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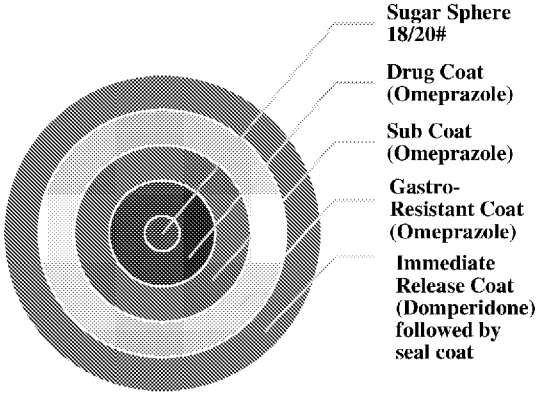

Figure.1

(57) Abstract: The present invention provides a fixed dose combination of Omeprazole and Domperidone in a single solid dosage form, wherein the formulation comprises immediate release Domperidone and delayed release Omeprazole for effective management of Gastro-intestinal disorder. The present invention related to multi-layer pellet composition comprising enteric coated Omeprazole layer which releases Omeprazole at specific pH and immediate release Domperidone layer. The single multi-layer pellet manufacturing technology of the present invention is cost effective and required less manufacturing time as compared to existing formulation which generally involves preparation of separate Omeprazole Enteric coating pellets & Domperidone pellets and then filling the same in capsule.

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MULTI-LAYER PELLET FORMULATION AND PROCESS OF PREPARATION THEREOF

FIELD OF INVENTION:

[001] The present invention relates to multi-layer dosage form. The multi-layer formulation of the present invention comprises fixed dose combination of proton pump inhibitors and prokinetic agents more particularly to a multi-layer formulation comprising Omeprazole and Domperidone in a single pellet and process of preparation thereof.

BACKGROUND:

[002] Proton pump inhibitors are the most common over-the counter and prescribed medication which are generally used for treatment of various Gastrointestinal Diseases such as Gastroesophageal reflux disease, peptic ulcers, heartburn, acidity and Zollinger-Ellison syndrome. Gastroesophageal reflux disease (GERD) is a gastrointestinal condition in which stomach acid repeatedly flows back to the esophagus and causes heart burn and acid regurgitation. Proton pump inhibitors used to relive GERD. Peptic ulcers are a condition where stomach acid damages the lining of digestive tracts and form sores on the lining of oesophagus, stomach and small intestines. Zollinger-Ellison syndrome is a rare gastrointestinal disorder which occurs when one or more tumors are formed in pancreas or duodenum which release the hormone gastrin causing the stomach to release too much acid. PPIs are generally available in combination with histamine type 2-receptor antagonists (H2 blocker), Prokinetics agents and Antacids. Proton pump inhibitors alone (PPIs) were found to be less effective than combination therapy. The most preferable combination with PPIs are Prokinetics agents.

[003] Proton pump inhibitors (PPIs) for example Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole and Rabeprazole decreased the

secretion of acid in stomach by inhibiting H+/K+ ATPase enzyme. Since PPIs are acid labile there are generally available in enteric coated formulation.

[004] Prokinetic agents, or prokinetics for example Cisapride, Domperidone, Metoclopramide helps in controlling the acid reflux by strengthening the contractions of lower esophageal sphincter (LES) muscles and fasten Gastric emptying.

[005] Thus, combining PPIs and prokinetic agents is a rational approach for effective treatment of gastrointestinal disorders such as acidity, heartburn, peptic ulcers, Gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome.

[006] Prior art WO2013/122554 A1 discloses pellet formulation comprising Esomeprazole, the pellets of the invention comprises an inner core and an active agent layer coating coated over inner core, an intermediate and enteric coated layer.

[007] CN1723897 discloses a formulation comprising combination of omeprazole and domperidone. The invention focuses on enteric-coated tablet containing 10mg of omeprazole and 10mg of domperidone.

[008] IN265244 B discloses an oral composition comprising at least one gastric acid suppressing agent and one or more prokinetic agent, the prior art discloses preparation of two different tablets enclosed in a capsule.

[009] Commercially available products and literatures known in the prior art are in form of either sustained release or delayed release tablets or pellets which are further filled in a capsule. The process generally involves preparation of Omeprazole Enteric coating pellets/tablets & Domperidone Tablets/pellets separately which added cost to the manufacturing and is time consuming, involved manufacturing of two different dosage form, less time consuming and cost effective.

Objective:

[0010] The objective of the present invention is to provide a fixed dose combination of Proton pump inhibitors (PPIs) and Prokinetic in a single composition.

[0011] Another objective of the present invention is to provide fixed dose combination of Omeprazole and Domperidone in a single composition for effective treatment of Gastroesophageal reflux disease (GERD), peptic ulcers, acidity, heart burns and Zollinger-Ellision syndrome.

[0012] Yet another objective of the present invention is to provide a fixed dose combination of Omeprazole and Domperidone in a single pellet composition wherein the single pellet composition is a multi-layer composition comprising delayed release Omperazole layer and immediate release Domperidone layer. The delayed release Omperazole layer is enteric coated and is pH dependent.

[0013] Yet another objective of the present invention is to provide process of preparation of pellet formulation comprising fixed dose combination of Omeprazole and Domperidone wherein the pellets are enclosed in a capsule.

SUMMARY OF THE INVENTION:

[0014] The present invention discloses fixed dose combination of Omeprazole and Domperidone in a single solid dosage form, wherein the formulation comprises immediate release Domperidone and delayed release Omeprazole for effective management of Gastroesophageal reflux disease (GERD), heart burn, acidity, peptic ulcers and Zollinger-Ellison Syndrome.

[0015] In an aspect the present invention provides a multi-layer pellet formulation wherein Omeprazole and Domperidone are contained in the separated layers, such that on administration, Domperidone releases immediately and Omeprazole release in delayed manner, thus maximizing the therapeutic effect against various gastro-intestinal disorders.

[0016] The dual release formulation of the present invention is formulated in a single pellet dosage form and provide a novel process of preparation thereof. The process of preparing multi-layer pellet formulation comprising delayed release omeprazole and immediate release Domperidone in a single pellet which is cost effective process and required less time for manufacturing as compared to marketed products.

BRIEF DESCRIPTION OF THE FIGURES:

[0017] FIG. 1 is a diagrammatic representative of layering process on inner core (Sugar sphere).

[0018] FIG. 2 is a comparative representative of present invention V/S marketed formulation wherein present invention is a multi-layer single pellet comprising delayed release omeprazole and immediate release Domperidone as a separate layer wherein marketed formulation comprises white tablet of Omeprazole and pellets of Domperidone.

DETAILED DESCRIPTION OF INVENTION:

[0019] Those skilled in the art will be aware that the present disclosure is subject to variations and modifications other than those specifically described. It is to be understood that the present disclosure includes all such variations and modifications. The disclosure also includes all such compositions, components of the composition, referred to or indicated in this specification, individually or collectively and all combinations of any or more of such components or composition.

Definitions

[0020] For convenience, before further description of the present disclosure, certain terms employed in the specification, and examples are collected here. These definitions should be read in the light of the remainder of the disclosure and understood as by a person of skill in the art. The terms used herein have

their meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

[0021] The articles "a", "an" and "the" are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included. It is not intended to be construed as "consists of only".

[0022] Throughout this specification, unless the context requires otherwise the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated element or step or group of element or steps but not the exclusion of any other element or step or group of element or steps.

[0023] The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

[0024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the disclosure, the preferred methods, and materials are now described. All publications mentioned herein are incorporated herein by reference.

[0025] The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purposes of exemplification only. Functionally equivalent products and processes are clearly within the scope of the disclosure, as described herein.

[0026] The term "pharmaceutical composition" refers to delivery system in which active agents are delivered to the patients. This could be in the form of tablet, capsule, injection, liquid etc.

[0027] The term "pharmaceutically acceptable excipient" refers to inert substances other than active ingredients which are used in the preparation of pharmaceutical products. The excipients that are useful in preparing a pharmaceutical composition are generally safe and non-toxic.

[0028] The term "inert core" as used herein refers to spheres/pellets which doesn't comprises any active agents; wherein the core is coated with multi-layer coating system.

[0029] The term "delayed release" as used herein refers to drug delivery system which release the active agents in delayed on prolonged period of time and prevents the release of active agent in acidic environment. For the purpose of this invention enteric-coated articles are delayed release dosage forms.

[0030] The term "immediate release" as used herein refers to drug delivery system which release the active agent immediately after administration of active agents.

[0031] In an embodiment the present invention provides a novel drug delivery system comprising fixed dose combination of Proton pump inhibitors(PPIs) and Prokinetic in a single composition wherein one of the active agents exhibits pH dependent drug release.

[0032] In an embodiment the PPI's are selected from but not limited to Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole, Dexlansoprazole and leminoprazole, including isomers, enantiomers and tautomers thereof, and alkaline salts thereof or combinations thereof.

[0033] In an embodiment the prokinetic agents are selected from but not limited to metoclopramide, Domperidone, erythromycin, and cisapride or its salts or combinations thereof.

[0034] In an another embodiment, the present invention provides a solid oral drug delivery system comprising delayed release PPIs and immediate release prokinetic agents wherein PPIs is preferably Omeprazole or its pharmaceutical acceptable salts thereof and Prokinetic agent is Domperidone or its pharmaceutical acceptable salts thereof.

[0035] In an another embodiment the present invention is used in the treatment of Gastroesophageal Reflux Disease (GERD), heart burn or acidity, peptic ulcers or Zollinger-Ellison syndrome.

[0036] In another embodiment the present invention provides a solid drug delivery system wherein the drug delivery system is a multilayer formulation comprising a gastro-resistant delayed drug release layer and an immediate drug release layer, wherein the gastro-resistant delayed drug release layer comprises of Omeprazole and the immediate drug release layer comprises of Domperidone.

[0037] In another embodiment the present invention provides a multilayer composition comprising a gastro-resistant delayed drug release layer, wherein the drug is omeprazole.

[0038] In an another embodiment the present invention provides a multilayer composition comprising an immediate drug release layer, wherein the drug is Domperidone.

[0039] In a preferred embodiment the present invention provides a multilayer composition comprising a gastro-resistant delayed drug release layer, wherein the drug is omeprazole and an immediate release layer, wherein the drug is Domperidone.

[0040] In a preferred embodiment the multilayer composition of the present invention is present in the form of pellets, granules, beads, mini-tablets or tablets. In a preferred embodiment the multilayer composition of the present invention is present in the form of pellets, granules, beads, mini-tablets or tablets, which are encapsulated in a capsule shell. In a most preferred embodiment the multilayer composition of the present invention is present in the form of pellets encapsulated in a capsule shell.

[0041] In an another embodiment the present invention provides a multi-layer pellet composition comprising a gastro-resistant Omeprazole layer which is soluble at specific pH and an immediate release Domperidone layer and wherein the multilayer pellets are encapsulated in a capsule shell.

[0042] The hard capsule of the present invention can be manufactured by a method known to those skilled in the art, or a commercially available hard capsule can be also used. In an embodiment the hard capsule shell is made of hydroxypropyl methyl cellulose or gelatin.

[0043] In an another embodiment the multilayer pellet composition of the present invention comprises a gastro-resistant delayed release layer, wherein the drug is omeprazole and an immediate release layer, wherein the drug is domperidone, further comprises an inert core, wherein the gastro-resistant delayed drug release layer is coated over the inert core and the immediate release layer is coated over the delayed drug release layer.

[0044] In another embodiment the gastro-resistant delayed release layer of the present invention comprises of a first drug coating layer, a sub coating layer and a gastro-resistant polymer coating layer. Wherein the sub coating layer is coated over the first drug coating layer and the gastro-resistant layer is coated over the sub-coating layer.

[0045] In an embodiment the immediate release layer comprises of the second drug coating layer and seal coating layer, wherein the seal coating layer is coated over the drug coating layer.

[0046] In an embodiment the inert core of the present invention comprises of sugar sphere.

[0047] Thus in an embodiment the present invention provides a multilayer pellet composition comprising:

a. an inert core,
b. a gastro-resistant delayed drug release layer comprising a first drug coating layer, a sub-coating layer and a gastro-resistant layer
c. an immediate drug release layer comprising second drug coating layer and seal coating layer.

wherein the inert core of the present invention is a sugar sphere.

[0048] In an embodiment the first drug coating layer of the present invention comprises dispersion of 13.33% w/w of omeprazole, 2.33% w/w of hydroxypropyl methyl cellulose and 0.49% w/w of magnesium oxide.

[0049] In an embodiment the sub-coating layer of the gastro resistant delayer drug release layer of the present invention comprises of a film forming agent and a glidant.

[0050] In an embodiment Gastro-resistant layer coating of the Gastro resistant delayed drug release layer present invention is pH sensitive layer which is insoluble in acidic pH and soluble in basic pH.

[0051] In an another embodiment the Gastro resistant layer comprises Gastro-resistant polymer, plasticizer, surfactant, anti-tacking agent, colorant, basifier, wherein Gastro-resistant polymer is selected from group consisting of hydroxypropyl methylcellulose phtalate (HMPCP), polyvinyl acetate phtalate (PVAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), alginate,

carbomer, carboxymethylcellulose, methacrylic acid copolymer (Eudragit L, Eudragit S, Acrycoat), shellac, cellulose acetate phthalate (CAP), starch glycolate, polacrylin, methyl cellulose acetate phtalate, hydroxypropyulcellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate and cellulose acetate trimellitate.

[0052] In a preferred embodiment the Gastro-resistant layer is methacrylic acid copolymer present in an amount of 16.00 %w/w based on dry polymer and 53.33 % w/v based on dispersion weight. The enteric coated pellet is further coated with layer comprising Domperidone and further protected with a seal coat.

[0053] In an another embodiment the Gastro-resistant coating layer stops the release of PPIs in acidic environment thus protecting the PPIs by forming a Gastro resistant layer.

[0054] In an embodiment the second drug coating layer of the present invention comprises of domeperidone, a film forming agent, plasticizer and a colorant, In a preferred embodiment, domperidone is present in an amount of 6.67% w/w, hydroxypropyl methylcellulose is present as film forming agent in an amount of 0.97%. triethyl citrate as plasticizer present in an amount 0.33% and colorant present in an amount 0.33% w/w based on total weight of pellet formulation.

[0055] In an embodiment the seal coating layer of the immediate release layer of the present invention is comprised a film forming agent and anti-tacking agent.

[0056] In a further embodiment the film forming agent is hydroxypropyl methylcellulose present in an amount 0.54% w/w and anti-tacking agent is talc present in an amount of 0.37% w/w based on total weight of pellet formulation.

[0057] In an embodiment, the present invention provides a multi-layer pellets which is further filled into a hard gelatin capsule. The multi-layer pellets of the present invention are formed by forming a layer containing Omerprazole on an inert core, more particularly a sugar sphere, subjected the drug loading core to

sub coating and enteric coating and the forming a layer containing Domperidone on the enteric coated layer wherein Domperidone layer is an immediate release layer.

[0058] In an embodiment the present invention provides a pharmaceutical composition comprising:

i. An inert core
ii. First drug coating layer
iii. A sub coating
iv. Enteric coating
v. Second drug coating layer
vi. Seal coating layer

[0059] In an embodiment the present invention comprises a multi-layer composition comprising:

i. an inert core wherein inert core is a sugar sphere and;
ii. first drug coating layer comprising omeprazole
iii. a sub-coating layer surrounding the first drug coating layer
iv. a gastro-resistant layer comprising methacrylic acid copolymer
v. second drug coating layer comprising Domperidone
vi. a seal coating layer

[0060] In an embodiment the present invention provides a multiplayer pellet composition comprising:

i. an inert core wherein the inert core is a sugar sphere
ii. a first drug coating layer comprising omeprazole in the amount of 13.33% w/w
iii. a sub-coating surrounding the drug coating layer
iv. a gastro-resistant layer comprising methacrylic acid copolymer present in the amount of 16.00%

v. a second drug coating layer comprising Domperidone in the amount of 6.67% w/w,

vi. a seal coating layer over the Domperidone drug coating layer

[0061] The pellets of the present invention can be prepared by different process based on three principles i.e. Layering, extrusion-Spheronization and build-up granulation. In an embodiment the present invention utilizes layering technology for preparation of pellets comprising delayed release PPIs and immediate release prokinetic agents.

[0062] The multi-layer pellet manufacturing technology of the present invention is cost effective and required less time for manufacturing as compared to existing formulation which generally involves preparation of separate Omeprazole Enteric coating pellets & Domperidone pellets and then filling the same in capsule.

[0063] Preferably, the multi-layer pellet in accordance with the present invention, provides a novel formulation and process resulting in a reduced size, average weight and fill weight as compared to marketed capsule formulation (OMEJEL-DM). In an embodiment the present invention provides a multilayer pellets wherein the weight of the capsule was reduced by about 55% in comparison to the weight of the marketed capsule. Thus the subject invention has the advantage of reduction in cost and manufacturing process as well increasing the patient's convenience as some patients have difficulty in swallowing large size capsules.

[0064] In an another embodiment, the present invention provides a process of preparation of multi-layer pellets wherein the process involves following steps:

i. Drug loading of omeprazole on an inert core wherein inert core is a sugar pellet

ii. Sub-coating the drug loaded pellet with polymer dispersion.

iii. Enteric coating the sub coated pellet with a Gastro-resistant polymer

iv. Drug loading of Domperidone on enteric coated pellet

v. Barrier coating of Domperidone with a seal coating polymer dispersion

[0065] The present invention will hereinafter be described in further details by examples. It is to be understood that these examples are presented for illustrative purpose only and not intended to limit the scope of the present invention.

Example-1

Table 1-Formula for Omeprazole EC 13.33% w/w + Domperidone IR 6.67% w/w (Single pellet)

S.no	Ingredients	Function	Weight (mg/unit)
1	Sugar sphere	Core Material	42.00
2	Omeprazole	API	13.33
3	Hydroxypropyl Methylcellulose E15	Film Forming Agent	2.33
4	Heavy Magnesium Oxide	Basicity agent	0.49
5	Purified Water	Coating Solvent	q.s.
Total			58.15
Sub Coating (Omeprazole SC) (Sub-coating dispersion 20 % Solid Content)			
6	Hydroxypropyl Methylcellulose)Hypromellose E15)	Film Forming Agent	1.20
7	Talc	Glidant	4.67
8	Purified Water	Coating Solvent	q.s.
	Total		64.02
Gastro-resistant Coating (Omeprazole GR) (Enteric-coating dispersion 20 % Solid Content)			
9	Methacrylic Acid Copolymer dispersion	Gastro-resistant Polymer	16.00 (Dry polymer) 53.33 (Dispersion)
10	Triethyl Citrate	Plasticizer	2.51
11	Polysorbate 80	Surfactant	0.25
12	Talc	Anti-Tacking Agent	6.15
13	Titanium Dioxide	Colorant	1.21
14	Sodium Hydroxide	Basifier	0.04
15	Purified Water	Coating Solvent	q.s.
Total			90.18

Domperidone IR Layer (Drug loading dispersion 20 % Solid Content)			
16	Domperidone	API	6.67
17	Hypromellose E15	Film Forming Agent	0.97
18	Triethyl Citrate	Plasticizer	0.33
19	FD&C Yellow No.06 (Sunset Yellow)	Colorant	0.33
20	Purified Water	Coating Solvent	q.s.
Total			98.48
Seal Coating (Seal Coating dispersion 5 % Solid Content)			
21	hydroxypropyl methylcellulose (Hypromellose E15)	Film Forming Agent	0.54
22	Talc	Anti-Tacking Agent	0.37
23	Purified Water	Coating Solvent	q.s.
Total			99.39
24	Talc	Anti-adherent	0.61
Total			100.00

Example-2:

Process of Preparation Omeprazole EC 13.33% w/w + Domperidone IR 6.67% w/w (Single pellet)

Coating of inert core with Omeprazole:

[0066] Inert sugar pellets were placed in a fluid bed system for fluidization of pellets. A dispersion solution of 13.33% w/w Omeprazole, 2.33% hydroxypropyl Methylcellulose, 0.49% magnesium oxide in water were sprayed on sugar pellets to for a layer.

Sub coating:

[0067] After loading the sugar pellets with Omeprazole dispersion, a sub-coating dispersion solution consisting of Hydroxypropyl methylcellulose, talc dissolved in purified water were sprayed on omeprazole loaded pellets to form a sub-coating layer.

Enteric coating:

[0068] Polysorbate 80, triethyl citrate were mixed in purified water, to this solution talc, titanium dioxide and Methacrylic acid copolymer were mixed into the solution to form enteric coating dispersion. This enteric coating solution was coated over sub-coated pellets to form enteric coating layer.

Domperidone coating:

[0069] Enteric coated pellets were loaded into fluid bed system were fluidized with domperidone dispersion comprising hydroxypropyl methylcellulose, triethyl citrate. The dispersion was coated over enteric coated pellets to form a layer containing Domperidone.

Seal coating:

[0070] Hydroxypropyl methylcellulose and talc were dissolved in purified water to form dispersion solution; the dispersion was coated over Domperidone coated layer to form a film or barrier layer.

Example-3:

COMPARATIVE STUDIES

[0071] The multi-layer formulation of present study as per example-1 was compared with marketed formulation of OMEJEL-DM, which is hardgel capsule comprising Omeprazole 20mg mini-tablet & Domperidone 10mg pellets. The formulations were subjected for different experimental study whose results are mentioned in below tables:

3.a: Table-2 Comparative product Characterization

Tests:	Formulation as per Example 1	OMEJEL-DM (Omeprazole 20mg & Domperidone 10mg)
Description	"Hard gelatin capsules of size “3” with Transparent pink cap and Transparent body containing orange spherical pellets"	Hard Gelatin capsules of size “1” with violet cap and opaque white body containing white spherical pellets and white tablet
Capsule size	Size-3	Size-1

Capsule weight (mg)	48 mg	79.9 mg
Average weight of capsule	198 mg	470 mg
Fill weight (mg)	150 mg	384 mg
Individual pellets (mg)	Omeprazole + Domperidone: 150 mg (as a single pellet)	Omeprazole: 322mg (Min -312.43 –Max – 331.76) Domperidone: Tab – 55mg (Min- 53.4 – Max- 55.8) Description- White color, Uncoated biconvex tablets plain on both side. Hardness-25.53-27.11 N Thickness-2.34-2.38 mm DT- 12 to 17sec Diameter- 5.03 mm

[0072] From table 2, it was clearly observed that multi-layer single pellet composition has reduced capsule size, average weight and fill weight as compared to market capsule therefore the present invention is a cost effective process.

3.b. Table-3: Comparative chemical evaluation of market Product Omejel-Dm vs multi-layer pellet of present invention

Sr. No.	Name of Test	Specification	Omejel-Dm	Formulation as per Example 1
1	Assay			
	Omeprazole	NLT 90.0% and NMT than 110.0% of the labeled amount of Claim for Omeprazole & Domperidone.	98.1	98.4
	Domperidone		102.2	98.3
2	Dissolution			
Dissolution condition		Medium: 0.1M HCl		
Acid Stage				
For Omeprazole		Not More Than 10% of the stated amount of Omeprazole is dissolved in 2 hours.	0.00	0.00
For Domperidone		Not less than 75% (D) of the stated amount of Domperidone is dissolved in 60 minutes.	99.0	99.0

Buffer Stage			
Dissolution condition	Medium: Phosphate Buffer pH 6.8		
For Omeprazole	Not less than 70% (D) of the stated amount of Omeprazole is dissolved in 45 minutes.	91.0	93.0

[0073] As per table-3 it was observed that present composition is chemically non-inferior and have similar chemical characteristic as that of present marketed formulation.

3.c.: Table-4 Stability data of formulation as per Example 1

Formulation as per Example 1									
Label claim: Each 100 mg Pellets contains: Omeprazole IP .....13.33 mg (As Enteric Coated Pellets) Domperidone IP .....6.67 mg (Dispersed as Immediate Release pellets) Excipients..... q. s Approved colors used in pellets									
Sr. No.	Name of Test	Specification	Result						
			Initial	40°C/75 % RH 1 M	40°C/75 % RH 2 M	40°C/75 % RH 3 M	30°C/75 % RH 3 M	30°C/65 % RH 3 M	25°C/60 % RH 3 M
1.	Description	Orange color spherical pellets	Complies						
2.	Loss On Drying	NMT 7.0%	2.7	3.6	4.4	3.5	3.6	5.2	5.5
3.	Assay								
	Omeprazole	90.0%-110.0% amount of label claim	98.4	96.2	96.5	98.5	98.7	97.6	98.3
	Domperidone	90.0% -110.0% amount of label claim	98.3	98.9	100.3	102.9	102.6	102.3	102.1
4.	Dissolution								
	Dissolution Condition	Medium: 0.1 M HCL; Time 60 min (Domperidone) Medium: 0.1 M HCL; Time 2 hrs (Omeprazole) Medium: Phosphate buffer pH 6.8; Time 45 min (Omeprazole)							

5.	Acid Stage		% Drug Release						
	For Omeprazole	NMT 10% in 120 minutes.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	For Domperidone	NLT 75% (Q) in 60 minutes.	99	99	99	95	93	96	97
6.	Buffer Stage								
	For Omeprazole	NLT 70% (Q) in 45 minutes.	93	83	86	88	88	90	90

3.d. Table 5- Stability data of Omejel-DM

Omejel-DM									
Label claim: Each hard gelatin capsule contains: Omeprazole IP .....20 mg (As Enteric Coated Pellets) Domperidone IP .....10 mg (Dispersed as Immediate Release pellets) Excipients..... q. s Colour : Sunset Yellow FCF									
Sr. No.	Name of Test	Specification	Result						
			Initial	40°C/ 75 % RH	40°C/75 % RH	40°C/75 % RH	30°C/75 % RH	30°C/ 65 % RH	25°C/ 60 % RH
				1 M	2 M	3 M	3 M	3 M	3 M
1.	Description	"Hard gelatin capsules of size “3” with Transparent pink cap and Transparent body containing orange spherical pellets"	Complies						
2.	Loss On Drying	NMT 7.0%	2.7	3.3	4.5	4.9	3.5	5.1	5.0
3.	Assay								
	Omeprazole	90.0%-110.0% amount of label claim	98.4	99.4	96.4	99.5	97.5	99.1	96.1
	Domperidone	90.0%-110.0% amount of label claim	98.3	101.3	99.6	101.5	102.1	102.7	99.0
4.	Dissolution								
	Dissolution Condition	Medium: 0.1 M HCL; Time 60 min (Domperidone) Medium: 0.1 M HCL; Time 2 hrs (Omeprazole)							

		Medium: Phosphate buffer pH 6.8; Time 45 min (Omeprazole)							
5.	Acid Stage		% Drug Release						
	For Omeprazole	NMT 10% in 120 minutes.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	For Domperidone	NLT 75% (Q) in 60 minutes.	99	102	100	104	102	102	101
6.	Buffer Stage								
	For Omeprazole	NLT 70% (Q) in 45 minutes.	93	86	88	84	84	87	88

[0074] Conclusion – From Table 2 it can be observed that the fill weight of the capsule prepared from the pellets based on the present invention was more then 60-70% less than the marketed formulation. Thus the multi-layer single pellet composition has reduced capsule size, average weight and fills weight as compared to market capsule therefore the present invention is cost-effective

[0075] Although the weight of the capsule was 60 to 70% lesser compared to the marketed conventional formulation, from table 3 to 5 it can be observed that the stability and dissolution and disintegration profiles were non-inferior or better than the marketed formulation.

We claim:

1. A multi-layer solid dosage form comprising:
    a. an inert core and;
    b. a first drug coating layer comprising an effective amount of proton pump inhibitors surrounding the inert core and;
    c. a sub-coating layer surrounding the drug coating layer and;
    d. a gastro-resistant layer surrounding the inert core and;
    e. a second drug coating layer comprising an effective amount of Prokinetic agents.
    f. a seal coating layer,
2. A multi-layer solid dosage form as claimed in claim 1 wherein the inert core is a sugar sphere.
3. A multi-layer solid dosage form as claimed in claim 1 wherein the first drug coating layer comprises omeprazole or a pharmaceutically acceptable salts thereof as proton pump inhibitors
4. A multi-layer solid dosage form as claimed in claim 1 wherein the second drug coating layer comprises Domperidone or a pharmaceutically acceptable salts thereof as Prokinetic agent.
5. A multi-layer solid dosage form as claimed in claim 1 is in form of pellet or granules, or minitablets form wherein multi-layer solid dosage form is a pellet.
6. A multi-layer pellet composition as claimed in any of claims 1-5 comprising:
    a) an inert sugar core and;
    b) a drug coating layer comprising omeprazole present in an amount 13.33% w/v and;
    c) a sub-coating layer surrounding the drug coating layer and;
    d) a gastro-resistant layer comprising methacrylic acid copolymer present in amount 16.00 % w/w surrounding the sub-coating layer and;
    e) a second drug coating layer comprising Domperidone present in amount 6.67% w/w surrounding the gastro-resistant layer and;
    f) a seal coating layer

7. A multilayer pellet as claimed in claim 1 and 6 comprises:
    a) the inert core,
    b) the first drug coating layer,
    c) the sub-coating layer and
    d) the gastro resistant layer forms the gastro resistant delayed drug release layer and
    e) the second drug coating layer and
    f) the seal coating layer forms the immediate drug release layer
8. A multi-layer pellet as claimed in claim 6 wherein drug coating layer further comprises excipients selected from film forming agent, basicity agent and a coating solvent wherein film forming agent is hydroxypropyl methylcellulose and basicity agent is magnesium oxide.
9. A multi-layer pellet as claimed in claim 6, wherein immediate layer further comprises excipients selected from film forming agent, plastricizer and a colorant, this layer is further coated with a protective seal coating layer comprising film forming agent and anti-tacking agent wherein film forming agent is hydroxypropyl methylcellulose and plasticizer is triethyl citrate.
10. A multi-layer pellet as claimed in claim 6 are further enclosed in a hard gelatin capsule.
11. A process of preparation of multi-layer pellet composition comprising:
    i. Drug loading of omeprazole on an inert core wherein inert core is a sugar pellet and;
    ii. Sub-coating the drug loaded pellet with polymer dispersion and;
    iii. Enteric coating the sub coated pellet with a Gastro-resistant polymer and;
    iv. Drug loading of Domperidone on enteric coated pellet and;
    v. Barrier coating of Domperidone with a seal coating polymer dispersion

Wherein the pellets are further filled in a hard gelatin capsule.

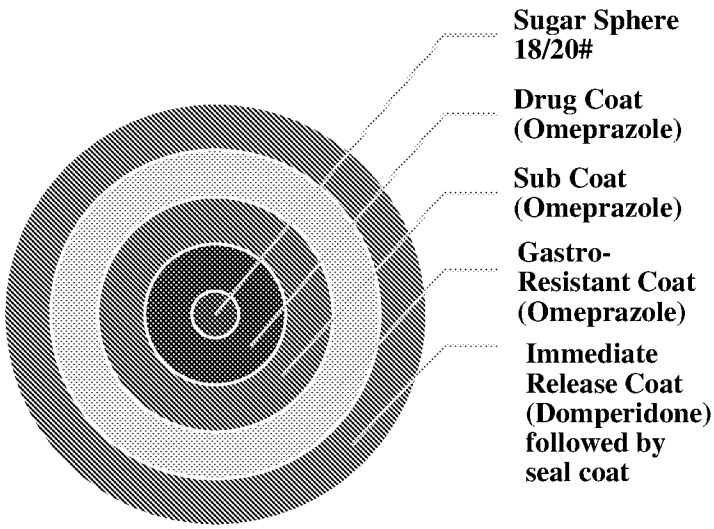
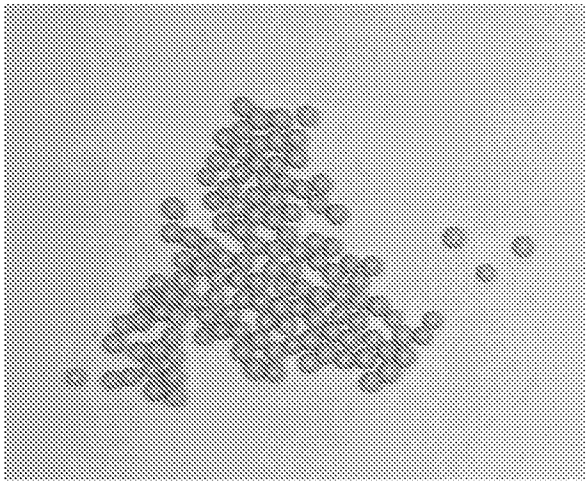
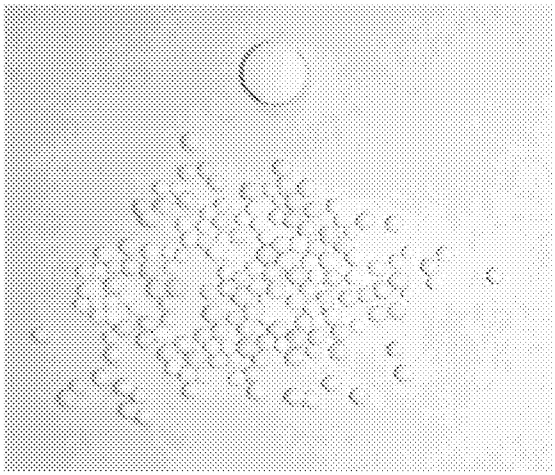

Sugar Sphere 18/20#
Drug Coat (Omeprazole)
Sub Coat (Omeprazole)
Gastro-Resistant Coat (Omeprazole)
Immediate Release Coat (Domperidone) followed by seal coat

Figure.1



Multi-layer single pellet of present invention



Marketed formulation (Pellets+ Minitablets)

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2023/051118

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/454,A61K31/4439,A61K9/20,A61K9/24,A61K9/28,A61K9/48,A61K9/36,A61K47/26,A61K47/36,A61K47/02,A61K9/52,A61K9/54 Version=2024.01
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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MX PA06007779 A (RAJESH JAIN, KOUR CHAND JINDAL, PANACEA BIOTEC LTD, SING SUKHJEET); 13th Dec 2006 (13/12/2006) Abstract; Example-1 to 4; Table-1; Claims 1 to 13	1-11
X	IN 4090/MUM/2015 A (MEDLEY PHARMACEUTICALS LIMITED); 11th Dec 2015 (11/12/2015); [FAMILY:NONE] Page 22 to 29; Example 1 to 3; Claims 1-13	1-11
X	WO 2010/038241 A2 (PANACEA BIOTEC LIMITED); 08th April 2010 (08/04/2010) Abstract; Page 17-33; Example 1-6; Claims 1-22	1-11
X	WO 2004/071374 A2 (TORRENT PHARMACEUTICALS LIMITED); 26th Aug 2004 (26/08/2004) Figure 1-9; Example 1-16; Claims 1-44	1-11
X	IN 196/MUM/2004 A (TORRENT PHARMACEUTICALS LIMITED); 20th Jan 2006 (20/01/2006); [FAMILY:NONE] Claims 1-39	1-11

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
22-02-2024	22-02-2024
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Dr Gundeboina Narasimha Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2023/051118

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1997/025065 A1 (ASTRA AKTIEBOLAG); 17th July 1997 (17/07/1997) Abstract; Figure 1-4; Example 1-14; Claims 1-30	1-11
X	WO 2005/065664 A1 (PANACEA BIOTEC LTD); 21st July 2005 (21/07/2005) Page 8-19; Example 1-4; Claims 1-42	1-11
A	WO 2006/089493 A1 (OSMOTICA CORP); 31st Aug 2006 (31/08/2006) Title; Abstract; Examples 1-9; Claims 1-86	1-11
A	JP 2007/153884 A (ASAHI KASEI CHEMICALS CORP); 21st June 2007 (21/06/2007); [FAMILY:NONE] Whole document	1-11
A	EP 1356808 A2 (ETHICON INC); 29th Oct 2003 (29/10/2003) Abstract; Example 1-3; Claims 1-10	1-11
A	WO 2004/039357 A1 (RÖHM GMBH & CO. KG); 13th May 2004 (13/05/2004) Abstract; Example 1-4; Claims 1-12	1-11

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2023/051118

Citation	Pub.Date	Family	Pub.Date
MX PA06007779 A	13-12-2006	ID 480881 A	06-03-2008
WO 2010038241 A2	08-04-2010	IN 2284/DEL/2008 A	09-04-2010
WO 2004071374 A2	26-08-2004	EP 1596838 A2	23-11-2005
		IN 196117 A1	14-10-2005
WO 1997025065 A1	17-07-1997	AU 712572 B2	11-11-1999
		BR 9607344 A	30-12-1997
		CN 1142792 C	24-03-2004
		DE 69624910 T2	04-09-2003
		EP 0814840 B1	20-11-2002
		JP H11501949 A	16-02-1999
		KR 100486057 B1	08-09-2005
		US 6132771 A	17-10-2000
WO 2005065664 A1	21-07-2005	AP 2006003703 A0	31-08-2006
		AU 2005204014 B2	28-02-2008
		EP 1729743 A1	13-12-2006
		US 2007160664 A1	12-07-2007
		ZA 200606409 B	25-06-2008
		PH 12006501304 B	20-09-2010
		IN 265244 A1	13-02-2015
WO 2006089493 A1	31-08-2006	AR 0515950 A1	21-02-2007
EP 1356808 A2	29-10-2003	JP 2004035547 A	05-02-2004
		US 2003203027 A1	30-10-2003
		US 2005158385 A1	21-07-2005
WO 2004039357 A1	13-05-2004	US 2006204576 A1	14-09-2006
		JP 4819362 B2	24-11-2011
		IN 215420 A1	31-03-2008
		CN 1688295 B	24-08-2011
		EP 1556016 B1	03-09-2008
		AU 2003266351 A1	25-05-2004
		KR 20050083847 A	26-08-2005
		PL 206707 B1	30-09-2010