(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 December 2009 (23.12.2009)

PCT

(10) International Publication Number
WO 2009/154810 A2

(51) **International Patent Classification**:
A61K 9/24 (2006.01) *A61P 19/02* (2006.01)
A61K 31/196 (2006.01) *A61P 1/04* (2006.01)
A61K 31/557 (2006.01) *A61K 31/19* (2006.01)

(21) **International Application Number**:
PCT/US2009/035100

(22) **International Filing Date**:
25 February 2009 (25.02.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
463/CHE/2008 25 February 2008 (25.02.2008) IN
61/046,566 21 April 2008 (21.04.2008) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2009/154810 A2

(54) **Title**: DELIVERY SYSTEMS FOR MULTIPLE ACTIVE AGENTS

(57) **Abstract**: Pharmaceutical compositions for the simultaneous delivery of multiple active agents, processes for preparing compositions and methods of using such compositions. The compositions include tablets containing an active agent, contained within a tablet or tablet layer, and optionally contain, or have an external deposit containing, the same or a different active agent. The compositions can deliver chemically incompatible active ingredients having different release profiles, from a single pharmaceutical composition.

DELIVERY SYSTEMS FOR MULTIPLE ACTIVE AGENTS

INTRODUCTION

The present invention relates to pharmaceutical compositions for the simultaneous delivery of multiple active substances. The present invention also provides process of preparation of such compositions, and methods of using them. Further, the invention relates to the delivery of incompatible active having different release profiles, from a single pharmaceutical composition.

The present invention provides stable compositions having reduced active-active and/or active-excipient interactions associated with the simultaneous administration of more than one active agent, or provides simultaneous administration of active agents having different release profiles, or both concomitantly, from a single pharmaceutical composition.

U.S. Patent No. 5,593,696 discloses coating famotidine with an inert material to combine it with sucralfate in a unit dosage form, which otherwise would not be stable. U.S. Patent No. 6,039,974 discloses a pharmaceutical composition for the combination of a therapeutically effective decongestant in a sustained release layer and an antihistaminic amount of a piperidinoalkanol in an immediate release layer; a tablet formulation contains immediate release and delayed release granules. U.S. Patents Nos. 5,601,843 and 5,698,225 disclose a tablet having a core of an NSAID selected from diclofenac and piroxicam, which is surrounded by a mantle coating of a prostaglandin such as misoprostol. European Patent Application No. 1020182 A1 discloses a two-layer pharmaceutical tablet comprising an NSAID and misoprostol. U.S. Patent Nos. 6,183,779 and 6,287,600 disclose solid pharmaceutical compositions comprising a therapeutically effective amount of enterically coated granules of a nonsteroidal anti inflammatory drug (NSAID), an effective anti-ulcerogenic amount of a prostaglandin, and a prostaglandin stabilizer. U.S. Patent No. 6,087,386 discloses use of the bilayer tablet principle for a pharmaceutical composition of enalapril and losartan, wherein each active agent is present in different layers of the tablet. U.S. Patent No. 6,511,680 discloses a tablet containing a non-steroidal anti-inflammatory drug, and misoprostol, wherein the NSAID is in the form of coated pellets. U.S. Patent Application Publication No. 2005/0163847 discloses a solid oral dosage form comprising a first portion of an NSAID and a coating comprising an antiulcerative

compound, wherein the said coating partially surrounds the first NSAID portion. International Application Publication No. WO 2006/099618 discloses a delivery system for multiple actives.

The selection of a suitable dosage form designed for the simultaneous delivery of incompatible active agents poses a particularly strong challenge to the pharmaceutical formulations scientist. Similarly there is a need for development of robust pharmaceutical compositions having incompatible actives in single dosage form, wherein the actives are physically separated.

SUMMARY

The present invention relates to drug delivery systems for the simultaneous delivery of multiple active agents. Further, the invention relates to the delivery of incompatible active agents having different release profiles, from a single pharmaceutical composition.

The present invention provides stable compositions having reduced active-active and/or active-excipient interactions associated with the simultaneous administration of more than one active agent or provides simultaneous administration of active agents having different release profiles, or both concomitantly, from a single pharmaceutical composition.

The present invention further provides robust pharmaceutical compositions having incompatible actives in single dosage form, wherein the actives are physically separated.

Further the invention also relates to processes for preparing the compositions for multiple active agents, and their methods of use, treatment and administration.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a cross-sectional view of a bilayer tablet of the invention, wherein one layer contains an embedded tablet.

Fig. 2 shows a cross-sectional view of a bilayer tablet of the invention, wherein one layer contains an inlaid tablet.

Fig. 3 shows a cross-sectional view a tablet of the invention, containing an embedded tablet and being provided with an indentation, into which a composition is filled.

Fig. 4 shows a cross-sectional view of a bilayer tablet of the invention, one layer having an inlaid tablet that is of the inlaid tablet-in-a-tablet type.

Fig. 5 shows a cross-sectional view of a bilayer tablet, one layer having an embedded tablet-in-a-tablet.

Fig. 6 shows a cross-sectional view of a tablet containing an embedded tablet-in-a-tablet and being provided with an indentation, into which a composition is filled.

DETAILED DESCRIPTION

Aspects of the present invention relate to drug delivery systems for the simultaneous delivery of multiple active agents, different forms of a single active agent, or combinations thereof. Further, the invention relates to the delivery of chemically incompatible active agents having different release profiles, from a single pharmaceutical composition.

Aspects of the present invention further relate to stable compositions having reduced active-active and/or active-excipient interactions associated with the simultaneous administration of more than one active agent, or provide simultaneous administration of active agents having different release profiles, or both concomitantly, from a single pharmaceutical composition.

Aspects of the present invention relate to solid pharmaceutical composition comprising at least two active agents, or comprising a single active agent in two or more different forms, comprising a substrate containing a first active agent present in a first tablet, the first tablet being disposed within a second tablet, and a different active agent or a second form of a first active agent deposited onto one or more areas of a surface of a second tablet, present in a layer or between layers of a second tablet, or both. In an aspect, the compositons comprise diclofenac and misoprostol as the first and second active agents. In another aspect, the compositions further comprise a third active agent, or a different form of a first active agent, that is present in a matrix of a second tablet, deposited on a surface of a second tablet, present in a layer or between layers of a second tablet, or any combination thereof. In another aspect, a said solid pharmaceutical composition comprises a first tablet disposed within a first layer or between two layers of a second tablet, and a different active agent is present in a second layer of a second tablet.

In an aspect, the invention relates to solid dosage forms having the same active agent in more than one form, where the composition of each form releases the active with a different release profile.

In another aspect, the invention relates to solid dosage forms having more than one active agent, placed in more than one portion, where the composition of each portion releases the respective active agent.

Embodiments of the invention may include different active agents having different release profiles.

The terms “drug substance,” “active agent,” and “active” are used interchangeably herein, referring to the pharmacological active compounds and its derivatives, prodrugs, active metabolites, and/or its polymorphs, solvates, hydrates, enantiomers, racemates, salts and mixtures thereof.

The terms “modified release,” “extended release,” “delayed release,” and “controlled release” are used herein, referring to different forms of a drug having release profiles other than immediate release.

In an aspect the invention includes solid dosage forms having a “substrate” or “matrix” that contains at least one active agent (which frequently comprises a larger portion of the dosage forms), the substrate having an indentation or other surface feature that further contains a deposit of one or more active agents.

In an aspect, drug delivery systems are provided in the form of solid compositions comprising at least two layers wherein at least one of the layers contains at least one indentation holding at least one composition comprising a first active agent, and the other layer comprises a second active agent.

“Indentation” or “surface feature” as used herein refers to any one or more depressions or recessed areas on the surface of at least one of the layers of a tablet and/or tablet-in-tablet, which can hold an active agent. An indentation generally will not extend completely through the tablet, layer, etc., where it has been formed.

Embodiments of the indentation may include one or more of internal holes, cavities, hollow cores, concavity, recesses, and donut shaped configurations, and notches that do not extend completely through the layer.

"Deposit" as used herein refers to a composition comprising an active agent which is located in an indentation, or at least partially or completely filling the indentation.

Embodiments of the deposit may include one or more of immediate, delayed, extended, or modified release forms of an active agent.

In an aspect the invention includes robust pharmaceutical compositions having incompatible active agents in a single dosage form, wherein the actives are physically separated.

Embodiments of the robust pharmaceutical compositions having incompatible actives may include one or more of following features. For example the dosage form includes solid dosage forms comprising drug delivery systems in the form of tablet-in-tablet, or an inlay tablet, or a tablet-in-(tablet-in-tablet).

Embodiments of the solid dosage forms may include one or more of a single layer, bilayer, or multi-layer arrangement. The solid dosage form can be of any dimension and size, such that it can accommodate an inner tablet and/or inner tablet-in-tablet. Further the inner and/or the outer tablet or tablet-in-tablet or tablet-in-(tablet-in-tablet) (including the finished dosage form), can be coated, uncoated, dispersible, film coated, immediate, modified, or delayed release forms.

"Tablet-in-tablet" or "tablet within a tablet", as used herein refers to an inner tablet placed within an outer tablet, wherein the inner tablet can be placed at any position within the outer tablet.

"Tablet-in-(tablet-in-tablet)" as used herein refers to an inner tablet being placed within an outer tablet such that the inner tablet is in the form of a "tablet-in-tablet," or "tablet within a tablet", which can be placed at any position within the outer tablet.

"Inlay tablet" or "inlaid tablet" as used herein refers to an inner tablet placed within an outer tablet, such that after the outer tablet is formed, at least one surface of the inner tablet is exposed to the external environment.

A first tablet is "disposed within" a second tablet if it is completely surrounded by the matrix of the second tablet. A first tablet is "inlaid within" a second tablet if it has an exposed surface, but otherwise is surrounded by the matrix of the second tablet.

In a general embodiment of the present invention, an inner tablet, or inner tablet-in-tablet, may have any geometric form such as but not limited to round,

oval, caplet, oblong, elliptical, triangular, square, rectangular, hexagonal, heptagonal, and polygonal and the like, and may also be presented in any dimensions that fit into the outer tablet dimensions. Inner tablets, or an inner tablet-in-tablet, of the present invention further may be presented as coated, uncoated, dispersible, film coated, immediate or modified or delayed release forms.

Various aspects of the drug delivery systems of the present invention include, but are not limited to, the embodiments shown in the drawings.

Fig. 1 shows a cross-section of a bilayer tablet **10** comprising first layer **11** and second layer **12,** and inner tablet **13.** The first layer **11** comprises an active agent B. The inner tablet **13** comprising an active agent A is disposed within the second layer which forms one portion of the second layer, and the remaining portion of the second layer comprises a pharmacologically inert material and/or another active agent C.

Fig. 2 shows a cross-section of a bilayer tablet **20** having first layer **21** and second layer **22,** and an inner tablet **23** comprising an active agent A inlaid in the second layer. The first layer **21** comprises an active agent B, and the second layer **22** comprises a pharmacologically inert material and/or another active agent C.

Fig. 3 shows a cross-section of a tablet **30** comprising outer tablet **31** optionally comprising an active agent C that contains inner tablet **32** comprising an active agent A and the outer tablet is provided with indentation **33** into which a composition **34** comprising an active agent B is deposited.

Fig. 4 shows a cross-section of a tablet formulation **40,** comprising an inner tablet **41** comprising an active agent A, inlaid within a tablet **42,** which itself is inlaid within one layer **43** of a bilayer tablet formed from layer **43** comprising an active agent C and/or a pharmacologically inert material and layer **44** comprising an active agent B and/or a pharmacologically inert material.

Fig. 5 shows a cross-section of a tablet formulation **50,** comprising an inner tablet **51** comprising an active agent A, within tablet **52,** which is placed within one layer of a bilayer tablet formed by layer **53** comprising an active agent C and/or a pharmacologically inert material and layer **54** comprising an active agent B and/or a pharmacologically inert material.

Fig. 6 shows a cross-section of a tablet formulation **60** wherein an inner tablet **61** comprising an active agent A is contained within tablet **62**, and tablet **62**

is contained within outer tablet **63** that is provided with an indentation **64** into which a composition **65** containing an active agent B is deposited. Tablet **62** comprises another active agent C that is compatible with both the active agents A and B and/or a pharmacologically inert material.

In an embodiment the invention relates to tablet-in-tablet formulations, comprising: a) an inner tablet comprising first active agent A; b) an outer tablet in which the inner tablet is present, having at least two layers, wherein a first layer comprises second active agent B which is either incompatible with active agent A or has a different release profile compared to active agent A, or is both incompatible and has a different release profile compared to active agent A, and a second layer comprises pharmacologically inert material and/or an active agent C that is compatible with both active agents A and B; c) wherein an inner tablet is positioned in one layer of an outer tablet that contains pharmacologically inert material and/or an active agent that is compatible with active agent contained in an inner tablet.

In another embodiment the invention related to tablet-in-tablet formulations, comprising: a) an inner tablet comprising diclofenac or pharmaceutically acceptable salts thereof; b) an outer tablet in which the inner tablet is present, having at least two layers, wherein a first layer comprises misoprostol or its pharmaceutically acceptable salts; c) wherein an inner diclofenac tablet is positioned in a second layer comprising pharmacologically inert material.

In another embodiment the invention relates to multi-layer inlay tablets comprising: a) an inner tablet comprising an active agent A; b) a multi-layer tablet comprising at least two layers, wherein a first layer comprises second active agent B which is either incompatible with active agent A or has a different release profile compared to active agent A, or is both incompatible and has a different release profile compared to active agent A, and a second layer comprises pharmacologically inert material and/or an active agent C that is compatible with both active agents A and B; and an inner tablet is positioned in one of the outer layers that comprises pharmacologically inert material and/or an active agent that is incompatible with active agent present in an inner tablet.

In another embodiment the invention relates to bilayer inlay tablets wherein one of the layers comprises an inner tablet, comprising: a) an inner tablet comprising diclofenac or a pharmaceutically acceptable salt; and b) a bilayer

tablet, wherein a first layer comprises misoprostol and a second layer comprises pharmacologically inert material; an inner tablet being positioned in a second layer of a bilayer tablet comprising a pharmacologically inert material.

In another embodiment the invention relates to tablet-in-tablet formulations comprising: a) an inner tablet comprising active agent A; b) an outer tablet comprising at least one indentation wherein an active agent B that is incompatible with, or has a different release profile compared to, active agent A, or is incompatible and has a different release profile compared to active agent A, is deposited; an outer tablet further comprising pharmacologically inert material and/or a third active agent C that is compatible with both A and B.

In another embodiment the invention relates to solid compositions comprising: a) an inner tablet comprising diclofenac or a pharmaceutically acceptable salt; and b) an outer tablet comprising at least one indentation wherein misoprostol or a pharmaceutically acceptable salt is deposited; an outer tablet further comprising pharmacologically inert material and/or a third active agent C that is compatible with both diclofenac and misoprostol.

In another embodiment the invention relates to tablet-in-(tablet-in-tablet) formulations comprising: a) an inner tablet-in-tablet (1) comprising active agent A together with pharmacologically inert material; b) an outer tablet in which the inner tablet-in-tablet (1) is present, having at least two layers, wherein a first layer comprises second active agent B which is either incompatible with active agent A or has a different release profile compared to active agent A, or is both incompatible and has a different release profile compared to active agent A, and a second layer comprises pharmacologically inert material and/or an active agent C that is compatible with both active agents A and B; wherein an inner tablet-in-tablet (1) is placed at any position in one of the layers of an outer tablet that contains a pharmacologically inert material and/or an active agent that is compatible with active agent contained in an inner tablet-in-tablet.

In another embodiment the invention relates to bilayer tablet-in-(tablet-in-tablet) formulations, comprising: a) an inner tablet-in-tablet (1) comprising diclofenac or pharmaceutically acceptable salts thereof together with pharmacologically inert material; and b) an outer tablet in which the inner tablet-in-tablet (1) is present, having at least two layers, wherein a first layer comprises misoprostol or its pharmaceutically acceptable salt; wherein an inner diclofenac

tablet-in-tablet (1) is placed at any position in a second layer comprising a pharmacologically inert material.

In another embodiment the invention relate to tablet-in-(tablet-in-tablet) formulations comprising: a) an inner tablet-in-tablet (1) comprising active agent A together with pharmacologically inert material; and b) an outer tablet comprising at least one indentation wherein an active agent B that is incompatible with or has a different release profile compared to active agent A, or is incompatible and has a different release profile compared to active agent A, is deposited; an outer tablet further comprising a pharmacologically inert material and/or a third active agent C that is compatible with both A and B.

In another embodiment the invention relates to tablet-in-(tablet-in-tablet) compositions comprising: a) an inner tablet-in-tablet (1) comprising diclofenac or a pharmaceutically acceptable salt together with pharmacologically inert material; and b) an outer tablet comprising at least one indentation wherein misoprostol or a pharmaceutically acceptable salt is deposited; an outer tablet further comprising pharmacologically inert material and/or a third active agent that is compatible with both diclofenac and misoprostol.

In general embodiments of the invention there are provided compositions for the simultaneous delivery of two or more incompatible active agents in a stable unit dose composition.

Stability of pharmaceutical compositions may be defined as the capability of a particular dosage form, in specified packaging, to maintain its physical, chemical, microbiological, therapeutic and toxicological specifications during a period of storage and use. Stability of pharmaceutical compositions may be affected by several factors, including the chemical stability of the active, active-active interactions, and active-excipient incompatibility.

In general aspects the invention relates to delivery system for multiple actives. The multiple actives or drugs that can be used include, but are not limited to, the following classes of compounds: non-steroidal anti-inflammatory drugs (NSAIDs) such as: propionic acid derivatives like ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen and fluprofen; acetic acid derivatives like tolmetin sodium, zomepirac, sulindac and indomethacin; fenamic acid derivatives like mefenamic acid and meclofenamate sodium; biphenylcarboxylic acid derivatives like diflunisal and flufenisal; oxicams like

piroxicam, sudoxicam and isoxicam; benzeneacetic acid derivatives like diclofenac; COX-2 inhibitors like celecoxib and rofecoxib; ulcer protective prostaglandins or their analogues such as misoprostol, carboprost, ornoprostil, dinoprost, gemeprost, metenoprost, sulprostone and tiaprost; bronchodilators like guaiphenesin; anti-tussitives such as dextromethorphan, codeine and pholcodine; opoid analgesics like naltrexone; HMG CoA reductase inhibitors such as atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, pitvastatin, fluindostatin, mevastatin, velostatin and dalvastatin; biguanides such as metformin, phenformin and buformin; sulfonylureas such as acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, gliclazide, glibornuride, glisoxepide, tolazamide, phenbulamide and tolcyclamide; other classes of antidiabetic agents including glitazones such as rosiglitazone, troglitazone and pioglitazone, glucosidase inhibitors such as acarbose and meglitol, and meglitinides such as nateglinide and repaglinide; lipid lowering agents such as fibrates including clofibrate, gemfibrozil, fenofibrate and fenofibric acid; triptans such as sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, and frovatriptan; ACE inhibitors such as captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, and fosinopril; calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, cinalong, clevidipine, efonidipine, felodipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, verapamil, gallopamil, diltiazem, mibefradil, bepridil, and fluspirilene; angiotensin II receptor antagonists such as losartan, irbesartan, olmesartan, candesartan, valsartan, and telmisartan; diuretics such as furosemide, ethacrynic acid, torsemide, bumetanide, hydrochlorothiazide, spironolactone, potassium canreonate, amiloride, and triamterene; dopamine and its derivatives such as levodopa, droxidopa, melevodopa, and etilevodopa; DOPA decarboxylase inhibitors such as carbidopa and benserazide; catechol-O-methyl transferase (COMT) inhibitors such as entacapone; renin inhibitors such as aliskiren; angiotensin II receptor antagonist such as eprosartan; and immunosuppressants including purine synthesis inhibitor such as azathioprine, mycophenolic acid; pyrimidine synthesis inhibitor such as leflunomide, teriflunomide; antifolate such as methotrexate; macrolides such as tacrolimus,

ciclosporin or cyclosporin, pimecrolimus; mTOR inhibitors such as sirolimus, deforolimus, everolimus, temsirolimus, zotarolimus.

Embodiments of the delivery system for multiple actives include but are not limited to specific combinations like: olmesartan with amlodipine and hydrochlorothiazide; entacapone with carbidopa and levodopa; diclofenac with misoprostol; amlodipine with atorvastatin; naproxen with sumatriptan; amlodipine with benazepril, hydrochlorothiazide in combination with one or more of telmisartan, quinapril, aliskiren hemifumarate, amiloride, enalapril, eprosartan mesylate, valsartan with amlodipine; sirolimus in combination with one or more of , azathioprine, mycophenolic acid, leflunomide, teriflunomide, methotrexate, tacrolimus, ciclosporin or cyclosporin, pimecrolimus, deforolimus, everolimus, temsirolimus, and zotarolimus and other similar combinations.

It is to be understood that the invention is not limited to the specific actives or drugs mentioned above or the specific combinations discussed in the embodiments.

The “inert material” or “inert substance” as used herein refers to pharmaceutically acceptable excipients. Examples of pharmaceutically acceptable excipients as used herein include diluents or fillers, binders, antioxidants, disintegrants, surfactants, lubricants and glidants, etc.

Suitable diluents or fillers include, but are not limited to, one or more of microcrystalline celluloses (MCC), silicified MCC (e.g. Prosolv™ HD 90), microfine celluloses, lactose, starch, corn starch, pregelatinized starches, calcium carbonate, calcium sulfate, sugar, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, and the like.

Suitable binders include one or more of povidone, starch, corn starch, pregelatinized starch, microcrystalline cellulose (MCC), silicified MCC (e.g., Prosolv™ HD 90), microfine cellulose, lactose, calcium carbonate, calcium sulfate, sugar, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, stearic acid, gums, hydroxypropylmethyl celluloses, and the like.

Suitable antioxidants include one or more of ascorbic acid, sodium pyrosulphite, glutathion, sorbic acid, butylatedhydroxytoluene (BHT), propyl

gallate, butylatedhydroxyanisole (BHA), vitamin E , vitamin E TPGS and derivatives thereof (e.g., the commercially available Speziol® TPGS Pharma supplied by Cognis GmbH.), citric acid, and the like.

Suitable disintegrants include one or more of methyl celluloses, microcrystalline celluloses, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium (e.g. Ac-Di-Sol®, Primellose®), crospovidones (e.g. Kollidon®, Polyplasdone®), povidones, such as the K-30 grade, guar gum, magnesium aluminum silicate, colloidal silicon dioxide (Aerosil®), polacrilin potassium, starch, pregelatinized starch, sodium starch glycolate (Explotab®), sodium alginate and the like.

Suitable surfactants include one or more of anionic, non-ionic or cationic surfactants. Useful surfactants are exemplified by, but not limited to, one or more of polyoxyethylene hardened castor oil, glycerin monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurate, polyoxyethylene-polyoxypropylene block copolymers, polysorbates, sodium lauryl sulfate, macrogols, sucrose fatty acid ester, and the like.

Suitable lubricants include one or more of magnesium stearate, zinc stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil, and the like.

Suitable glidants include one or more of colloidal silicon dioxide, talc and corn starch, and the like.

In general aspect the invention relates to delivery system for multiple actives, where in one or more active is having a modified release profile. The release of active agent into aqueous media can be modified by incorporating rate controlling agents including, but not limited to: water soluble polymers of various grades such as celluloses such as methylcelluloses, carboxymethyl celluloses, hydroxypropyl methylcelluloses (HPMC or hypromellose), cross-linked sodium carboxymethyl celluloses and cross-linked hydroxypropyl celluloses; carboxymethylamides; potassium methacrylate/divinylbenzene copolymers; polymethylmethacrylates; polyhydroxyalkyl methacrylates; cross-linked polyvinylpyrrolidones (PVP or povidone); gums such as agarose, gum arabic, gum ghatti, gum karaya, gum tragacanth; hydrophilic colloids such as alginates; other substances such as arbinoglactan, pectin, amylopectin, N-vinyl lactams, polysaccharides; and the like.

Water-insoluble substances or combinations thereof in various ratios can be used for coating compositions and are exemplified by, but are not limited to: oils; waxes such as beeswax, carnauba wax, and microcrystalline wax; fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol, and myristyl alcohol; fatty acid esters such as glyceryl monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, and glyceryl behenate; celluloses such as ethyl cellulose, low substituted hydroxypropyl celluloses (L-HPC), cellulose acetates, and their derivatives, cellulose acetate phthalates, hydroxylpropyl methylcellulose phthalates, cellulose acylates, cellulose diacylates, cellulose triacylates, cellulose acetates, cellulose diacetates, cellulose triacetates, mono-, di- and tri-cellulose alkanylates, mono-, di-, and tri-cellulose arylates, and mono-, di- and tri-cellulose alkenylates; polymers, including polymethacrylic acid based polymers and copolymers sold using the trademark EUDRAGIT (Eudragit RL and RS, NE-30D); zein; aliphatic polyesters; copolymers of the above polymers; or mixtures of any two or more in various ratios and proportions as required are within the scope of this invention without limitation. Of course, any other polymer, which aids in modulated release, is also acceptable in the practice of this invention. These agents alone or in combination with different classes of rate controlling substances are used to control the release of the active agent substances by matrix or reservoir or combination principles.

Embodiments related to modified release drug may include one or more aqueous or non-aqueous enteric coating that can optionally be used to aid in controlling the release of the active. The enteric coating aids in the prevention of an acid labile active agent with the acidic gastric juices after oral administration as well as providing direct delivery of the active agent in the lower gastro-intestinal tract rather than in the stomach.

Suitable enteric-coating polymers include but are not limited to the different grades of anionic polymers of methacrylic acid and methacrylates such as but not limited to Eudragit L100-55, spray dried Eudragit L30D-55, Eudragit L30D-55, Eudragit L100, Eudragit S100 and Eudragit FS30D.

Suitable plasticizers for coatings include materials such as acetyl alkyl citrates, phosphate esters, phthalate esters, amides, mineral oils, fatty acids and esters thereof with polyethylene glycol, glycerin, triacetin or sugars, fatty alcohols,

ethers of polyethylene glycol and vegetable oils. Useful fatty alcohols include cetostearyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol and myristyl alcohol.

Pharmaceutical coating compositions for tableting and film formation may further include but are not limited to pharmaceutically acceptable glidants, lubricants, flavoring agents, opacifiers, colorants and other commonly used excipients.

Further the invention also relates to processes for preparing the compositions having multiple actives. Certain compositions for multiple actives of the present invention are manufactured as described below.

In one general aspect there is provided a process of preparing compositions for multiple actives, wherein a substrate (containing at least one active) has an indentation that contains a deposit of one or more active.

Embodiments of processes for preparing compositions having multiple actives include separately preparing granules of each of the immediate release or controlled release or delayed release or sustained release actives by sifting the actives and excipients through a sieve and then mixing using a rapid mixer granulator, planetary mixer, mass mixer, ribbon mixer, fluid bed processor, or any other suitable device. The blend can be granulated, such as by adding a solvent like water, isopropyl alcohol, acetone, ethanol, dichloromethane, and the like and combinations thereof, or by adding a solution of a binder in any solvents described above in a low or high shear mixer, fluidized bed granulator and the like or by dry granulation. Granulate can be dried using a tray drier, fluid bed drier, rotary cone vacuum drier and the like. The sizing of the granules can be done using an oscillating granulator, comminuting mill or any other conventional equipment equipped with a suitable screen. Alternatively, granules can be prepared by extrusion and spheronization or roller compaction. The dried granulate particles are sieved, and then mixed with lubricants and disintegrants and compressed into a layered tablet having at least one indentation not extending through a layer.

In an alternative embodiment, the granules of the immediate release or controlled release or delayed release or sustained release actives can be made by mixing the directly compressible excipients or by roller compaction. The blend so obtained is compressed using a suitable device, such as a multi-station rotary machine to form slugs, which are passed through any of a multimill, fluid energy

mill, ball mill, colloid mill, roller mill, hammer mill, and the like, equipped with a suitable screen. The milled slugs of the immediate release or controlled release or delayed release or sustained release actives are then blended with a lubricant and compressed into a layered tablet having at least one indentation not extending through a layer.

Embodiments of processes for preparing compositions having multiple actives can include depositing of an active agent into indentations by compression coating, or may be accomplished by techniques known to one skilled in the art like spray coating, pouring active agent in solution or suspension or dispersion form in a volatile solvent into the indentation and allowing the solvent to evaporate, leaving the active agent intact in the indentations, pouring active agent in a solution or suspension or dispersion in a molten waxy material and allowing the same to solidify, leaving the active agent along with waxy material intact in the indentations, and the like, such that indentations will be at least partially or completely filled with the active.

Embodiments of processes for preparing compositions having multiple actives can include one or more of the steps of: a) embedding an enteric coated diclofenac tablet into a pharmacologically inert tablet matrix having an indentation; and b) filling the said indentation with a misoprostol deposit.

Various solvents can be used in the processes for preparation of pharmaceutical compositions of the present invention, including but not limited to water, methanol, ethanol, acidified ethanol, acetone, diacetone, polyols, polyethers, oils, esters, alkyl ketones, methylene chloride, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulphoxide, N,N-dimethylformamide, tetrahydrofuran and mixtures thereof.

In a general aspect there are provided processes for preparing robust pharmaceutical compositions having multiple actives, wherein the pharmaceutical compositions comprise drug delivery systems in the forms of a tablet-in-tablet, or an inlay tablet-in-(tablet-in-tablet), or a bilayer tablet-in-(tablet-in-tablet), or a tablet-in-(tablet-in-tablet) having at least one indentation comprising another active.

Embodiments of processes for preparing robust pharmaceutical compositions having multiple actives include one or more of the following: the dosage form can be made by compressing tablets of one active A, which can optionally be film coated, enteric coated or given a modified release coating; the tablet A can be placed into one of the layers of a bilayer tablet, wherein the other layer has another active B; the tablet can be placed at any position of the inert layer so as to obtain an inlay tablet or a conventional tablet-in-tablet; and the composition can further have active C which is compatible with both actives A and B.

Alternatively, the tablet of active A can be processed into a tablet-in-tablet (1), dosage form along with inert excipients, which can be placed into one of the layers of a bilayer tablet, wherein the other layer has another active B. The tablet-in-tablet (1) can be placed at any position of the inert layer so as to obtain an inlay tablet-in-(tablet-in-tablet) or a conventional tablet-in-(tablet-in-tablet). The composition can further have active C which is compatible with both actives A and B.

Embodiments of processes for preparing compositions having multiple actives include one or more of the steps of: a) pre-compressing a pharmacologically inert layer; b) placing an enteric coated diclofenac tablet at any position in the inert layer; c) optionally pre-compressing the tablet-containing inert layer; and d) compressing a misoprostol layer.

The compositions of the present invention may be administered to humans or animals for treatment of conditions or diseases of one or more organ systems.

In an embodiment, the composition of the present invention comprises diclofenac as one active agent and misoprostol as a second active agent, and may be administered for the treatment of signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications.

The following examples are provided solely to further illustrate certain specific aspects and embodiments of the invention in greater detail, and are not intended to limit the scope of the invention in any manner.

EXAMPLE 1: Formulation containing diclofenac and misoprostol.

I) Diclofenac tablet composition:

Ingredient	mg/Tablet
Core Tablet	
Diclofenac sodium	75
Microcrystalline cellulose (Avicel® PH101)	20
Corn starch	15
Lactose monohydrate	20
Polyvinylpyrrolidone (PVP K30)	3.6
Magnesium stearate	1.4
Water*	30
Subcoating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	2.7
Isopropyl alcohol*	36
Water*	24
Enteric Coating	
Eudragit® L30D55	4.27
Talc	0.5
Triethyl citrate	0.43
Sodium hydroxide	0.06
Water*	20
Inert Matrix	
Microcrystalline cellulose (Avicel® PH102)	250
Lactose monohydrate (Tablettose® 80)	215
Polyvinylpyrrolidone (PVP K-30)	10
Sodium starch glycolate	25
Seal Coating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	10.98
Isopropyl alcohol*	132
Water*	88
Film Coating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	10.98
Polyethylene glycol (PEG 400)	1.09
Titanium dioxide	1.34

Isopropyl alcohol*	60.3
Water*	60.3

* Evaporates during processing.

Manufacturing process:

A. Core Tablet:

1) Diclofenac sodium, lactose monohydrate, microcrystalline cellulose and starch were co-sifted through an ASTM #20 mesh sieve and blended.

2) Povidone® K-30 was dissolved in water to prepare binder solution.

3) The material of step (1) was granulated with the material of step (2).

4) Wet granules obtained from step (3) were dried in a rapid drier until loss on drying was less than about 3% w/w.

5) Materail of step (4) was sifted through an ASTM #30 mesh sieve.

6) Magnesium stearate was sifted through an ASTM #60 mesh sieve and blended with granules of step (5).

7) Step (6) blend was compressed into core tablets using 7 mm round standard concave punches.

B. Subcoating:

1) HPMC 5 cps was dissolved in isopropyl alcohol and water.

2) Core tablets containing diclofenac sodium were coated with the solution of step (1) to obtain a weight buildup of about 2% w/w.

C. Enteric Coating:

1) Eudragit® L30 D55 was dispersed in water.

2) Sodium hydroxide was added to dispersion of step (1).

3) Talc and triethyl citrate were homogenized using small quantity of water.

4) Material of step (3) was added to material of step (2) and stirred.

5) Sub-coated tablets of step (2) of 'B' were coated with the enteric coating dispersion of step (4) to obtain a weight gain of about 5% w/w.

D. Final Tablet:

1) Avicel® PH 102, Tablettose® 80, povidone and sodium starch glycolate were co-sifted through an ASTM #40 mesh sieve and blended with magnesium stearate to obtain an 'Inert matrix'.

2) Tablet-in-tablet compression was done by using a press coat machine with the following parameters:

Lower Punch: 12 mm, round, standard concave.

Upper Punch: 12 mm, round with central projection.

Die: 12 mm.

Machine was set with a special feed frame. A first layer of inert matrix material of step (1) of 'D' was filled in the die cavity followed by an enteric coated diclofenac tablet of step (5) of 'C' and finally a second layer of inert matrix material of step (1) of 'D'. The combination was compressed to form a final tablet. Compression force and weight of the final tablet were adjusted so that integrity of the inner tablet was not affected.

E. Seal Coating:

1) HPMC 5 cps was dissolved in isopropyl alcohol and water.

2) Final tablets were coated with the solution of step (1) of 'E' to obtain a weight build up of about 3% w/w.

F. Film Coating:

1) HPMC 5 cps was dissolved in isopropyl alcohol and water.

2) Titanium dioxide was dispersed in water and added to the material of step (1).

3) Polyethylene glycol 400 was added to the dispersion of step (2).

4) Seal coated tablets of step (2) of 'E' were coated with the dispersion of step (3) to obtain a weight build up of about 2% w/w.

II) Misoprostol composition:

Ingredient	mg/Tablet
Misoprostol	0.2
Polyvinylpyrrolidone (PVP K-30)	20
Methanol*	q.s.
Ethyl Acetate*	q.s.

* Evaporates during processing.

Manufacturing process:

1) PVP K-30 was dissolved in a mixture of methanol and ethyl acetate (75:25 v/v).

2) Misoprostol was dissolved in the solution of step (1).

III) Final manufacturing:

1) Diclofenac sodium tablets from step (4) of 'F' were placed on the trays of a Gilson 215 liquid handler.

2) Based on the concentration of the misoprostol solution, a 58 µL volume of misoprostol solution from step (2) of 'II' was filled into each cup shaped cavity of the diclofenac sodium-containing tablets.

3) Misoprostol-filled tablets of step (2) of 'III' were placed in a tray dryer for about 3 hours at 40°C for drying of the solution.

EXAMPLE 2: Formulation containing diclofenac and misoprostol.

I) Diclofenac tablets:

Ingredient	mg/Tablet
Core	
Diclofenac sodium	75
Microcrystalline cellulose (Avicel® PH101)	20
Corn starch	15
Lactose monohydrate	20
Polyvinylpyrrolidone (PVP K-30)	3.6
Magnesium stearate	1.4
Water*	30
Enteric Coating	
Eudragit® L30D55	4.27
Talc	0.5
Triethyl citrate	0.43
Sodium hydroxide	0.06
Water*	20
Pharmacologically Inert Matrix	
Avicel® PH102	250
Lactose monohydrate (Tablettose® 80)	215
Polyvinylpyrrolidone (PVP K-30)	10
Sodium starch glycolate	25
Seal Coating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	19.5
Isopropyl alcohol*	132

Water*	88
Film Coating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	10.98
Polyethylene glycol 400	1.09
Titanium dioxide	1.34
Isopropyl alcohol*	60.3
Water*	60.3

* Evaporates during processing.

Manufacturing process: similar to that of 'I' of Example 1, except the sub-coating layer i.e. 'I (B)' is excluded.

II) Misoprostol composition: composition and manufacturing process similar to that of 'II' in Example 1.

III) Final manufacturing: similar to that of 'III' in Example 1.

EXAMPLE 3: Bilayer tablet-in-tablet formulation containing diclofenac and misoprostol.

Ingredient	**mg/Tablet**
Core	
Diclofenac sodium	75
Microcrystalline cellulose (Avicel® PH 101)	22.3
Crosscarmellose sodium	6.8
Lactose monohydrate	22.4
Polyvinylpyrrolidone (PVP K30)	7.2
Magnesium stearate	1.3
Water*	q.s.
Subcoating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	2.7
Isopropyl alcohol*	q.s.
Water*	q.s.
Enteric Coating	
Eudragit® L30D55	4.27
Talc	2.13

Triethyl citrate	0.43
Sodium hydroxide	0.06
Water*	q.s.
Misoprostol Layer	
Misoprostol premix ₸	20
Microcrystalline cellulose (MCC RQ102)	133
Crospovidone	5.6
Colloidal silicon dioxide (Aerosil® 200)	0.29
Hydrogenated castor oil	1.15
Inert Layer I	
Silicified microcrystalline cellulose (Prosolv® HD90)	123.2
Silicified microcrystalline cellulose (Prosolv® 50)	32
Croscarmellose sodium	3.2
Sodium stearyl fumarate	1.6
Iron oxide red/yellow	0.08
Inert Layer II	
Silicified microcrystalline cellulose (Prosolv® HD90)	123.2
Silicified microcrystalline cellulose (Prosolv® 50)	32
Croscarmellose sodium	3.2
Sodium stearyl fumarate	1.6

* Evaporates during processing.

₸ Misoprostol premix is a dispersion having a weight ratio of 1:100 for misoprostol to HPMC, and is supplied by Johnson Matthey Pharmaceutical Materials, Ireland.

Manufacturing process:

A. Core Tablets:

1) Diclofenac sodium, lactose monohydrate, microcrystalline cellulose and croscamellose sodium were co-sifted through an ASTM #20 mesh sieve and mixed.

2) PVP K-30 was dissolved in water to prepare binder solution.

3) Blend of step (1) was granulated with binder solution of step (2).

4) Wet granules were dried in a rapid drier until loss on drying was about less than 3% w/w.

5) Granules of step (4) were sifted through an ASTM#30 mesh sieve.

6) Magnesium stearate was sifted through an ASTM #60 mesh sieve and blended with granules of step (5).

7) Blend of step (6) was compressed into tablets using 7 mm round standard concave punches.

B. Subcoating:

1) HPMC 5 cps was dissolved in a mixture of isopropyl alcohol and water.

2) Core tablets containing diclofenac sodium were coated with the solution of step (1) to produce a weight build-up of about 2% w/w.

C. Enteric Coating:

1) Eudragit® L30 D55 was dispersed in water.

2) Sodium hydroxide was added to the dispersion of Eudragit® L30 D55.

3) Talc and triethylcitrate were homogenized for about 5 minutes using a small quantity of water.

4) The mixture of 3) was added into the Eudragit® L30D55 dispersion of 2) and stirred for 10 minutes.

5) Subcoated tablets were coated with the enteric coating dispersion to produce a weight gain of 5% w/w.

D. Misoprostol Layer:

1) Misoprostol premix was mixed and co-sifted with MCC RQ 102 geometrically through a #20 mesh sieve and transferred to a double cone blender.

2) Crospovidone and Aerosil were co-sifted through a #20 mesh sieve and added to step 1) ingredients.

3) Hydrogenated castor oil was sifted through a #60 mesh sieve and added to the step 2) mixture.

4) The mixture was blended.

E. Inert Layers I and II:

1) Prosolv HD 90, silicified microcrystalline cellulose 50, and croscarmellose sodium were co-sifted through a #20 mesh sieve.

2) Sodium stearyl fumarate was sifted through a #60 mesh sieve and combined with step 1) ingredients.

3) For Inert layer I, iron oxide was sifted through a #80 mesh sieve and added to step 2).

4) The mixture was blended for 10 minutes in a double cone blender.

F. Bilayer Tablet Compression:

A bilayer tablet in tablet in was compressed using 11.8 mm round standard concave punches.

A first layer comprising misoprostol and excipients was compressed, an inert Layer I was subsequently filled in the die cavity followed by an enteric coated diclofenac tablet of step (5) of 'C', and finally inert layer II was added and compressed. The combination was compressed to form a final bilayer tablet-in-tablet. Compression force and weight of the final tablet were adjusted so that integrity of the inner tablet was not affected.

The compression was done using compression machine having various attachments like mechanical transfer arm, and change parts for tablet-in-tablet.

EXAMPLE 4: Bilayer inlay tablet-in-tablet formulation containing diclofenac and misoprostol.

The composition is similar to Example 3, and the enteric coated diclofenac tablet is placed as an inlay tablet-in-tablet (i.e. such that at least one surface of the inner diclofenac tablet is exposed to the external environment).

EXAMPLE 5: Bilayer tablet-in-tablet formulation containing sumatriptan and naproxen.

Ingredient	mg/Tablet
Core	
Sumatriptan succinate	85
Microcrystalline cellulose (Avicel PH101)	85
Crosscarmellose sodium	6.8
Lactose anhydrous	45

Polyvinylpyrrolidone K30	7.2
Magnesium stearate	1.5
Water*	q.s
Subcoating	
Hydroxypropyl methylcellulose (HPMC 5 cps)	5.5
Isopropyl alcohol*	q.s
Water*	q.s
Naproxen Layer	
Naproxen sodium	500
Microcrystalline cellulose	52
Povidone	23.5
Colloidal silicon dioxide 200	0.29
Talc	1.15
Inert Layer I	
Silicified microcrystalline cellulose (Prosolv HD90)	52
Croscarmellose sodium	13.2
Magnesium stearate	1.6
Inert Layer II	
Silicified microcrystalline cellulose (Prosolv HD90)	52
Croscarmellose sodium	13.2
Magnesium stearate	1.6

* Evaporates during processing.

Manufacturing process: similar to that described in Example 3.

EXAMPLE 6: Tablet-in-(tablet-in-tablet) formulation containing entacapone with carbidopa and levodopa.

Ingredient	**mg/Tablet**
Core Tablet	
Entacapone	200
Microcrystalline cellulose (Avicel® PH101)	80

Crosscarmellose sodium	10
Mannitol	65
Polyvinylpyrrolidone (PVP K30)	7.2
Magnesium Stearate	1.3
Water*	q.s
Inert I	
Silicified microcrystalline cellulose (Prosolv® HD90)	85
Croscarmellose sodium	22
Magnesium stearate	2.6
Carbidopa Granules	
Carbidopa	12.5
Corn starch	2.5
Polyvinylpyrrolidone (PVP K30)	2.5
Water*	q.s
Microcrystalline cellulose	25
Croscarmellose sodium	5
Hydrogenated castor oil	1.15
Levodopa Granules	
Levodopa	50
Corn starch	5
Polyvinylpyrrolidone (PVP K30)	7
Water*	q.s
Microcrystalline cellulose	50
Silicified microcrystalline cellulose (Prosolv® HD90)	50
Croscarmellose sodium	12
Hydrogenated castor oil	1.15

* Evaporates during processing.

Manufacturing process:

A. Core Tablets:

1) Entacapone, microcrystalline cellulose, crosscarmellose sodium, and mannitol were co-sifted through a #40 mesh sieve and mixed.

2) PVP K30 was dissolved in water to prepare a binder solution.

3) Blend of step (1) was granulated with binder solution of step (2).

4) Wet granules were dried in a rapid drier until loss on drying was about less than 3% w/w.

5) Granules of Step (4) were sifted through a sieve.

6) Magnesium stearate was sifted through an ASTM#60 mesh sieve and blended with granules of step (5).

7) Tablets were compressed from the blend of step (6).

B. Tablet-in-tablet (1):

1) Prosolv® HD90 and croscarmellose sodium were co-sifted through an ASTM #20 mesh sieve.

2) Magnesium stearate was sifted through an ASTM #60 mesh sieve and combined with step (1) ingredients.

3) The mixture was blended for 10 minutes.

4) The blend of step (3) and an entacapone tablet were compressed together as a tablet-in-tablet (1).

C. Carbidopa granules:

1) Carbidopa was mixed and co-sifted with corn starch geometrically through an ASTM #20 mesh sieve.

2) The blend of step (1) was granulated using PVP K30 binder solution in water.

3) The granules were sifted through a sieve and dried,

4) The granules of step (3) were mixed with MCC and croscarmellose sodium.

5) The mixture of (4) was blended with hydrogenated castor oil.

D. Levodopa granules:

1) Levodopa was co-sifted with corn starch geometrically through an ASTM #20 mesh sieve, and blended.

2) The blend of step (1) was granulated using PVP K30 binder solution in water.

3) The granules were sifted through a sieve and dried,

4) The granules of step (3) were mixed with MCC and croscarmellose sodium.

5) The mixture was blended with hydrogenated castor oil.

E. Compression:

The compression was done in following sequence to obtain a bilayer tablet-in-(tablet-in-tablet): the levodopa granules layer was compressed, followed by pre compression of half of the total quantity of carbidopa granules; an entacapone containing core tablet was placed into the die cavity, followed by addition of the remaining half of the carbidopa granules and then final compression.

The compression was done using compression machine having various attachments like a mechanical transfer arm, and change parts for tablet-in-tablet manufacturing.

CLAIMS:

1. A solid pharmaceutical composition comprising at least two active agents, or comprising a single active agent in two or more different forms, comprising a substrate containing a first active agent present in a first tablet, a first tablet being disposed within a second tablet, and a different active agent or a second form of a first active agent deposited onto one or more areas of a surface of a second tablet, present in a layer or between layers of a second tablet, or both.

2. The solid pharmaceutical composition of claim 1, containing a single active agent.

3. The solid pharmaceutical composition of claim 1, further comprising a third active agent, or a different form of a first active agent, that is present in a matrix of a second tablet, deposited on a surface of a second tablet, present in a layer or between layers of a second tablet, or any combination thereof.

4. The solid pharmaceutical composition of claim 3, containing a single active agent.

5. The solid pharmaceutical composition of claim 1, wherein a first tablet is disposed within a first layer or between layers of a second tablet, and a different active agent is present in a second layer of a second tablet.

6. The solid pharmaceutical composition of claim 5, wherein a first layer has a pharmacologically inert matrix.

7. The solid pharmaceutical composition of claim 1, wherein a first tablet is inlaid within a first layer of a second tablet, and a different active agent is present in a second layer of a second tablet.

8. The solid pharmaceutical composition of claim 7, wherein a first layer has a pharmacologically inert matrix.

9. The solid pharmaceutical composition of claim 1, wherein a second tablet has a pharmacologically inert matrix and a different active agent or a second form of a first active agent is deposited onto one or more areas of a surface of a second tablet.

10. The solid pharmaceutical composition of claim 1, wherein a first tablet is a tablet within a tablet.

11. The solid pharmaceutical composition of claim 1, wherein a first tablet is a tablet that is inlaid within a tablet.

12. The solid pharmaceutical composition of claim 1, wherein a first tablet has a coating that affects drug release of a first active agent.

13. The solid pharmaceutical composition of claim 1, wherein a first tablet has an enteric coating.

14. The solid pharmaceutical composition of claim 1, wherein an active agent in a first tablet comprises diclofenac.

15. The solid pharmaceutical composition of claim 14, wherein a different active agent comprises misoprostol.

16. The solid pharmaceutical composition of claim 1, wherein an active agent in a first tablet comprises diclofenac, a first tablet has an enteric coating and is disposed within a layer of a second tablet, and misoprostol is present in a different layer of a second tablet.

17. The solid pharmaceutical composition of claim 1, wherein an active agent in a first tablet comprises diclofenac, a first tablet has an enteric coating and is disposed within a second tablet having one or more surface indentations, and a misoprostol composition is deposited into an indentation.

18. The solid pharmaceutical composition of claims 16 or 17, wherein a first tablet is in the form of a tablet within a tablet, or a tablet inlaid within a tablet.

19. The solid pharmaceutical composition of claim 1, wherein an active agent comprises ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, fluprofen, tolmetin sodium, zomepirac, sulindac, indomethacin, mefenamic acid, meclofenamate sodium, diflunisal, flufenisal, piroxicam, sudoxicam, isoxicam, diclofenac, celecoxib, rofecoxib, misoprostol, carboprost, ornoprostil, dinoprost, gemeprost, metenoprost, sulprostone, tiaprost, guaiphenesin, dextromethorphan, codeine, pholcodine, naltrexone, atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, pitvastatin, fluindostatin, mevastatin, velostatin, dalvastatin, metformin, phenformin, buformin, acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, gliclazide, glibornuride, glisoxepide, tolazamide, phenbulamide, tolcyclamide, rosiglitazone, troglitazone, pioglitazone, acarbose, meglitol, nateglinide, repaglinide, clofibrate, gemfibrozil, fenofibrate, fenofibric acid, sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, amlodipine, aranidipine, azelnidipine,

barnidipine, benidipine, cilnidipine, cinalong, clevidipine, efonidipine, felodipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, verapamil, gallopamil, diltiazem, mibefradil, bepridil, fluspirilene, losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan, furosemide, ethacrynic acid, torsemide and bumetanide, hydrochlorothiazide, spironolactone, potassium canreonate, amiloride, triamterene, levodopa, droxidopa, melevodopa, etilevodopa, carbidopa, benserazide, entacapone, aliskiren , eprosartan, azathioprine, mycophenolic acid, leflunomide, teriflunomide, methotrexate, tacrolimus, ciclosporin or cyclosporin, pimecrolimus, sirolimus, deforolimus, everolimus, temsirolimus, or zotarolimus.

20. The solid pharmaceutical composition of claim 1, containing the active agents: diclofenac and misoprostol; amlodipine and atorvastatin; naproxen and sumatriptan; amlodipine and benazepril; hydrochlorothiazide and telmisartan, quinapril, aliskiren, amiloride, enalapril, or eprosartan; valsartan and amlodipine; or sirolimus and azathioprine, mycophenolic acid, leflunomide, teriflunomide, methotrexate, tacrolimus, ciclosporin, cyclosporin, pimecrolimus, deforolimus, everolimus, temsirolimus, or zotarolimus.

21. The solid pharmaceutical composition of claim 3, wherein a first active agent is contained in an inner tablet of a tablet-in-tablet, the tablet-in-tablet optionally has a coating and is disposed within a layer or between the layers of the second tablet, and second and third active agents are present in different layers of the second tablet.

22. The solid pharmaceutical composition of claim 3, wherein a first active agent is contained in an inner tablet of a tablet-in-tablet, the tablet-in-tablet optionally has a coating and is disposed within the second tablet, comprising a second active agent and further having one or more surface indentations, into which a third active agent is deposited.

23. The solid pharmaceutical composition of claims 21 or 22 wherein the first, second and third active agents respectively comprise olmesartan, amlodipine and hydrochlorothiazide, or entacapone, carbidopa, and levodopa.

24. A process for preparing a pharmaceutical formulation, comprising compressing a second tablet around a first tablet, while forming an indentation in the second tablet, and depositing a drug-containing composition into the

indentation, wherein the first tablet optionally is in the form of a tablet within a tablet.

25. A process for preparing a pharmaceutical formulation, comprising compressing a tablet layer around a first tablet, and compressing a second layer to form a bilayered second tablet, wherein the first tablet optionally is in the form of a tablet within a tablet.

26. The process of claim 24, wherein the first tablet is an enteric coated diclofenac tablet, the second tablet is a pharmacologically inert matrix, and an indentation is provided with a misoprostol deposit.

27. The process of claim 25, wherein the first tablet is an enteric coated diclofenac tablet, a tablet layer around the enteric coated diclofenac tablet is a pharmacologically inert matrix, and a second layer comprises misoprostol.

28. A method for treating the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications, comprising administering the solid pharmaceutical composition according to claim 1 wherein one active agent is diclofenac and a second active agent is misoprostol.

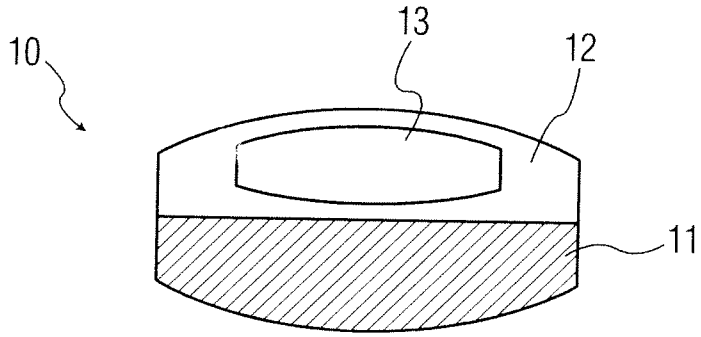

FIG. 1

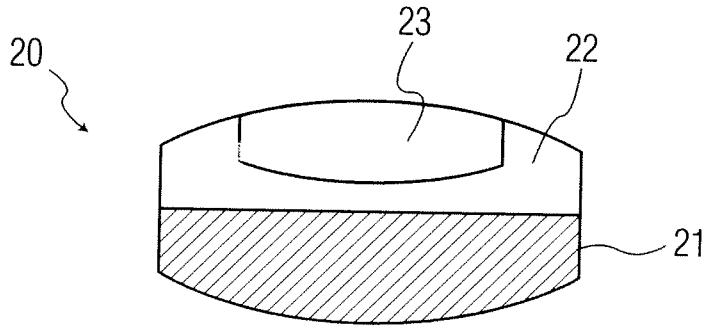

FIG. 2

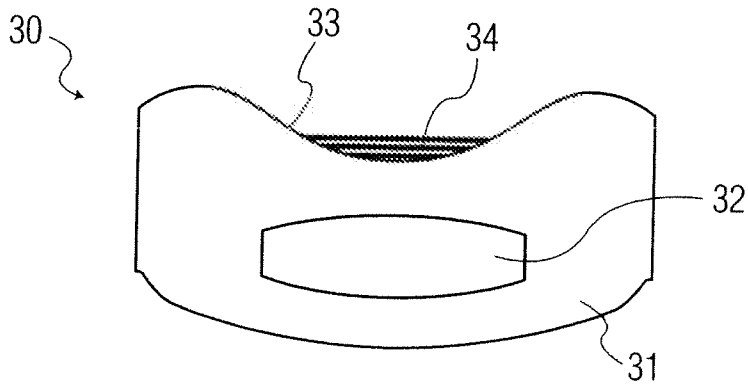

FIG. 3

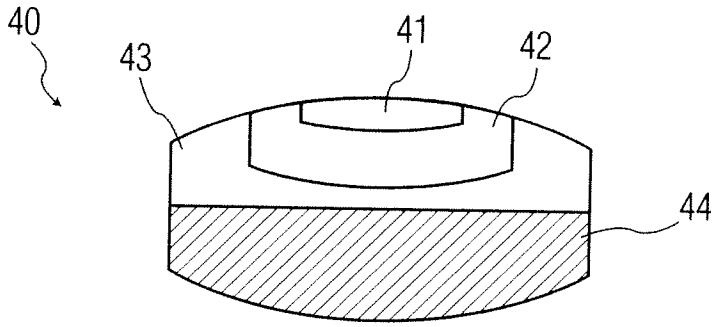

FIG. 4

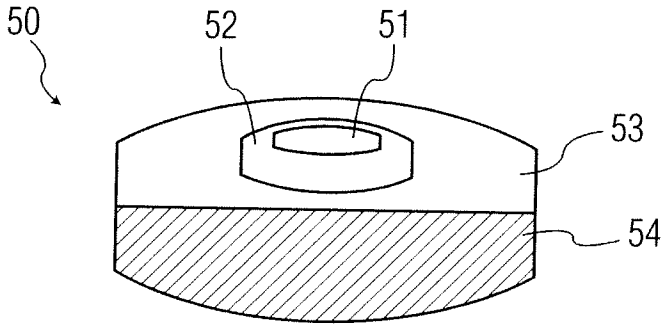

FIG. 5

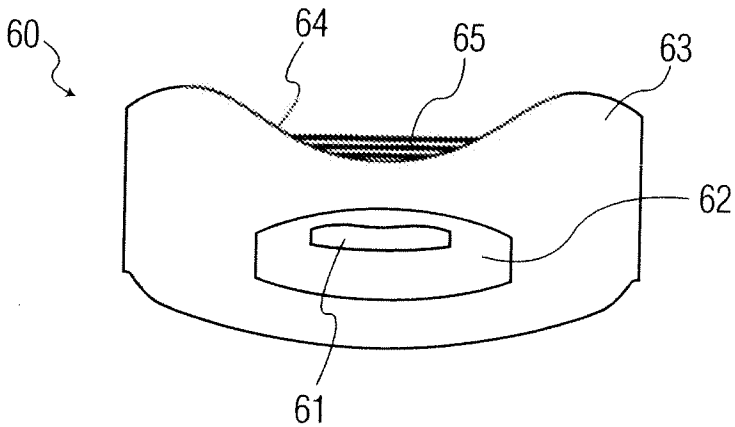

FIG. 6