dosage form of claim 1, in which the first and second portions have different dissolution rates in acidic, alkaline or neutral aqueous media.

24. The dosage form of claim 1, in which the first and second portions have different disintegration times in acidic, alkaline or neutral aqueous media.

25. The dosage form of claim 1, in which the first and second portions have different hydrophilicities.

26. The dosage form of claim 1, in which the first and second portions have different topographies.

27. The dosage form of claim 1, in which the first and second portions have different elasticities.

28. The dosage form of claim 1, in which the first and second portions have different plasticities.

29. The dosage form of claim 1, in which the first and second portions have different tensile strengths.

30. The dosage form of claim 1, in which the first and second portions have different crystallinities.

31. The dosage form of claim 1, in which the first and second portions each comprise at least one active ingredient, and release active ingredient at different rates.

32. The dosage form of claim 1, wherein the first portion is obtained by injection molding.

33. The dosage form of claim 1, wherein the second portion is a substrate, and the first portion is formed directly upon the first portion.

34. The dosage form of claim 1, in which the first portion comprises at least one active ingredient.

35. The dosage form of claim 1, in which the second portion comprises at least one active ingredient.

36. The dosage form of claim 1, in which both the first and the second portions comprise at least one active ingredient which may be the same or different.

37. The dosage form of claim 1, in which the first portion further comprises an insert.

38. The dosage form of claim 1, in which the first portion further comprises an insert.

39. The dosage form of claim 37, in which the second portion further comprises an insert.

40. The dosage form of claim 1, in which the insert is molded.

41. The dosage form of claim 1, in which at least one active ingredient is capable of dissolution, and dissolution of the active ingredient meets USP specifications for immediate release tablets containing the active ingredient.

42. The dosage form of claim 1, in which the second material is a compressed material.
43. The dosage form of claim 1, in which either the first portion, the second portion or both comprises a microelectronic device.

44. The dosage form of claim 1, in which a shell resides upon the outer surfaces of the first and second portions.

45. The dosage form of claim 1, wherein the surface of the first portion at the interface has indentations and protrusions corresponding substantially inversely to indentations and protrusions on the surface of the second portion at the interface.

46. The dosage form of claim 45, wherein the indentations and protrusions have a length, width, height or depth greater than 10 microns.

47. The dosage form of claim 1, wherein the area of the interface surfaces is at least 50% of the area of a major face of either the first or second portion.

48. The dosage form of claim 1, wherein an entire face of the first portion is in substantial contact with the second portion.

49. The dosage form of claim 1, wherein an entire face of the second portion is in substantial contact with the first portion.

50. The dosage form of claim 1 wherein one face or side of the second portion comprises a cavity, and the first portion is in contact with the entire surface of the cavity.

51. The dosage form of claim 1, wherein at least one exterior surface of the first portion is flush with at least one exterior surface of the second portion.

52. The dosage form of claim 38, in which the insert is molded.

* * * * *