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(54) **Title**: CONTROLLED RELEASE SOLID ORAL COMPOSITIONS OF DEXLANSOPRAZOLE

(57) **Abstract**: CONTROLLED RELEASE SOLID ORAL COMPOSITIONS OF DEXLANSOPRAZOLE ABSTRACT: The present invention relates to controlled release solid oral compositions of dexlansoprazole or its pharmaceutically acceptable salts and process for preparation thereof and its use for healing of erosive esophagitis, maintenance of healed erosive esophagitis and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

CONTROLLED RELEASE SOLID ORAL COMPOSITIONS OF DEXLANSOPRAZOLE

PRIORITY

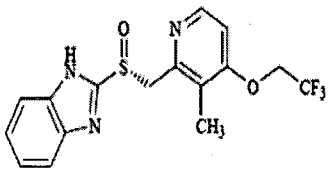
This patent application claims priority to Indian patent application number 4489/CHE/2011, filed on December 21, 2011, the contents of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to controlled release solid oral compositions of dexlansoprazole or its pharmaceutically acceptable salts and process for preparing the same.

BACKGROUND

The chemical name of dexlansoprazole is (+)-2-[(*R*)-{[3-methyl-4-(2,2,2trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-*1H*-benzimidazole. Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*-enantiomers). Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$, corresponding to a molecular weight of 369.36 and having the following structural formula:



Dexlansoprazole is marketed under the trade name of DEXILANT® in United States by Takeda in the form of 30 mg and 60 mg delayed release oral capsules, indicated for the healing of erosive esophagitis, maintenance of healed erosive esophagitis and for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

U.S. Patent Nos. 6,462,058, 6,664,276, 6,939,971 and 7,285,668 disclose various polymorphic forms of dexlansoprazole and process for their preparation.

U.S. Patent No. 7,790,755 discloses capsule comprising: (i) a tablet, granule, or fine granule comprising a core particle containing the active ingredient and a pH dependent soluble release-controlled coating layer that releases the active ingredient in a pH range of 6 to 7.5; and (ii) a tablet, granule or fine granule comprising a core particle containing the active ingredient and an enteric coating, such that the active ingredient is released in the pH range of no less than 5 to no more than 6.

U.S. Patent No. 7,732,474 describes inert core coated with drug which is further coated with one or more optional separating layers and an outer layer comprising an enteric coating, wherein the drug is mixed with a stabilizer comprising microcrystalline cellulose.

U.S. Patent Application Publication No. 2011/0189271 describes dexlansoprazole composition comprising inert core coated with dexlansoprazole solution containing metal compound, thereby insitu formation of dexlansoprazole salt, which is further coated with enteric layer.

Inventors of the present invention have developed controlled release pharmaceutical compositions of dexlansoprazole with pH-independent polymer/ material using simplified process that were found to be comparable with marketed DEXILANT® capsules.

SUMMARY

The present invention relates to controlled release solid oral pharmaceutical composition comprising dexlansoprazole, a pH independent polymer/ material and at least one pharmaceutically acceptable excipient.

One embodiment of the present invention, pharmaceutical capsule composition of dexlansoprazole comprising pellets or spheres or mini tablets or multiunit particulate systems (MUPS) wherein release of the active ingredient is controlled by pH independent polymer/ material selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

In another embodiment, pharmaceutical composition comprising dexlansoprazole in the form of capsule which comprises: a) a core in the form of i) an active core comprising dexlansoprazole and release control pH independent polymer/ material, wherein the pH independent polymer/ material is present either in the matrix or coated on active core, or ii) an inert core coated with drug layer, followed by a release control coating comprising pH independent polymer/ material and (b) the resulting product is coated with dexlansoprazole followed by a separating layer, and finally (c) coated with enteric polymer.

In specific embodiment, the present invention provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising pH independent polymer/ material and (c) the resulted product is

coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer.

In a more specific embodiment, the present invention provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising ethyl cellulose as pH independent controlled release polymer and (c) the resulted product is coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer.

In another embodiment, the present invention also provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an active core comprising dexlansoprazole and release control pH independent polymer/ material prepared by extrusion and spheronization or granulation, wherein pH independent polymer/ material is present either in the matrix or coated on the active core and (b) the resulted product was coated with dexlansoprazole followed by a separating layer and finally (c) coated with enteric polymer.

Another embodiment of the present invention relates to pharmaceutical composition comprising dexlansoprazole or its pharmaceutically acceptable salts thereof, pH independent polymer/ material or non-gelling polymer or hydrophobic polymer and one or more pharmaceutically acceptable excipients.

In embodiments, the present invention provides delayed and controlled release solid oral compositions comprising dexlansoprazole or a pharmaceutically acceptable salt thereof.

In yet another embodiment, pharmaceutical composition according to the present invention is used for healing of erosive esophagitis, maintenance of healed erosive esophagitis and for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

DETAILED DESCRIPTION

In accordance with the present invention, the term "dexlansoprazole" includes dexlansoprazole in the form of free base or its pharmaceutically acceptable salt, amorphous dexlansoprazole, crystalline dexlansoprazole or any isomer or derivative, hydrate or solvate, prodrug or combinations thereof.

In context of the invention, terms such as "active" or "active ingredient" or "drug" or "drug substance" or "pharmacologically active agent" or "active substance" may be used interchangeably and synonymously for dexlansoprazole or its pharmaceutically acceptable salts thereof.

The term "effective amount" or "therapeutically effective amount" used interchangeably, are defined to mean the amount or quantity of the active drug (e.g. dexlansoprazole) which is sufficient to elicit an appreciable biological response when administered to a patient.

The term "excipients" as used herein means a component of a pharmaceutical product that is not an active ingredient such as, for example, fillers, diluents, carriers and the like. The excipients that are useful in preparing a pharmaceutical composition are generally safe and non-toxic.

The term "intermediate layer" or "sub coating" or "separating layer" used here in synonymously refers to a layer formed between drug and an enteric layer/ control release layer.

The term "controlled-release" in accordance with the present invention is intended to composition that releases the drug from its dosage form over a period of about 6 hours.

The term "delayed-release" refers to composition that resists drug release in gastric fluid and disintegrates in intestinal fluid.

The term "composition or formulation" refers to solid oral dosage form such as a capsule or tablet comprising dexlansoprazole.

Pharmaceutical compositions of the present invention can be made into solid dosage forms such as tablets, capsules, multiunit particulate systems (MUPS), granules, solid dispersions, pellets, spheres, beads, particles, mini-tablets and the like.

The present invention relates to controlled release pharmaceutical composition comprising dexlansoprazole or a pharmaceutically acceptable salt thereof, pH-independent polymer/ material and one or more pharmaceutically acceptable excipients.

pH independent polymer/ material according to the present invention is selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

Accordingly, excipients of the present invention comprise diluents, basic inorganic salts, binders, disintegrants, glidants, lubricants and combinations thereof.

Suitable diluents include mannitol, microcrystalline cellulose, sorbitol, talc, lactose, sugar, starches, modified starches, inorganic salts, calcium sulfate, xylitol, lactitol, starch, pregelatinized starch, kaolin, sucrose, dextrates, dextrin, maltodextrin, dextrose, calcium carbonate, calcium sulfate, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide and the like and combinations thereof.

Suitable basic inorganic salts include carbonates/ bicarbonates/ phosphates/ hydroxides/ oxides of calcium, sodium, magnesium and the like and combinations thereof. Preferably, magnesium carbonate and sodium bicarbonate were used alone or in combination.

Suitable binders include hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, guar gum, xanthan gum, lactose, starches such as corn starch, potato starch, modified starches, sugars, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, copolyvidone, sodium alginate, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, ethyl cellulose, gelatin, liquid glucose, povidone and pregelatinized starch and the like and combinations thereof.

Suitable disintegrants include crospovidone, polacrillin potassium, croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose, polyvinylpyrrolidone, carboxymethyl cellulose calcium, starches such as corn starch, potato starch, pre-gelatinized and modified starches, clays, bentonite and the like and combinations thereof.

Suitable glidants include colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc and the like and combinations thereof.

Suitable lubricants include talc, magnesium stearate, calcium stearate, sodium stearyl fumarate, zinc stearate, stearic acid, fumaric acid, palmitic acid, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols and the like and combinations thereof.

Useful additives for coating include, but are not limited to, plasticizers, antiadherents, opacifiers, solvents, and optionally colorants, lubricants, pigments, antifoam agents, and polishing agents.

The term "plasticizer" as used herein is intended to mean a compound used in solid dosage forms to provide the desired plasticity to the coating. Suitable plasticizers include triethyl citrate, polyethylene glycol, propylene glycol, acetyl triethyl citrate, acetyltributyl citrate, benzyl benzoate, chlorbutanol, dextrin, glycerin, glycerin monostearate, mannitol, lanolin alcohol, 2-pyrrolidine, sorbitol, triacetin, diacetylated monoglyceride, tri butyl citrate, triethanolamine and the like and combinations thereof.

Other ingredients such as stabilizers and antiadherants conventionally used for pharmaceutical formulations may also be included in the present formulation.

In one aspect, pharmaceutical capsule composition of dexlansoprazole comprising pellets or spheres or mini tablets or multiunit particulate systems (MUPS) wherein release of the active ingredient is controlled by pH independent polymer/ material selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

In another aspect, pharmaceutical composition comprising dexlansoprazole in the form of capsule which comprises: a) a core in the form of i) an active core comprising dexlansoprazole and release control pH independent polymer/ material, wherein the pH independent polymer/ material is present either in the matrix or coated on active core, or ii) an inert core coated with drug layer, followed by a release control coating comprising pH independent polymer/ material and (b) the resulting product is coated with dexlansoprazole followed by a separating layer, and finally (c) coated with enteric polymer.

Controlled release compositions of dexlansoprazole may be processed either by layering technology or extrusion and spheronization or wet granulation.

In another aspect, the present invention provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising pH independent polymer/ material and (c) the resulted product is coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer; wherein the composition optionally comprise a separating layer between the first active layer/ second active layer and release control coating.

In particular, the present invention provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising ethyl cellulose as pH independent controlled release polymer and (c) the resulted product is coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer.

Inert core according to the present invention may be in the form of sugar spheres, microcrystalline cellulose spheres, lactose spheres, non-pareil seeds, silicon dioxide glass beads or sodium bicarbonate beads.

In another aspect, the present invention also provides process for the preparation of dexlansoprazole capsule composition comprises: (a) an active core comprising dexlansoprazole and release control pH independent polymer/ material prepared by extrusion and spheronization or wet granulation, wherein pH independent polymer/ material is present either in the matrix or coated on the active core and (b) the resulted product was coated with dexlansoprazole followed by a separating layer and finally (c) coated with enteric polymer; wherein the composition optionally comprise a separating layer between active core/ drug layer and release control coating.

Extrusion and spheronization process comprise the steps of: (i) blending dexlansoprazole, one or more excipients and optionally a pH independent polymer/ material (ii) granulating the blended mixture of step no (i) with binder solution to form a wet mass, (iii) extruding the wet mass of step no (ii) followed by spheronization using spherodizer to obtain spheroids/ spherical granules/ spheres, (iv) coating the spheroids of step no (iii) with dexlansoprazole followed by a separating layer, and finally (v) coating the with enteric polymer, (vi) blending the enteric coated spheroids of step no (v) with a lubricant and filling into capsules or alternatively compressing into tablets.

Mini-tablets of the present invention may be prepared by wet granulation process including: (i) sifting and blending dexlansoprazole with one or more excipients to form a dry mix, (ii) granulating the dry mix of step no. (i) using binder solution to form granules followed by drying, (iii) blending the granules of step no. (ii) with lubricant and finally compressing into mini-tablets, (iv) optionally, subcoating the mini-tablets, (v) coating the mini-tablets of step no. (iii or iv) with pH independent polymer/ material, (vi) coating the resulted product of step no. (v) with

active layer of dexlansoprazole followed by a separating layer, (vii) coating the the mini tablets of step no. (vi) with an enteric polymer, and finally (viii) filling the coated mini-tablets of step no. (vii) into hard gelatin capsules. Minitablets of the present invention have a size of 5mm to 7mm in diameter.

In further aspect, core is in the form of pellets or spheres or granules or mini tablets or multiunit particulate systems (MUPS).

Enteric coated multiple unit cores/ minitablets of the present invention were further lubricated/ or mixed with one or more pharmaceutically acceptable excipients and finally filled into capsules or alternatively compressed into tablets.

The present invention further relates to a pharmaceutical composition comprising dexlansoprazole or its pharmaceutically acceptable salts thereof, pH independent polymer/ material or non-gelling polymer or hydrophobic polymer and one or more pharmaceutically acceptable excipients.

The present invention provides delayed and controlled release solid oral pharmaceutical compositions comprising dexlansoprazole or a pharmaceutically acceptable salt thereof and a pH independent hydrophobic material selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

Delayed release is release delayed for a period of time after administration and can be accomplished, for example, by applying a coating of enteric materials. For example, the enteric polymer may be one or more selected from a group consisting of Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7: 3 :1 (e.g., Eudragit FS 30D), Poly(methacrylic acid, methyl methacrylate) 1 : 1 (e.g., Eudragit L 100), Poly(methacrylic acid, ethyl acrylate) 1 : 1 (e.g., Eudragit® L 30 D-55), hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxymethylethyl cellulose phthalate, carboxymethylethyl cellulose and the like.

A method for healing of erosive esophagitis, maintenance of healed erosive esophagitis, symptomatic non-erosive gastroesophageal reflux disease comprising administering a composition comprising a therapeutically effective amount of dexlansoprazole.

The following examples further illustrate the invention and do not limit the scope of the invention.

EXAMPLE 1-2

Dexlansoprazole delayed release capsules:

Ingredients	Example 1 mg/ cap	Example 2 mg/ cap
Drug layering-I		
Dexlansoprazole	45.00	45.00
Hydroxypropyl cellulose	4.00	4.00
Crospovidone	18.00	18.00
Cremophore	13.00	13.00
Magnesium carbonate light	4.50	4.50
Sugar spheres	100.00	100.00
Methanol	q.s.	q.s.
Purified water	q.s.	q.s.
Extended release coating		
Ethyl cellulose	4.42	4.42
Hydroxypropyl methylcellulose	1.10	1.10
Purified water	q.s.	q.s.
Subcoating-I		
Mannitol	5.70	5.70
Purified water	q.s.	q.s.
Drug layering-II		
Dexlansoprazole	15.00	15.00
Hydroxypropyl cellulose	1.33	1.33
Crospovidone	6.00	6.00
Cremophore	4.33	4.33
Magnesium carbonate light	1.50	1.50
Methanol	q.s.	q.s.
Purified water	q.s.	q.s.
Subcoating-II		
Hydroxypropyl methylcellulose	8.95	8.95
Talc	2.23	2.23
Purified water	q.s.	q.s.
Enteric coating		
Eudragit FS30D	37.61	-
Eudragit L 100	-	37.61
Plascryl T20	9.40	9.40
Purified water	q.s.	q.s.
Lubrication		
Talc	1.14	1.14
Total	283.55	283.55

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, magnesium carbonate light was dissolved in methanol and both the solutions were mixed together.
2. crospovidone was also dispersed in solution of step 1.
3. dexlansoprazole and cremophore were dispersed in dispersion of step 2 and coated over sugar spheres in wurster coater.
4. ethylcellulose and hydroxypropyl methylcellulose were dispersed in purified water and coated over the pellets obtained in step 3 till desired weight gain is achieved.
5. mannitol was dissolved in purified water and the resulted solution was coated over the pellets obtained in step 4 till desired weight gain is achieved.
6. hydroxypropyl cellulose and magnesium carbonate light were dissolved in purified water and methanol separately.
7. crospovidone was also dispersed in solution of step 6.
8. dexlansoprazole and cremophore were dispersed in dispersion of step 7 and coated over step 4 pellets in wurster coater.
9. hydroxypropyl methylcellulose was dissolved in purified water and talc was dispersed with stirring or homogenization.
10. solution of step 9 was sprayed on coated pellets of step 9 till desired weight gain is achieved.
11. eudragit FS30D/ eudragit L 100 and plasacryl T20 were dispersed in purified water and coated over pellets obtained in step 10 till desired weight gain is achieved.
12. the pellets of step 11 were lubricated with talc and encapsulated in hard gelatin capsules.

Dissolution study:

Comparative dissolution study was performed for capsules prepared according to the example 1 and Dexilant® capsules with the following conditions:

Medium:	Acid stage: 500 ml of 0.1N HCl Buffer stage: 900 ml of pH 7.0 phosphate buffer with 5 mM of SLS
Apparatus:	USP Type I Apparatus (Basket)
Speed (rpm)	100 rpm

The dissolution results are shown in Table 1.

Table 1:

Time in minutes	Cumulative % of drug release	
	Dexilant®	Example 1
Acid stage:		
120	2.0	3.0
Buffer stage:		

10	17	15
20	18	25
40	33	40
50	46	46
60	58	53
75	74	62
105	87	78
120	87	86

EXAMPLE 3

Dexlansoprazole delayed release capsules:

Ingredients	mg/ cap
Drug layering 1	
Dexlansoprazole	45.000
Hydroxypropyl cellulose	22.500
Crospovidone	30.000
Sodium bicarbonate	15.000
Sugar spheres	50.000
Methanol	q.s.
Purified water	q.s.
Sub coating 1	
Hypromellose	20.250
Talc	5.400
Titanium dioxide	1.350
Purified water	q.s.
Extended release coating	
Ethyl cellulose	33.720
Purified water	q.s.
Drug layering 2	
Dexlansoprazole	15.000
Hydroxypropyl cellulose	7.500
Crospovidone	15.000
Sodium bicarbonate	7.5
Methanol & Purified water	q.s.
Sub coating 2	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.
Enteric coating	
Eudragit L30D55	41.634
Triethyl citrate	4.164

Talc	5.412
Titanium dioxide	2.082
Purified water	q.s.
Lubrication	
Talc	1.188
Total	339.00

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, sodium bicarbonate was dissolved in methanol and both the solutions were mixed together.
2. crospovidone was also dispersed in solution obtained in step 1.
3. dexlansoprazole was dispersed in dispersion of step 2 and coated over sugar spheres in wurster coater.
4. hypromellose was dissolved in purified water; talc and titanium dioxide was dispersed with stirring or homogenization.
5. solution of step 4 was sprayed on the drug coated pellets of step 3 till desired weight gain is achieved.
6. ethycellulose was dispersed in purified water and coated over the pellets obtained in step 5 till desired weight gain is achieved.
7. hydroxypropyl cellulose and sodium bicarbonate were dissolved in purified water and methanol separately.
8. crospovidone was also dispersed in solution obtained in step 7.
9. dexlansoprazole was dispersed in dispersion of step 8 and coated over pellets obtained in step 6 in wurster coater.
10. hypromellose was dissolved in purified water; talc and titanium dioxide was dispersed with stirring or homogenization.
11. solution of step 10 was sprayed on coated pellets of step 9 till desired weight gain is achieved.
12. talc and titanium dioxide were dispersed in purified water.
13. eudragit, triethyl citrate was dispersed in dispersion of step 12 and coated over pellets obtained in step 11 till desired weight gain is achieved.
14. the pellets were lubricated with talc and encapsulated in hard gelatin capsules.

EXAMPLE 4

Dexlansoprazole delayed release capsules:

Ingredients	mg/ cap
Mini tablets	

Dexlansoprazole	48.000
Hydroxypropyl cellulose	6.400
Crospovidone	32.000
Sodium bicarbonate	16.000
Mannitol	102.400
Methanol	q.s.
Purified water	q.s.
Magnesium stearate	3.200
Sub coating 1	
Hypromellose	20.250
Talc	5.400
Titanium dioxide	1.350
Purified water	q.s.
Extended release coating	
Ethyl cellulose	16.520
Talc	4.130
Purified water	q.s.
Drug layering	
Dexlansoprazole	12.000
Hydroxypropyl cellulose	7.500
Crospovidone	15.000
Methanol & Purified water	q.s.
Sub coating 2	
Hypromellose	20.250
Talc	5.400
Titanium dioxide	1.350
Purified water	q.s.
Enteric coating	
Eudragit L 30D55	11.421
PEG 8000	1.713
Talc	1.599
Purified water	q.s.
Lubrication	
Talc	1.188
Total	333.07

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, sodium bicarbonate was dissolved in methanol and both the solutions were mixed together.
2. mannitol, crospovidone and dexlansoprazole were mixed together.

3. mixture obtained in step 2 was granulated with solutions obtained in step 1, dried and milled to get desired granules; obtained granules were lubricated with magnesium stearate and compressed to mini tablets of 5.2 mm using suitable punches.
4. hypromellose was dissolve in purified water; talc and titanium dioxide were dispersed in it with stirring or homogenization.
5. solution of step 4 was sprayed on mini tablets of step 3 till desired weight gain is achieved.
6. ethycellulose was dispersed in purified water and coated over pellets obtained in step 5 till desired weight gain is achieved.
7. hydroxypropyl cellulose and sodium bicarbonate were dissolved in purified water and methanol separately.
8. crospovidone was also dispersed in solution of step 7 .
9. dexlansoprazole was dispersed in dispersion of step 8 and coated over mini tablets obtained in step 6 in wurster coater.
10. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
11. solution of step 10 was sprayed on to coated pellets of step 9 till desired weight gain is achieved.
12. talc was dispersed in purified water.
13. eudragit, PEG 8000 were dispersed in dispersion of step 12 and coated over pellets obtained in step 11 till desired weight gain is achieved.
14. The obtained pellets were lubricated with talc and encapsulated in hard gelatin capsules.

EXAMPLE 5

Dexlansoprazole delayed release capsules:

Ingredients	mg/cap
Extrusion-Spheronization	
Dexlansoprazole	45.000
Hydroxypropyl cellulose	22.500
Mannitol	45.000
Sodium bicarbonate	15.000
Microcrystalline cellulose	60.000
Purified water	q.s.
Sub coating 1	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.

Extended release coating	
Ethyl cellulose	33.720
Purified water	q.s.
Drug layering	
Dexlansoprazole	15.000
Hydroxypropylcellulose	7.500
Crospovidone	15.000
Sodium bicarbonate	7.5
Methanol & Purified water	q.s.
Sub coating 2	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.
Enteric coating	
Eudragit L30D55	41.634
Triethyl citrate	4.164
Talc	5.412
Titanium dioxide	2.082
Purified water	q.s.
Lubrication	
Talc	1.188
Total	352.00

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, sodium bicarbonate was dissolved in methanol and both the solutions were mixed together.
2. mannitol, microcrystalline cellulose and dexlansoprazole were mixed and granulated with solution obtained in step 1.
3. the wet mass was passed through extruder and spherodiser to get spheroids.
4. the spheroids were dried in fluid bed dryer till required LOD and the desired fraction of pellets were collected.
5. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
6. solution of step 5 was sprayed on pellets of step 4 till desired weight gain is achieved.
7. ethycellulose was dispersed in purified water and coated over pellets obtained in step 6 till desired weight gain is achieved.
8. hydroxypropyl cellulose and sodium bicarbonate were dissolved in purified water separately.

9. crospovidone was also dispersed in solution of step 8 .
10. dexlansoprazole was dispersed in dispersion of step 9 and coated over pellets obtained in step 7 in wurster coater.
11. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
12. solution of step 11 was sprayed on coated pellets of step 10 till desired weight gain is achieved.
13. talc and titanium dioxide were dispersed in purified water.
14. eudragit, triethyl citrate were dispersed in step 13 dispersion and coated over pellets of step 12 till desired weight gain is achieved.
15. the pellets were lubricated with talc and encapsulated in hard gelatin capsules.

EXAMPLE 6-7

Dexlansoprazole delayed release capsules:

Ingredients	Example 6 mg/cap	Example 7 mg/cap
Extrusion-Spheronization		
Dexlansoprazole	45.000	45.000
Hydroxypropyl cellulose	22.500	22.500
Mannitol	45.000	45.000
Sodium bicarbonate	15.000	15.000
Microcrystalline cellulose	60.000	60.000
Purified water	q.s.	q.s.
Sub coating 1		
Hypromellose	11.850	11.850
Talc	3.160	3.160
Titanium dioxide	0.790	0.790
Purified water	q.s.	q.s.
Extended release coating		
Starch acetate	33.720	-
Zein	-	33.720
Dichloromethane	q.s.	q.s.
Drug layering		
Dexlansoprazole	15.000	15.000
Hydroxypropyl cellulose	7.500	7.500
Crospovidone	15.000	15.000
Methanol & Purified water	q.s.	q.s.
Sub coating 2		

Hypromellose	11.850	11.850
Talc	3.160	3.160
Titanium dioxide	0.790	0.790
Purified water	q.s.	q.s.
Enteric coating		
Eudragit L30D55	41.634	41.634
Triethyl citrate	4.164	4.164
Talc	5.412	5.412
Titanium dioxide	2.082	2.082
Purified water	q.s.	q.s.
Lubrication		
Talc	1.188	1.188
Total	345.000	345.000

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, sodium bicarbonate was dissolved in methanol and both the solutions were mixed together.
2. mannitol, microcrystalline cellulose and dexlansoprazole were mixed together and granulated with solution obtained in step 1.
3. the wet mass was passed through extruder and spherodiser to get spheroids.
4. the spheroids were dried in fluid bed dryer till to get required LOD and the desired fraction of pellets were collected.
5. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
6. solution of step 5 was sprayed on pellets of step 4 till desired weight gain is achieved.
7. starch acetate/ zein was dispersed in dichloromethane and coated over pellets obtained in step 6 till desired weight gain is achieved.
8. hydroxypropyl cellulose was dissolved in purified water.
9. crospovidone was dispersed in solution of step 8.
10. dexlansoprazole was dispersed in dispersion of step 9 and coated over pellets of step 7 in wurster coater.
11. hypromellose was dissolved in purified water; talc and titanium dioxide were dispersed in it with stirring or homogenization.
12. solution of step 11 was sprayed on coated pellets of step 10 till desired weight gain is achieved.
13. talc and titanium dioxide were dispersed in purified water.

14. eudragit, triethyl citrate were dispersed in the dispersion obtained in step 13 and coated over pellets obtained in step 12 till desired weight gain is achieved.
15. the pellets were lubricated with talc and encapsulated in hard gelatin capsules.

EXAMPLE 8

Dexlansoprazole delayed release capsules:

Ingredients	mg/cap
Extrusion-Spheronization	
Dexlansoprazole	45.000
Xanthan gum	22.500
Guar gum	45.000
Sodium bicarbonate	15.000
Microcrystalline cellulose	60.000
Dichloromethane	q.s.
Sub coating 1	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.
Extended release coating	
Zein	33.720
Dichloromethane	q.s.
Drug layering	
Dexlansoprazole	15.000
Hydroxypropyl cellulose	7.500
Crospovidone	15.000
Methanol & Purified water	q.s.
Sub coating 2	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.
Enteric coating	
Eudragit L30D55	41.634
Triethyl citrate	4.164
Talc	5.412
Titanium dioxide	2.082
Purified water	q.s.
Lubrication	
Talc	1.188
Total	345.000

Brief manufacturing process:

1. Sodium bicarbonate was dissolved in dichloromethane.
2. xanthan gum, guar gum, microcrystalline cellulose and dexlansoprazole were mixed together and granulated with solution of step 1.
3. the wet mass was passed through extruder and spherodiser to get spheroids.
4. the spheroids were dried in fluid bed dryer till required LOD and the desired fraction of pellets were collected.
5. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
6. solution of step 5 was sprayed on to pellets of step 4 till desired weight gain is achieved.
7. zein was dispersed in dichloromethane and coated over pellets obtained in step 6 till desired weight gain is achieved.
8. hydroxypropyl cellulose was dissolved in purified water and methanol.
9. crospovidone was dispersed in solution of step 8.
10. dexlansoprazole was dispersed in dispersion of step 9 and coated over pellets obtained in step 7 in wurster coater.
11. hypromellose was dissolved in purified water; talc and titanium dioxide were dispersed in it with stirring or homogenization.
12. solution of step 11 was sprayed on to the coated pellets of step 10 till desired weight gain is achieved.
13. talc and titanium dioxide were dispersed in purified water.
14. eudragit, triethyl citrate were dispersed in dispersion of step 13 and coated over pellets obtained in step 12 till desired weight gain is achieved.
15. the pellets were lubricated with talc and encapsulated in hard gelatin capsules.

EXAMPLE-9

Dexlansoprazole delayed release capsules:

Ingredients	mg/ cap
Extrusion-Spheronisation	
Dexlansoprazole	45.000
Hydroxypropyl cellulose	22.500
Mannitol	45.000
Sodium bicarbonate	15.000
Microcrystalline cellulose	60.000
Ethyl cellulose	42.500
Purified water	q.s.

Drug layering	
Dexlansoprazole	15.000
Hydroxypropylcellulose	7.500
Crospovidone	15.000
Methanol & purified water	q.s.
Sub coating	
Hypromellose	11.850
Talc	3.160
Titanium dioxide	0.790
Purified water	q.s.
Enteric coating	
Eudragit L30D55	41.634
Triethyl citrate	4.164
Talc	5.412
Titanium dioxide	2.082
Purified water	q.s.
Lubrication	
Talc	1.188
Total	338.00

Brief manufacturing process:

1. Hydroxypropyl cellulose was dissolved in purified water, sodium bicarbonate was dissolved in methanol and both the solutions were mixed together.
2. mannitol, microcrystalline cellulose and dexlansoprazole were mixed together and granulated with solutions obtained in step 1 and ethylcellulose aqueous dispersion.
3. the wet mass was passed through extruder and spherodiser to get spheroids.
4. the spheroids were dried and the desired fraction of pellets were collected.
5. hydroxypropyl cellulose was dissolved in purified water.
6. crospovidone was also dispersed in solution of step 5.
7. dexlansoprazole was dispersed in dispersion of step 6 and coated over pellets of step 4 in wurster coater.
8. hypromellose was dissolved in purified water; talc and titanium dioxide were also dispersed in it with stirring or homogenization.
9. solution of step 8 was sprayed on coated pellets of step 7 till desired weight gain is achieved.
10. talc and titanium dioxide were dispersed in purified water.
11. eudragit, triethyl citrate were also dispersed in dispersion of step 10 and coated over pellets obtained in step 9 till desired weight gain is achieved.
12. the pellets were lubricated with talc and encapsulated in hard gelatin capsules.

WE CLAIM:

1. A pharmaceutical capsule composition of dexlansoprazole comprising pellets or spheres or mini tablets or multiunit particulate systems (MUPS) wherein release of the active ingredient is controlled by pH independent polymer/ material selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

2. A pharmaceutical composition comprising dexlansoprazole in the form of capsule which comprises: a) a core in the form of i) an active core comprising dexlansoprazole and release control pH independent polymer/ material, wherein the pH independent polymer/ material is present either in the matrix or coated on active core, or ii) an inert core coated with drug layer, followed by a release control coating comprising pH independent polymer/ material and (b) the resulting product is coated with dexlansoprazole followed by a separating layer, and finally (c) coated with enteric polymer.

3. A process for the preparation of dexlansoprazole capsule composition comprises: (a) an active core comprising dexlansoprazole and release control pH independent polymer/ material prepared by extrusion and spheronization or granulation, wherein pH independent polymer/ material is present either in the matrix or coated on the active core and (b) the resulted product was coated with dexlansoprazole followed by a separating layer and finally (c) coated with enteric polymer.

4. The composition according to claim 2 and 3, optionally comprise a separating layer between the active core/ drug layer and release control coating.

5. A process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising pH independent polymer/ material and (c) the resulted product is coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer.

6. The composition according to claim 2, 3 and 5, wherein said release control pH independent polymer/ material selected from ethyl cellulose, starch acetate, protein based zein and combinations thereof.

7. The pharmaceutical composition according to claims 2 to 5, wherein said core is in the form of pellets or spheres or mini tablets or multiunit particulate systems (MUPS).

8. A process for the preparation of dexlansoprazole capsule composition comprises: (a) an inert core coated with first active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, (b) release control coating comprising ethyl cellulose as pH independent controlled release polymer and (c) the resulted product is coated with second active layer comprising dexlansoprazole and one or more pharmaceutically acceptable excipients, followed by a separating layer, and finally (d) coated with enteric polymer.

9. The process according to claim 5 and 8, optionally comprise a separating layer between the active layer and release control coating.

10. The pellets, spheres, mini tablets or multiunit particulate systems (MUPS) according to any of the preceding claims further comprise one or more excipients selected from microcrystalline cellulose, starch, mannitol, crospovidone, basic inorganic salt, xanthan gum, and guar gum.

11. The pharmaceutical composition according to any of the preceding claims is useful for healing erosive esophagitis, maintenance of healed erosive esophagitis and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2012/000818

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/48 (2013.01)
USPC - 424/490
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 9/14, 9/24, 9/28, 9/32, 9/34, 9/36, 9/38, 9/48, 9/50, 9/52, 9/60, 31/4439, 31/454; A61P 1/00, 1/04 (2013.01)
USPC - 424/451, 459, 474, 489, 490, 495; 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 9/48, 9/4808, 9/4891; C07D 401/12 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patent, ProQuest

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/117756 A2 (LAD et al) 14 October 2010 (14.10.2010) entire document	2, 3
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Y		1
Y	EP 1086694 A2 (LOPEZ CABRERA et al) 28 March 2001 (28.03.2001) entire document	1
A	US 2009/0098199 A1 (LEE et al) 16 April 2009 (16.04.2009) entire document	1-3, 5, 8

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2013	15 MAY 2013

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2012/000818

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4, 6, 7, 9-11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.