# COLON TARGETED PHARMACEUTICAL COMPOSITION OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE AND CURCUMIN


## ABSTRACT

The present invention relates to a colon targeted pharmaceutical composition comprising synergistic combination of Esomeprazole Magnesium Trihydrate and curcumin for treatment of Ulcerative Colitis having pH dependent release profile in colon.

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We claim,

1. A colon targeted pharmaceutical composition comprising combination of Esomeprazole Magnesium Trihydrate (EOT) and Curcumin for treatment of Ulcerative Colitis.

2. The colon targeted pharmaceutical composition according to claim wherein

   I. Core comprises

      a) Esomeprazole Magnesium Trihydrate;

      b) Complex of Curcumin and one or more Solubilizer and

      c) *Diluent/Pelletizing* aids and one or more pharmaceutical excipient;

   II. pH dependent coating layer comprises release controlling polymer and one or more pharmaceutically excipient.

3. The colon targeted pharmaceutical composition according to claim 1 containing

   a) a pellet of Esomeprazole Magnesium Trihydrate and

   b) a pellet of complex of Curcumin and one or more Solubilizer

   wherein said pellet is individually coated with pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

4. The colon targeted pharmaceutical composition according to claim 2 wherein the amount of Esomeprazole Magnesium Trihydrate is rang from 2 to 20% by weight of total composition.

5. The colon targeted pharmaceutical composition according to claim 3 wherein the amount of Esomeprazole Magnesium Trihydrate is at least 50 % by weight of total composition of Esomeprazole Magnesium Trihydrate pellet.

6. The colon targeted pharmaceutical composition according to claim 2 or 3 wherein one or more solubilzer is selected form surfactants, β-cyclodextrin and β-hydroxyl propyl cyclodextrin or mixture thereof.

7. The colon targeted pharmaceutical composition according to claim 2 wherein

   a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

   b) Complex of Curcumin and one or more Solubilizer at least 50% by weight of total composition; and

   c) Diluent/Pelletizing aids in range of 2 to 40 by weight of total composition and one or more pharmaceutical excipient in range from 2 to 18% by weight of total composition.

8. The colon targeted pharmaceutical composition according to claim 3 wherein

   a) pellet comprises Esomeprazole Magnesium Trihydrate at least 50%, diluent/pelletizing aids in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet compoistion;

   b) pellet comprises complex of Curcumin and one or more solubilizer at least 50%, diluent/pelletizing in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet composition.

9. The colon targeted pharmaceutical composition according to claim 1 wherein

   I. Core comprises

      a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

      b) Complex of Curcumin and β-cyclodextrin at least 50% by weight of total composition wherein ratio of curcumin to β-cyclodextrin is 1:2; and

      c) Microcrystalline cellulose in range of 2 to 40 by weight of total composition and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and

croscarmellose sodium (CCS) or combination thereof in range from 2 to 18 % by weight of total composition;

II. pH dependent coating layer comprises of release methacrylic acid-methyl methacrylate copolymers, glycerin and talc.

10. The colon targeted pharmaceutical composition according to claim 1 comprising

a) pellet comprises of Esomeprazole Magnesium Trihydrate in range of 70 to 90%, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition;

b) pellet comprises complex of Curcumin and β-cyclodextrin at least 50% wherein ratio of curcumin to β-cyclodextrin is 1:2, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition

wherein said pellet is individually coated with pH dependent coating layer comprises methacrylic acid-methyl methacrylate copolymers, glycerine and talc.

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**Dr. SUBHASHKUMAR S. VAGHANI**

## FIELD OF INVENTION

The present invention relates to a colon targeted pharmaceutical composition comprising synergistic combination of Esomeprazole Magnesium Trihydrate and Curcumin for treatment of Ulcerative Colitis.

## BACKGROUND OF INVENTION

Esomeprazole Magnesium Trihydrate (EOT) (5-methoxy-2-[(R)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methane]sulfinyl]-1H-1,3-benzodiazole) is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the $H^+/K^+$-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

Proton Pump Inhibitors blocked NADPH-dependent ROS (Reactive oxygen Species) formation in the cell lines. It also increases the level of Glutathione. *In Vitro* studies suggest that Proton Pump inhibitors might protect against oxidative damage in the GIT by inducing enzyme heme-oxygenase-I in endothelial and epithelial cells. Heme-oxygenase-I enzyme catalyse the Heme degradation that generate the Bilirubin and Carbon Monoxide. Bilirubin has Antioxidant effect and Carbon Monoxide which have Cytoprotective effect. Proton Pump Inhibitors induced Heme-oxygenase-I mRNA & Protein in human endothelial cells and Cancer cell line.

Esomeprazole Magnesium Trihydrate has been approved for the treatment of GERD and Ulcerative colitis and has been marketed since 2007 in several European countries under the trademark Nexium® (Astrageneca, Wilmington). The recommended starting oral dose of Esomeprazole Magnesium Trihydrate is 20 mg twice daily.

Curcumin ((1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is herbal anti inflammatory and antioxidant drug and is a highly pleiotropic molecule capable of interacting with numerous molecular targets that modulates the inflammatory response by down regulating the activity of COX-2, lipooxygenase inducible (iNOS) enzyme. COX-2 and iNOS inhibition is accomplished via supression of nuclear factor-kappa(NF-kβ)activation.

Curcumin reduce the level of Nitric Oxide and $O_2$ radicals and Supressed NF-kβ activation in colonic mucosa cause reduced inflammation, Symptom improvement and improved colonic architecture. Curcumin reduce the rise of TNF-α , reduce nitrites colonic levels and induce down regulating of COX-2 & iNOS expression cause reduction in the activation of p38 MAPKs.Reduction in p38 MAPKs cause the reduced the levels of COX-2 and iNOS immunosignals and nitrite production in Colonic Mucosa.

Surprisingly it was found that it is beneficial to use above mentioned action of curcumin on colonic mucosa to prepare colon targeted pharmaceutical composition of Esomeprazole Magnesium Trihydrate. Hence, the present invention provide colon targeted pharmaceutical composition comprises of synergistic combination of Esomeprazole Magnesium Trihydrate and Curcumin to fulfill the unmeet need of efficient and effective treatment Ulcerative Colitis.

## OBJECT OF THE INVENTION

An object of the present invention is to provide a colon targeted pharmaceutical composition comprising combination of Esomeprazole Magnesium Trihydrate (EOT) and Curcumin for treatment of Ulcerative Colitis.

Another object of the invention is to provide said pharmaceutical composition which show pH dependent release in colonic region.

Another object of the invention is to provide said pharmaceutical composition having improved bioavailability of curcumin.

Further object of the present invention is to provide process for preparation of said pharmaceutical composition.

**DETAILED DESCRIPTION OF INVENTON**

Accordingly the present invention provides a colon targeted pharmaceutical composition comprising combination of Esomeprazole Magnesium Trihydrate (EOT) and Curcumin for treatment of Ulcerative Colitis.

As per the preferred embodiment of the present invention a colon targeted pharmaceutical composition wherein :

I. Core comprises

   a) Esomeprazole Magnesium Trihydrate;

   b) Complex of Curcumin and one or more Solubilizer;

   c) Diluent/Pelletizing aids and one or more pharmaceutical excipient;

II. pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

As per another embodiment of the present invention a colon targeted pharmaceutical composition containing:

   a) a pellet of Esomeprazole Magnesium Trihydrate and

   b) a pellet of complex of Curcumin and one or more Solubilizer

wherein said pellet is individual coated with pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

As per another embodiment of the present invention a colon targeted pharmaceutical composition wherein:

I.Core comprising of

a) a pellet comprises Esomeprazole Magnesium Trihydrate, diluent/pelletizing aids and one or more pharmaceutical acceptable excipient;

b) a pellet comprises a complex of Curcumin and one or more Solubilizer, diluent/pelletizing aids and one or more pharmaceutical acceptable excipient

wherein said pellet is individual coated with pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

c) optionally one or more pharmaceutically acceptable excipient.

As per preferred embodiment of the present invention amount of Esomeprazole Magnesium Trihydrate (EOT) is range from 2 to 20%, preferably 5 to 15%, more preferably 7 to 10% by weight of total composition.

As per preferred embodiment of the present invention amount of Esomeprazole Magnesium Trihydrate (EOT) is at least 50 % by weight, preferably in range of 60 of 95 %, more preferably 70 to 90% by weight of total composition of Esomeprazole Magnesium Trihydrate pellet.

For the purpose of the present invention for preparation of curcumin complex one or more solubilizer is selected form but not limited to Solubilizer may be selected from surfactants, β-cyclodextrin (βCD) and β-hydroxyl propyl cyclodextrin or mixture thereof, preferably β-cyclodextrin (βCD).

For the purpose of the present invention in complex of curcumin ratio of curcumin to solubilizer is in range of 1:1 to 1:3, more preferably 1:2.

For the purpose of the present invention inclusion complex of curcumin with one or more solubilizer is prepared by Kneading Method. Accurately curcumin and solubilzer are mixed then mixture is kneaded using Water:Ethanol(1:1) ratio and dried.

As per preferred embodiment of the present invention amount of curcumin complex is at least 50% by weight of total composition or by weight of total composition of curcumin pellet.

For the purpose of the present invention diluent/pelletizing aids is selected from but not limited to microcrystalline cellulose grade like Avicel RC 581, Avicel RC 591, Avicel pH 101, Glyceryl Monostearate, hydroxyl propyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, lactose, sucrose, glucose, fructose, mannitol, sorbitol, xylitol, dextrose, dibasic calcium phosphate, tribasic calcium phosphate, calcium hydrogen phosphate dehydrate, magnesium carbonate, inorganic salts such as calcium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, dextrin/dextrates, maltodextrin, sodium chloride, starch, pregelatinised starch, magnesium oxide, , hypromellose or a combination thereof, preferably microcrystalline cellulose grade Avicel RC 581, Avicel RC 591 and Avicel pH 101 or combination thereof.

As per preferred embodiment, the amount of diluent/pelletizing aids is range from 2 to 40%, preferably 5 to 30% by weight of total composition or by weight of pellet composition.

For the purpose of the present invention one or more pharmaceutical excipient is selected from but not limited to a disintegrant, a binder, a lubricant or mixtures thereof.

For the purpose of the present invention a disintegrant is selected from but not limited sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP), pregelatinized starch, sodium carboxymethyl cellulose, croscarmellose sodium (CCS) natural starch, modified starch, microcrystalline cellulose, pregelatinized starch, cellulose, sodium alginate, silicone dioxide, clay, agar gum, guar gum, locust bean gum, karaya gum, pectin gum, tragacanth gum, polyvinylpyrrolidone, soy polysaccharides, ion exchange resins, sodium starch glycolate, croscarmellose sodium, crosslinked polyvinylpyrollidone, sodium carboxymethyl cellulose, carboxymethyl starch, Low-Substituted Hydroxypropyl Cellulose, Polacrilin Potassium or a combination thereof.

As per preferred embodiment, the amount of a disintegrant is range from 2 to 18% by weight of total composition or by weight of pellet composition.

For the purpose of the present invention a binder is selected from but not limited to polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose pregelatinised starch, corn starch, potato starch, cross-linked polyvinylpyrollidone,, polyvinyl alcohol (PVA), microcrystalline cellulose, methyl cellulose, ethyl cellulose, carnauba wax, alginic acid, guar gum, gum acacia, gum arabic, gelatin, agar, tragacanth, sodium alginate, wax binder such as carnauba wax, paraffin, spermaceti, gelatin or a combination thereof.

As per another embodiment of the present invention, pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient selected from plasticizer, opacifier/ antiadherent.

For the purpose of the present invention release controlling polymer may be water-insoluble, or may swell in water or dissolve in water to form a gel. Examples release controlling polymer substances used in the present invention include, but are not limited to, enteric polymeric substances. Examples of enteric polymeric substances include, but are not limited to, methacrylic acid-methyl methacrylate copolymers (Eudragit L100, Eudragit S100, Eudragit FS 30D, Eudragit NM 30D manufactured by Röhm GmbH & Co. K G, Darmstadt, Germany), methacrylic acid-ethyl acrylate copolymers (Eudragit L100-55, Eudragit L30D-55, manufactured by Röhm GmbH & Co. K G, Darmstadt, Germany), hydroxypropyl methylcellulose phthalate (HP-55, HP-50, manufactured by Shin-Etsu Chemical, Japan), hydroxypropyl methylcellulose acetate succinate (AQOAT, manufactured by Shin-Etsu Chemical, Japan), carboxymethyl ethylcellulose (CMEC, manufactured by Freund Corporation, Japan), and cellulose acetate phthalate.

For the purpose of the present invention the amount of pH dependent coating layer is in range of 2% to 7% by weight of total uncoated composition.

For the purpose of the present invention the amount of rate controlling polymer is in range of 15 % to 27 by weight of dry weight of pH dependent coating layer.

For the purpose of the present invention, plasticizers is selected from the group comprising of, but not limited to internal plasticizing agent comprises glycerine, propylene glycol, PEG 200-6000 grades and external plasticizing agent comprising diethyl phthalate (DEP), dibutyl phthalate (DBP), triethyl citrate (TEC), tributyl citrate (TBC), triacetin or mixture thereof.

For the purpose of the present invention the amount of plasticizers is in range of 60 % to 75 by weight of total weight of pH dependent coating layer.

For the purpose of the present invention, opacifier/ antiadherent is selected from the group comprising of, but not limited to titanium dioxide (TiO2), silicates like talc and aluminium carbonates, magnesium carbonate.

For the purpose of the present invention the amount of plasticizers is in range of 7 % to 15% by weight of total weight of pH dependent coating layer.

As per the most preferred embodiment of the present invention a colon targeted pharmaceutical composition wherein;

I. Core comprises

a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

b) Complex of Curcumin and one or more solubilizer at least 50% by weight of total composition; and

c) Diluent/Pelletizing aids in range of 2 to 40% by weight of total composition and one or more pharmaceutical excipient in range from 2 to 18% by weight of total composition;

II. pH dependent coating layer in range of 2% to 7% by weight of core, wherein said coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

As per another preferred embodiment of the present invention a colon targeted pharmaceutical composition wherein :

I. Core comprises

a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

b) Complex of Curcumin and β-cyclodextrin at least 50% by weight of total composition wherein ratio of curcumin to β-cyclodextrin is 1:2; and

c) Microcrystalline cellulose in range of 2 to 40 by weight of total composition and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range from 2 to 18 % by weight of total composition;

II. pH dependent coating layer in range of 2% to 7% by weight of core, wherein coating layer comprises a release methacrylic acid-methyl methacrylate copolymers in range of 15 to 27 %, glycerin 60 to 75% and talc 7 to 15% by weight of dry weight of pH dependent coating layer.

As per another preferred embodiment of the present invention a colon targeted pharmaceutical composition wherein :

I. Core comprises

a) Esomeprazole Magnesium Trihydrate in range from 7 to 10 % by weight of total composition ;

b) Complex of Curcumin and β-cyclodextrin at least 50% by weight of total composition wherein ratio of curcumin to β-cyclodextrin is 1:2; and

c) microcrystalline cellulose in range of 5 to 30% by weight and one or more disintegrant selected from sodium starch glycolate (SSG) and croscarmellose sodium (CCS) or combination thereof in range from 2 to 10% by weight of total composition;

II. pH dependent coating layer in range of 2% to 7% by weight of core, wherein coating layer comprises methacrylic acid-methyl methacrylate copolymers in range of 15 to 27 %, glycerin 60 to 75% and talc 7 to 15% by weight of dry weight of pH dependent coating layer.

As per another preferred embodiment of the present invention size of pellet comprises a Esomeprazole Magnesium Trihydrate and complex of curcumin is in range of 1.0 to 1.6 mm.

As per another embodiment of the present invention a colon targeted pharmaceutical composition wherein:

I.Core comprising

a) a pellet comprises Esomeprazole Magnesium Trihydrate at least 50%, diluent/pelletizing aids in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet composition;

b) a pellet comprises complex of Curcumin and one or more solubilizer at least 50%, diluent/pelletizing in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet composition;

wherein said pellet is individually coated with pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient and

c) optionally one or more pharmaceutically acceptable excipient.

As per another embodiment of the present invention a colon targeted pharmaceutical composition comprises

a) a pellet comprises of Esomeprazole Magnesium Trihydrate in range of 70 to 90%, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked

polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition;

b) a pellet comprises complex of Curcumin and β-cyclodextrin at least 50% wherein ratio of curcumin to β-cyclodextrin is 1:2, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition

wherein pellet is individually coated with pH dependent coating layer in range of 2% to 7% by weight of said pellet, wherein coating layer comprises methacrylic acid-methyl methacrylate copolymers in range of 15 to 27 %, glycerin 60 to 75% and talc 7 to 15% by weight of dry weight of pH dependent coating layer

As per another preferred embodiment of the present invention size of Esomeprazole Magnesium Trihydrate pellet or complex of curcumin pellet is in range of 1.2 to 1.7 mm.

As per another embodiment, the present invention also provides process for preparation a colon targeted pharmaceutical composition comprises the step of;

a) mix of Esomeprazole Magnesium Trihydrate, Complex of Curcumin with one or more, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulate the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b);

d) spheronizing extrudes of step c);

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient and

g) Coated pellet of step f) filled in capsules or compressed in tablet.

As per another embodiment, the present invention provides process for preparation a colon targeted pharmaceutical composition comprises the step of;

a) mixing of Esomeprazole Magnesium Trihydrate, Complex of Curcumin with one or more, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient and

g) Coated pellet of step f) filled in capsules or compressed in tablet.

As per another embodiment, the present invention also provides process for preparation a colon targeted pharmaceutical composition comprises the step of;

I. Esomeprazole Magnesium Trihydrate pellet

a) mix of Esomeprazole Magnesium Trihydrate, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulate the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b);

d) spheronizing extrudes of step c);

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient

II. Curcumin pellet

a) mixing of Complex of Curcumin with one or more, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulate the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b);

d) spheronizing extrudes of step c);

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient

Coated pellet of step I and II are filled in capsules or compressed in tablet.

As per another embodiment, the present invention also provides process for preparation a colon targeted pharmaceutical composition comprises the step of;

I. Esomeprazole Magnesium Trihydrate pellet

a) mix of Esomeprazole Magnesium Trihydrate, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient and

II. *Curcumin pellet*

a) mixing of Complex of Curcumin with one or more, diluent/pelletizing aids and one or more pharmaceutical excipient;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises of release controlling polymer and one or more pharmaceutically excipient

Coated pellet of step I and II are filled in capsules or compressed in tablet.

As per another embodiment, the present invention provides a process for preparation of pH dependent coating layer comprising the step of:

a) Mix of pH dependent coating polymer methacrylic acid-methyl methacrylate in Isopropyl Alcohol solvent;

b) Addition of Glycerin and mix of Step a);

c) Addition of talc and mix of Step b);

For the purpose of the present invention pharmaceutical composition may be tablet, capsules, pellets, beads or granules or minitablets.

The invention is illustrated by the following example which is only meant to illustrate the invention and not act as limitations. All embodiments apparent to

a process their in the art are deemed to fall within the scope of the present invention.

**Example 1A: Pellet Composition**

curcumin and β-cyclodextrin are mixed together. Complex of Curcumin and β-cyclodextrin is prepared by kneading the mixture using water:ethanol (1:1) solvent. Complex is dried in oven at $60^0$C. Then Esomeprazole Magnesium Trihydrate and Curcumin complex ,equivalent to dose of curcumin are mixed together and Extrudes are prepared by using pelletizing aid mcc (Avicel RC 581). Extruded mass is spheronized by Spheronizer at 700 rpm for 3 minutes. The Prepard pellets then allowed to dry at room temperature. The Prepared pellets are then coated with Eudragit S-100 using Fluidized Bed Processor.

**Example 1-4: Esomeprazole Magnesium Trihydrate and Curcumin combined pellet composition**

| Example | Curcumin: βCD (1:2) | EOT | MCC (Avicel RC581) | MCC (Avicel pH101) | SSG | CCS |
|---|---|---|---|---|---|---|
| | % W/W | | | | | |
| 1 | 70.0 | 10.0 | 10.0 | 10.0 | 0.0 | 0.0 |
| 2 | 70.0 | 10.0 | 15.0 | 0.0 | 5.0 | 0.0 |
| 2 | 65.3 | 9.2 | 15.3 | 0.0 | 5.1 | 5.1 |
| 4 | 52.8 | 7.4 | 24.9 | 0.0 | 7.5 | 7.5 |

**Process for preparation:**

a) mixing of Esomeprazole Magnesium Trihydrate (EOT), Complex of Curcumin with βCD, MCC (Avicel RC 581 & Avicel pH 101) and SSG or CCS or combination thereof.;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises methacrylic acid-methyl methacrylate copolymers (Eudragit S 100), glycerin and talc and

g) Coated pellet of step f) filled in capsules.

**Example 5-12: Esomeprazole Magnesium Trihydrate pellet composition**

| Example | EOT | MCC Avicel RC 581 | MCC Avicel PH 101 | CPP | SSG | CCS |
|---|---|---|---|---|---|---|
| | % W/W | | | | | |
| 5 | 90.0 | 5.0 | 5.0 | -- | -- | -- |
| 6 | 80.0 | 10.0 | 10.0 | -- | -- | -- |
| 7 | 80.0 | 20.0 | -- | -- | -- | -- |
| 8 | 77.0 | 10.0 | 10.0 | 3.0 | -- | -- |
| 9 | 77.0 | 20.0 | -- | 3.0 | -- | -- |
| 10 | 75.0 | 20.0 | -- | 5.0 | -- | -- |
| 11 | 73.1 | 19.2 | -- | -- | 7.7 | -- |
| 12 | 74.2 | 20.6 | -- | -- | -- | 5.2 |

**Process for preparation:**

a) mixing of Esomeprazole Magnesium Trihydrate (EOT), MCC (Avicel RC 581 or Avicel pH 101 or combination thereof ) and SSG or CPP or CCS;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises a methacrylic acid-methyl methacrylate copolymers (Eudragit S 100), glycerin and talc.

**Example 13-16: Curcumin pellet composition**

| Example | Curcumin: βCD (1:2) | MCC (Avicel RC 581) | MCC (Avicel pH 101) | SSG | CCS |
|---|---|---|---|---|---|
| | % W/W | | | | |
| 13 | 90.0 | 5.0 | 5.0 | -- | -- |
| 14 | 75.0 | 12.5 | 12.5 | -- | -- |
| 15 | 71.0 | 12.5 | 12.5 | 4.0 | -- |
| 16 | 67.0 | 25.0 | -- | 4.0 | 4.0 |

**Process for preparation:**

a) mixing of Complex of Curcumin with βCD, MCC (Avicel RC 581 or Avicel pH 101 or combination thereof ) and SSG or CCS or combination thereof;

b) granulating the mix of step a) with water till dough mass obtain;

c) extrusion of the dough mass of step b) at rpm in range of 200-800 in extruder;

d) spheronizing extrudes of step c) at rpm in range of 400-1000 rpm for 0.5 to 4 min;

e) drying of pellet of step d);

f) coating of pellet of step e) with pH dependent coating layer comprises a methacrylic acid-methyl methacrylate copolymers (Eudragit S 100), glycerin and talc.

Final compositions are prepared by using any of EOT pellet prepared according to example 5-12 and curcumin pellet prepared according to example 13-16 and filled in capsule.

**Example 17: Mean Particle Size of Pellet**

| Example | Mean Particle Size(mm) (n=25) | Example | Mean Particle Size(mm) (n=25) |
|---|---|---|---|
| 1 | 1.529 ±0.524 | 9 | 1.378 ±0.147 |
| 2 | 1.481±0.457 | 10 | 1.389 ±0.224 |
| 3 | 1.537±0.246 | 11 | 1.624 ±0.363 |
| 4 | 1.342±0.562 | 12 | 1.435 ±0.178 |
| 5 | 1.641 ±0.245 | 13 | 1.505 ±0.583 |
| 6 | 1.372 ±0.625 | 14 | 1.689±0.542 |
| 7 | 1.525 ±0.541 | 15 | 1.582±0.281 |
| 8 | 1.505 ±0.622 | 16 | 1.346±0.324 |

**Example 18: In Vitro dissolution Study**

An in-vitro dissolution study of a colon targeted pharmaceutical composition according to present invention is carried out using USP dissolution Apparatus type I (Basket type). The dissolution iswas carried out in HCl buffer pH 1.2 for 2 hours, in phosphate buffer pH 6.8 for next 1 hour and finally in Phosphate buffer pH 7.4 with 2% SLS for next 2 hours. Aliquots of 10 ml are withdrawn at specific time interval and the sample volume is replaced with an equal volume of fresh dissolution medium. The samples are filtered through whattman filter paper. The filtered samples are then analyzed by UV Spectrophotometer (Shimadzu).

**Dissolution Data**

| Time(Min.) | Capsules filled with pellet of Example 12 & 16 | | Example 4 | |
|---|---|---|---|---|
| | EOT | Curcumin | EOT | Curcumin |
| | % Drug Release | | | |
| In HCL Buffer pH-1.2 | | | | |
| 60 | 2.36±1.35 | 0.97±0.42 | 1.92±1.08 | 1.05±0.86 |
| 120 | 2.65±0.26 | 1.17±0.59 | 2.17±1.52 | 1.25±1.09 |
| In Phosphate Buffer pH-6.8 | | | | |
| 180 | 3.58±1.54 | 1.47±0.57 | 3.23±0.27 | 1.51±0.65 |
| 240 | 3.92±0.85 | 1.56±0.26 | 3.57±0.84 | 1.57±0.47 |
| In Phosphate Buffer pH-7.4 + 2% SLS | | | | |
| 255 | 26.79±1.54 | 23.56±2.48 | 26.76±1.67 | 24.93±1.92 |
| 270 | 41.98±2.64 | 41.77±1.53 | 42.01±3.46 | 45.47±2.59 |
| 285 | 74.69±0.94 | 69.29±1.58 | 74.78±1.34 | 68.14±1.64 |
| 300 | 92.15±3.87 | 98.36±1.83 | 93.12±2.43 | 97.79±1.76 |

E101/1094/2014-MUM

We claim,

1. A colon targeted pharmaceutical composition comprising combination of Esomeprazole Magnesium Trihydrate (EOT) and Curcumin for treatment of Ulcerative Colitis.

2. The colon targeted pharmaceutical composition according to claim wherein

   I. Core comprises

      a) Esomeprazole Magnesium Trihydrate;

      b) Complex of Curcumin and one or more Solubilizer and

      c) *Diluent/Pelletizing* aids and one or more pharmaceutical excipient;

   II. pH dependent coating layer comprises release controlling polymer and one or more pharmaceutically excipient.

3. The colon targeted pharmaceutical composition according to claim 1 containing

   a) a pellet of Esomeprazole Magnesium Trihydrate and

   b) a pellet of complex of Curcumin and one or more Solubilizer

   wherein said pellet is individually coated with pH dependent coating layer comprises a release controlling polymer and one or more pharmaceutically excipient.

4. The colon targeted pharmaceutical composition according to claim 2 wherein the amount of Esomeprazole Magnesium Trihydrate is rang from 2 to 20% by weight of total composition.

5. The colon targeted pharmaceutical composition according to claim 3 wherein the amount of Esomeprazole Magnesium Trihydrate is at least 50 % by weight of total composition of Esomeprazole Magnesium Trihydrate pellet.

6. The colon targeted pharmaceutical composition according to claim 2 or 3 wherein one or more solubilzer is selected form surfactants, β-cyclodextrin and β-hydroxyl propyl cyclodextrin or mixture thereof.

7. The colon targeted pharmaceutical composition according to claim 2 wherein

   a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

   b) Complex of Curcumin and one or more Solubilizer at least 50% by weight of total composition; and

   c) Diluent/Pelletizing aids in range of 2 to 40 by weight of total composition and one or more pharmaceutical excipient in range from 2 to 18% by weight of total composition.

8. The colon targeted pharmaceutical composition according to claim 3 wherein

   a) pellet comprises Esomeprazole Magnesium Trihydrate at least 50%, diluent/pelletizing aids in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet compoistion;

   b) pellet comprises complex of Curcumin and one or more solubilizer at least 50%, diluent/pelletizing in range of 5 to 30% and one or more pharmaceutical acceptable excipient in range of 2 to 18% by weight of pellet composition.

9. The colon targeted pharmaceutical composition according to claim 1 wherein

   I. Core comprises

      a) Esomeprazole Magnesium Trihydrate in range from 2 to 20 % by weight of total composition;

      b) Complex of Curcumin and β-cyclodextrin at least 50% by weight of total composition wherein ratio of curcumin to β-cyclodextrin is 1:2; and

      c) Microcrystalline cellulose in range of 2 to 40 by weight of total composition and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and

croscarmellose sodium (CCS) or combination thereof in range from 2 to 18 % by weight of total composition;

II. pH dependent coating layer comprises of release methacrylic acid-methyl methacrylate copolymers, glycerin and talc.

10. The colon targeted pharmaceutical composition according to claim 1 comprising

a) pellet comprises of Esomeprazole Magnesium Trihydrate in range of 70 to 90%, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition;

b) pellet comprises complex of Curcumin and β-cyclodextrin at least 50% wherein ratio of curcumin to β-cyclodextrin is 1:2, microcrystalline cellulose in range of 5 to 30% and one or more disintegrant selected from sodium starch glycolate (SSG), cross-linked polyvinylpyrrolidone (CPP) and croscarmellose sodium (CCS) or combination thereof in range of 2 to 18% by weight of pellet composition

wherein said pellet is individually coated with pH dependent coating layer comprises methacrylic acid-methyl methacrylate copolymers, glycerine and talc.

Dated: 15th day of March 2014

**Dr. SUBHASHKUMAR S. VAGHANI**