Abstract

There is provided an in-situ gastroretentive modified release pharmaceutical composition comprising Celiprolol or salts thereof. The present invention also provides the process for preparing the same.

We Claim:

1. A gastroretentive modified release oral pharmaceutical composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the pharmaceutical composition is in liquid form.

2. The gastroretentive modified release composition as claimed in claim 1, wherein the said solution when administered orally swells in-situ in gastrointestinal tract.

3. The gastroretentive modified release composition as claimed in claim 1, wherein one or more polymers are selected from the group consisting of polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, a fatty acid, a fatty acid ester, an alkyl alcohol, a wax, shellac, rosin, zein (prolamine from corn), povidone, kollidon SR, a poly(meth)acrylate, microcrystalline cellulose or poly(ethylene oxide), polyuronic acid salts, cellulose ethers, xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, ammonium alginate, hydroxypropyl cellulose, hydroxy ethyl cellulose, hydroxypropyl methyl cellulose, carboxyvinyl polymers, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers like methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with

copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS)

4. The gastroretentive modified release composition of claim 3, wherein the one or more polymers are selected from the group consisting of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, and ammonium alginate.

5. The gastroretentive modified release composition of claim 4, wherein the polymer if gellan gum.

6. The gastroretentive modified release composition of claim 1, further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of binders, fillers, disintegrants, glidants, lubricants, surfactants, thickening agents or viscosity modifiers, stabilizing agent, buffering agents, sweeteners, flavors and preservatives.

7. The gastroretentive modified release composition of claim 1, wherein the liquid form is solution, suspension, or emulsion.

8. A process for preparing gastroretentive modified release composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the process comprises a) preparing a dispersion of polymer in a vehicle and b) adding celiprolol or salts thereof to the polymer dispersion optionally along with one or more pharmaceutically acceptable excipients.

9. The process as claimed in claim 8, wherein the vehicle is selected from the group consisting of water, buffer solutions, hydroalcoholic solutions, polyethylene glycols and organic solutions.

10. A method for treating cardiovascular disorder, wherein the method comprises administering a gastroretentive modified release oral pharmaceutical composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the pharmaceutical composition is in liquid form to a patient in need thereof.

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4. Description

There is provided a gastroretentive modified release pharmaceutical composition comprising Celiprolol or salts thereof, wherein the pharmaceutical composition is in solution form. The invention further provides process for preparation of such compositions.

Celiprolol (brand names Cardem, Selectol, Celipres, Celipro, Celol, Cordiax, Dilanorm) is a medication in the class of beta blockers, used in the treatment of high blood pressure. It has a unique pharmacology: it is a selective β1 receptor antagonist, but a β2 receptor partial agonist. It is also a weak α2 receptor antagonist. Chemically Celiprolol is designated as (RS)-N'-{3-acetyl-4-[3-(tert-butylamino)-2-hydroxypropoxy]phenyl}-N,N-diethylurea.

Celiprolol demonstrates vasodilator properties and does not depress heart rate to the same extent as propranolol, atenolol or metoprolol. Celiprolol has shown equivalent antihypertensive efficacy to other beta-blockers, notably propranolol, atenolol, metoprolol and pindolol, in patients aged 18 to 75 years with mild to moderate essential hypertension. The drug has also shown similar antihypertensive efficacy to the angiotensin converting enzyme inhibitor enalapril and to combination diuretic therapy with hydrochlorothiazide and amiloride. Celiprolol was equally effective in adult patients of all ages.

Drug delivery has been a subject of intense studies over recent years. Conventional drug delivery system achieves and maintains the drug concentration within treatment only when taken several times a day. This often results in damaging side effects and leads to poor control of drug therapy and there is also significant fluctuation in drug level. Recently several technical advancement have been made, which have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery to achieve and maintain the concentration of administered drug

within therapeutically effective range. Controlled drug delivery systems have been introduced to overcome the drawbacks of fluctuating drug levels associated with conventional dosage forms. The concept of sustained or prolonged release of biologically active agents has been well appreciated and rationalized for decades. Controlled release refers to the use of delivery device with the objective of releasing the drug into patient's body at a predetermined rate, or at specific times or with special release profiles.

The importance of the controlled drug delivery system that releases the bioactive component over an extended period of time has long been recognized in pharmaceutical field. Amongst the major routes of drug delivery, Oral route remains the most convenient and commonly employed means of introducing drugs to the systemic circulation. Recent advances in controlled release technology have made it possible to release drugs at a constant rate for days to years. Application of such controlled release technology to oral drug delivery however has been limited because the actual time for effective drug delivery is restricted by the gastrointestinal transit time which typically ranges from 6 to 8 hours depending upon various factors. In pharmaceutical field, controlled/sustained release systems have been widely used in oral medication from as early as 1950s. A number of oral controlled drug delivery systems have been developed for this purpose and Gastro Retentive Drug Delivery System (GRDDS) is one more step forward in this regards.

A major constraint in Oral controlled release drug delivery is that not all drug candidates are absorbed uniformly throughout the gastro intestinal tract. Some drugs are absorbed in a particular portion of GI tract only or are absorbed to a different extent in various segments of GI tract. Such drugs are said to have an absorption window. Thus only the drugs which are released in the preceding region and in close vicinity to the absorption window are available for absorption. After crossing absorption window, the released drug goes to waste with negligible or no absorption. Thus the time available for drug absorption drastically

decreases. Also most of the drugs are sparingly soluble or insoluble in gastric fluids. In these type of drugs dissolution is directly related to time available for solubilization and thus in such cases Gastric retention time (GRT) or transit time becomes significant factor for drug absorption. Also if the dosage forms pass through the drug absorption site before the complete release of loaded dose it will not perform satisfactorily. Thus attention must be given to prolonging the GRT to get complete drug release in GI tract.

Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of drug absorption through gastrointestinal tract is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

It has been suggested that formulating narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of such drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of sustained release dosage forms for these drugs.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract.

Swelling to a large size is also an important factor in gastric retention of the system. Solids having a size less than 5 to 7 mm show delayed gastric emptying in fed conditions but they can still be emptied from the stomach because their size is smaller than the pyloric sphincter. Even floating systems of size less than 5 to 7 mm can be emptied if the patient is in supine position. The mean resting pyloric diameter is approx. 13+7 mm and it has been reported that dosage forms with a size of approx. 12-18 mm diameter in their expanded state would generally be excluded from the passage of the pyloric sphincter. The system should also be capable of retaining this size in the gastric fluids for long periods under agitation conditions created by gastric motility. Such large intact systems cannot be emptied until the arrival of the interdigestive migrating motor complex at the beginning of the interdigestive phase. The combination of increase in size and floatation results in increased gastric retention of the system.

Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). The gastro retentive drug delivery systems are designed on this rationale and prove really efficacious to deliver the drug candidates with above mentioned characters.

In-situ gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site. In the field of human and animal medicine, the sites of application refers to various injection sites, topical application sites, surgical sites, and others where the agents are brought into contact with tissues or body fluids. As a drug delivery agent, the in-situ gel has an advantage related to the gel or polymer network being formed in-situ providing sustained release of the drug agent. At the same time, it permits the drug to be delivered in a liquid form.

Polymers capable of in-situ gelation have been described. They include Poloxamer, Pluronics (Vadnere et al., Int. J. Pharm., 22, 207-218, 1984), various copolymers such as PEO-PLLA and PEG-PLGA-PEG (Jeong et al., Nature 388, 860-862, 1997; Jeong et al., J. Controlled Release 63, 155-163, 2000), cellulose acetophalate latex (Gurny et al. J. Controlled Release 353-361, 1985), Gelrite (Rozier et al., Int. J. Pham. 57, 163-168, 1989), Carbopol, and Matrigel. The gel formation is induced by temperature change (Poloxamer, Pluronics, PEO-PLLA diblock copolymer, PEG-PLGA-PEG triblock copolymer, and Matrigel), pH change (cellulose acetophalate latex and Carbopol), or reaction with mono- or di-valent cations (Gelrite). However, most of them require a high polymer concentration for in-situ gel formation (>20%) (Poloxamer, PEO-PLLA diblock copoly; PEG-PLGA-PEG triblock copolymer; cellulose and acetophalate latex). The thermally gelling polymers (Poloxamer, Pluronics, PEO-PLLA diblock copolymer, PEG-PLGA-PEG triblock copolymer, and Matrigel) also have the disadvantage of gelling before administration due to temperature change during packaging or storage. Unfortunately some of these polymers are not biodegradable such as Poloxamer or require manipulation of the temperature before administration (PEO-PLLA diblock copolymer) or during formulation (Pluronics and Gelrite). An ophthalmic in-situ gelling drug delivery formulation consisting of a mixture of Carbopol and Pluronic was found to be more effective than formulations consisting of either one. However, Pluronic is used at 14% (Lin and Sung, Journal of Controlled Release 69, 379-388, 2000). Such polymers are therefore not well suited for medical applications in humans and animals. Furthermore, many of these polymers form only a hydrogel which is a viscous but still flowing solution (e.g., Poloxamer and Pluronics).

Attwood.D *et al* [2000] evaluated Gels formed in situ following oral administration of aqueous solutions of sodium alginate (1.0–2.0%w/v) to rats as sustained release vehicles for the delivery of Theophylline. The liquid formulation contained calcium ions in complexed form, the release of which in the acidic environment of the stomach caused gelation of the alginate. Bioavailability of Theophylline from alginate gels formed by in situ gelation in the rat stomach was increased by 1.3–

2-fold in rats for alginate concentrations of 2.0 to 1.0 %w/v respectively compared with that from a proprietary oral sustained release formulation containing an identical drug concentration. There was no significant difference in the mean residence times of Theophylline when administered by these two vehicles.

Attwood.D *et al* [2006] examine the influence of variation of gastric pH over the range 1–3 on the gelation of liquid formulations of pectin and on the *In vitro* and *In vivo* release of paracetamol and ambroxol from the resultant gels. The formulations were dilute solutions of pectin containing complexed calcium ions that form gels when these ions are released in the acidic environment of the stomach. Gels suitable as vehicles for sustained delivery of these drugs were formed in vitro at pH < 3 from pectin solutions of concentrations 1.0–2.0% (w/v). Very weak gels were formed at pH 3.0 resulting in poor sustained release characteristics compared with those at pH 1.2; no significant in vitro gelation was observed at pH 3.5.

Alhaique.F *et al* [1996] studied the ability of gellan to form gels in the *presence* of calcium ions enabled to prepare capsules by gelation of this polysaccharide around a core containing starch, calcium chloride and a model drug. Release from the dried capsules was studied *in vitro* by means of the rotating basket technique (USP) in different environmental conditions (distilled water, pH = 2.0, pH = 6.8) and the effects of the presence of increasing amounts of drug in the formulation were also investigated. The behaviour of the gellan capsules was compared with that of beads prepared with the same polysaccharide but containing different additives. Results obtained indicate that gellan is suitable for the formulation of sustained release capsules and that solvent uptake by the dried capsules is most likely the main factor capable of affecting the rate of delivery from the tested preparations.

B.Mishra and Rajinikanth P.S [2008] prepared Floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as

floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The formulation parameters like concentrations of gellan gum and sucralfate influenced the rate and extent of in vitro drug release significantly from FIGC. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH.

Katarina .E *et al* [1999] performed the Rheological studies of the gelation of deacetylated Gellan gum (Gelrite®) in physiological conditions. In this study, the rheological behaviour of deacetylated Gellan gum (Gelrite®) was analyzed in order to better understand the reasons for the good performance in humans. Thermal scans were used to study gel formation and other changes in the structure of the samples when the macromolecular and ionic contents were altered. The effect the different ions in tear fluid (Na , K , Ca) had on the gel strength and the consequences of dilution due to the ocular protective mechanisms were examined. Na was found to be the most important gel-promoting ion in vivo. It was also found that gels are formed in tear fluid even when the concentration of Gelrite® is only 0.1%.Samples with concentrations of Gelrite® of 0.5–1% do not require more ions than 10–25% of those in tear fluid to form gels.

Katayama *et al* [1999] reported a liquid sustained release formulation containing sodium alginate intended for the eradication of Helicobacter pylori in which in situ gelling was achieved by the separate oral administration of a solution of a calcium salt immediately following that of the sodium alginate solution.

Miyazaki.S. *et al* [2001] assessed three liquid formulations with in situ gelling properties for their potential for the oral delivery of Cimetidine. The formulations were dilute solutions of: (a) enzyme-degraded Xyloglucan, which form thermally reversible gels on warming to body temperature; (b) Gellan gum and; (c) sodium alginate both containing complexed calcium ions that form gels when these ions

are released in the acidic environment of the stomach. The in vitro release of Cimetidine from gels of each of the compounds followed root-time kinetics over a period of 6 h. Plasma levels of Cimetidine after oral administration to rabbits of each of the formulations were compared with those resulting from administration of a commercial Cimetidine/alginate suspension with an identical drug loading.

Talwar *et al* [2001] developed once a daily formulation for CiprCeliprolol. The formulation was composed of CiprCeliprolol, Sodium alginate, Xanthan gum, Sodium bicarbonate and Crospovidone. The viscolysing agent and the gel forming polymer formed a hydrated matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine. The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug.

Zatz and Woodford [1987] developed a suspension formulation of theophylline which contained sodium alginate and which formed a gel when in contact with simulated gastric fluid.

Qureshi, M et al. (Indian Journal of Pharmaceutical Sciences; Vol. 69; Issue 3; Pages 360-364; 2007) discloses a hydrodynamically balanced system of celiprolol hydrochloride was developed as single unit floating capsule. Various grades of low d. polymers were used for formulation of this system. They were prepd. by phys. blending of celiprolol hydrochloride and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer at pH 3.0.

US Patent No. 4,101,650 ('650) assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai discloses a formulation in which granules containing sodium bicarbonate, lactose and polyvinylpyrrolidone are coated with a layer of hydroxypropyl methylcellulose. These are then further coated with a suspension containing the active ingredient pepstatin and hydroxypropyl methylcellulose to form floating minicapsules of a diameter in the range of 0.1 to 2 mm. The

drawback of this system is that the minicapsules are much smaller in size than required for long durations of retention in the stomach.

US Patent No. 7,147,885 discloses a native gellan gum-containing composition, and particularly based on the multifunctionality thereof, provides freeze/thaw-resistant gel compositions.

US Patent No. 7,678,387 disclose a modified release pharmaceutical compn. is provided and includes at least one pharmaceutical; at least one compressible material; and at least one tableting material; wherein the compn. has a diam. of from about 1 mm to about 7 mm and a length from about 1 mm to about 7 mm *and provides modified release of the pharmaceutical independent of a modified* release coating.

PCT Publication No. 00/15198 and 01/10419 assigned discloses a pharmaceutical composition comprising a drug, a gas-generating component, a swelling agent, a viscolyzing agent, and optionally a gel-forming polymer.

However, the use of gelling agent and other polymers in the compositions leads to increased weight of the dosage form, which makes the dosage form bigger in size and unsuitable for administration to geriatric and pediatric patients.

Thus, there is need of compositions comprising effective amounts of one or more therapeutic agents, which can not only provide site specific absorption of the drug, provides sustained and controlled release of the drug, thus reducing the frequency of administration but also are suitable for administration to geriatric and pediatric patients.

Several attempts have been made to develop modified release pharmaceutical compositions comprising celiprolol.

The present inventors have developed a gastroretentive modified release pharmaceutical composition comprising Celiprolol or salts thereof, wherein the pharmaceutical composition is in solution form. The said solution when administered orally, swells in-situ in gastrointestinal tract and achieves flotation rapidly. The pharmaceutical composition retains the swellable structure in the gastric region for prolonged periods, resulting in the controlled release of the drug from the gastro-retentive structure.

Pharmaceutical composition of the invention not only exhibit modified release characteristics that reduce the number of administrations required to maintain consistent blood levels of said active agents, but also display excellent *palatability and stability as a solution.*

Further, the modified release gastro-retentive pharmaceutical compositions of the present invention are especially suitable for geriatric and pediatric patients as the formulation is in form of solution.

One of the aspects of the invention provides a gastroretentive modified release pharmaceutical composition comprising Celiprolol or salts thereof, wherein the pharmaceutical composition is in liquid form.

The term "gastroretentive," as used herein, is intended to represent the ability of the pharmaceutical delivery system of the invention to remain within the gastrointestinal tract while delivering a therapeutic agent. As used herein, "gastroretentive" also refers to the ability of the pharmaceutical delivery system of the invention to insulate a therapeutic agent from the gastric environment that would otherwise degrade the therapeutic agent or remove the therapeutic agent from the gastric environment (e.g., gastric emptying).

"Modified release dosage forms" are defined by the USP as those whose drug release characteristics of time course and/or location are chosen to accomplish

therapeutic or convenience objectives not offered by conventional forms. The USP considers that the terms controlled release, prolonged release and sustained release are interchangeable with extended release. Accordingly, the terms "modified-release", controlled-release", "prolonged-release", "extended-release", and "sustained-release" are used interchangeably herein.

Another aspect of the invention provides a gastroretentive modified release pharmaceutical composition comprising Celiprolol or salts thereof, wherein the pharmaceutical composition is in liquid form and the said solution when administered orally swells in-situ in gastrointestinal tract.

Another aspect of the present invention comprises a process for preparing gastroretentive modified release composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the process comprises a) preparing a dispersion of polymer in a vehicle and b) adding celiprolol or salts thereof to the polymer dispersion optionally along with one or more pharmaceutically acceptable excipients.

Yet another aspect of the present invention comprises a method for treating cardiovascular disorder, wherein the method comprises administering a gastroretentive modified release oral pharmaceutical composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the pharmaceutical composition is in liquid form to a patient in need thereof.

The modified release pharmaceutical formulation of the invention may also be comprised of two different components: the immediate release component and extended release component.

The modified release may also be achieved by mixing or coating the drug with one or more polymers.

Polymers include hydrophillic and hydrophobic polymers. Suitable hydrophilic or hydrophobic polymers comprise one or more of polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, a fatty acid, a fatty acid ester, an alkyl alcohol, a wax, shellac, rosin, zein (prolamine from corn), povidone, kollidon SR, a poly(meth)acrylate, microcrystalline cellulose or poly(ethylene oxide), polyuronic acid salts, cellulose ethers, xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, ammonium alginate, hydroxypropyl cellulose, hydroxy ethyl cellulose, hydroxypropyl methyl cellulose, carboxyvinyl polymers, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers like methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) .

The pharmaceutical composition of the invention further may comprise pharmaceutically acceptable excipients wherein excipients may be selected from one or more of binders, fillers, disintegrants, glidants, lubricants, surfactants, thickening agents or viscosity modifiers, stabilizing agent, buffering agents, sweeteners, flavors and preservatives.

Suitable binder may include one or more of, povidone, starch, stearic acid, gums, celluloses, alginic acids, chitosan, chitin, polyethylene glycol and the like.

Suitable fillers may include one or more of saccharose, glucose, fructose, maltose, maltitol, mannitol, dextrins such as maltodextrins; xylitol, sorbitol, microcrystalline cellulose, titanium dioxide, calcium phosphate, calcium sulfate, kaolin, dry starch, powdered sugar, silicates such as magnesium aluminium silicate and the like.

Suitable disintegrant may include one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like.

Suitable glidant may include one or more of colloidal silicon dioxide, talc or cornstarch and the like.

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

Suitable surfactants are those known to ordinary skilled in the art and may include one or more of amphoteric, non-ionic, cationic or anionic surfactants. Suitable surfactants comprises one or more of sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, cremophore RH 40 and the like.

Suitable thickening agents or viscosity modifiers may include one or more of methylcellulose, carboxymethylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, alginate, carageenan, xanthan gum, acacia,

tragacanth, locust bean gum, guar gum, carboxypolymethylene, polyvinyl pyrrolidone, polyvinyl alcohol, poloxamer, magnesium aluminum silicate (veegum), bentonite, hectorite, povidone, maltitol, chitosan or combination thereof and the like.

Suitable sweetener may include one or more of monosaccharides, disaccharides and polysaccharides, e.g. xylose, ribose, glucose, mannose, galactose, fructose, sucrose, maltose, invert sugar, partially hydrolyzed starch, corn syrup solids, mannitol, xylitol, D-sorbitol, erythritol, pentitol, hexitol, malitol, dihydrochalcones, monellin, steviosides or glycyrrhizin; saccharin in free acid form, soluble saccharin salts, e.g. sodium or calcium saccharin salts, cyclamate salts or *acesulfame K; dipeptide based sweeteners, such as L-aspartic acid derived* sweeteners, e.g. aspartame; water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, e.g. sucralose; and protein based sweeteners, e.g. thaumatococcus danielli (Thaumatin I and II) and the like.

Suitable flavoring agents may include those known to the skilled artisan, such as natural, "natural-like" and artificial flavors. These flavors may be chosen e.g. from synthetic flavor oils, flavoring aromatics, oleo-resins and extracts derived e.g. from plants, leaves, flowers or fruits.

Representative flavors may include one or more of spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, vanilla, chocolate, coffee, cocoa and citrus oil, lemon, orange, cherry, grape, lime or grapefruit, and fruit essences, e.g. apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple or apricot; mints such as peppermint (including menthol, especially levomenthol), aldehydes and esters, e.g. cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate or p-methylanisol; alpha-citral (geranial) and beta-citral (neral); decanal; ethyl vanillin; piperonal (heliotropine); vanillin; alpha-amyl cinnamaldehyde; butyraldehyde; valeraldehyde; citronellal; decanal; aldehyde C-

8; aldehyde C-9; aldehyde C-12; 2-ethyl butyraldehyde; hexenal, i.e. trans-2; tolyl aldehyde; veratraldehyde; 2,6-dimethyl-5-heptenal (melonal); 2-6-dimethyloctanal; 2-dodecenal and the like.

Preservatives may include one or more of sodium benzoate, sorbates, such as potassium sorbate, salts of edetate (also known as salts of ethylenediaminetetraacetic acid or EDTA, such as disodium edetate), benzaldionium chloride, parabens and the like.

The formulations of the invention optionally include one or more stabilizing agents to increase the stability and/or compatibility of the suspension when formulated into a dosage form. Suitable stabilizing agents are suspending agents, flocculating agents, thickening agents, gelling agents, buffering agents, antioxidants, preservatives, antimicrobial agents, and mixtures thereof.

Ideally, the agent acts to minimize irreversible aggregation of suspended particles, and to maintain proper flow characteristics to ease manufacturing processes, e.g., to ensure that the formulation can be readily pumped and filled into desired container.

Suspending agents may include one or more from cellulose derivatives, clays, natural gums, synthetic gums, or other agents known in the art. Specific suspending agents, by way of example, include microcrystalline cellulose, sodium carboxymethylcellulose, powdered cellulose, ethymethylcellulose, hydroyxypropyl methylcellulose, methylcellulose, ethylcellulose, ethylhydroxy ethylcellulose, hydroxypropyl cellulose, attapulgite, bentonite, hectorite, montmorillonite, silica gel, fumed silicon dioxide, colloidal silicon dioxide, acacia, agar, carrageenan, guar gum, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, xanthan gum, carbomer, povidone, sodium starch glycolate, starches, tragacanth, magnesium aluminum silicate, aluminum silicate, magnesium silicate, gelatin, glycyrrhizin and the like. These

suspending agents can further impart different flow properties to the suspension. The flow properties of the suspension can be Newtonian, plastic, pseudoplastic, thixotropic or combinations thereof. Mixtures of suspending agents may also be used to optimize flow properties and viscosity.

Suitable buffering agents may include one or more of a bicarbonate salt of a Group IA metal, an alkali earth metal buffering agent, a calcium buffering agent, a magnesium buffering agent, an aluminum buffering agent and the like, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium aluminate, magnesium carbonate, magnesium silicate, magnesium citrate, aluminum hydroxide, aluminum phosphate, aluminum hydroxide/magnesium carbonate, potassium carbonate, potassium citrate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, aluminum magnesium hydroxide, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium (polyphosphate, sodium dihydrogen phosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium gluconate, calcium bicarbonate, calcium citrate, calcium phosphate magnesium phosphate, potassium phosphate, sodium phosphate, trihydroxymethylaminomethane, ail amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, and combinations of any of the foregoing.

Moreover, the composition of the invention optionally include usual auxiliaries known in the art such as saliva stimulating agents like citric acid, lactic acid, malic acid, succinic acid, ascorbic acid, adipic acid, fumaric acid, tartaric acids; cooling sensation agents like maltitol, monomenthyl succinate, ultracool; stabilizers like gums, agar; taste masking agents like acrylic polymers, copolymers of acrylates, celluloses, resins; coloring agents like titanium dioxide,

natural food colors, dyes suitable for food, drug and cosmetic applications; preservatives like alpha-tocopherol, citric acid, butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid, fumaric acid, malic acid, sodium ascorbate or ascorbic acid palmitate or effervescing agents like citric acid, tartaric acid, sodium bicarbonate, sodium carbonate and the like.

The pharmaceutical composition of the present invention is in liquid form selected from the group consisting of solution, suspension, and emulsion.

The pharmaceutical composition of the present invention can be formulated by the various processes known in the art.

The vehicle suitable for preparing the pharmaceutical composition of the present invention comprises one or more of water, buffer solutions, hydroalcoholic solutions, polyethylene glycols and organic solutions.

The vehicle suitable for preparing the pharmaceutical composition of the present invention is water.

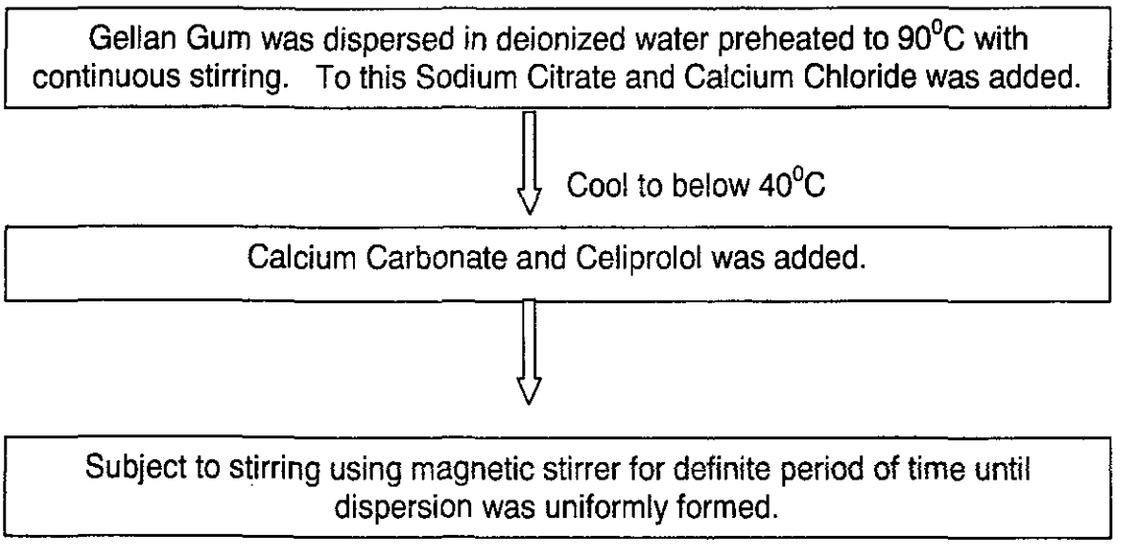
Use of the gastro retentive modified release pharmaceutical composition of the present invention for manufacture of the medicament for the treatment of cardiovascular disorders.

The cardiovascular disorders are selected from the group consisting of hypertension, angina pectoris, arrhythmias and cardiac arrest.

The invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

Example 1 – Preparation of Celiprolol insitu gelling solution (Sol):

The formulation of insitu gelling solution of Gellan gum containing Celiprolol involved following sequential steps.



The above steps results in the formation of liquid preparation which has adequate viscosity that governs its flow properties, pourability, and uniform dispersion of the drug. Gellan gum shows clear solution in water at 90°C and remains clear thereafter on cooling. Sodium citrate and Calcium chloride are added to impart proper consistency to Gellan solution that governs dispersibility of calcium carbonate and Celiprolol in Gellan solution.

FORMULATION TRIALS OF INSITU GELLING SOLUTION:

Table 1. Composition of instu geling solution.

Formulation code	Gallan Gum (Gelrite) % w/V	Calcium Carbonate W/V	Sodium citrate	Calcium Chloride
G1	0.5	0.5	0.25%	0.016%
G2	0.5	0.75		
G3	0.5	1.00		
G4	0.75	0.5		
G5	0.75	0.75		
G6	0.75	1.00		
G7	1	0.5		
G8	1	0.75		
G9	1	1.00		

* Quantities in %w/v.

Example 2: *In -Vitro* Buoyancy study:

In Vitro Buoyancy study is characterized by floating lag time and total floating duration. In Vitro Buoyancy study of the sol was carried out using USP dissolution apparatus Type II. The medium used was 500 ml of 0.1N HCl. The testing was carried out at rotation speed of 50 rpm. The temperature of the bath and medium was maintained at 37 ± 0.5 °C throughout the study. 10ml of the insitu gelling solution was transferred in a petriplate (Diameter 2") using a syringe. The plate was then placed on the surface of the medium and plunged in to the medium with the moving paddle. The time required for gelled mass to rise to the surface of the dissolution medium [Floating Lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [Floating duration] was noted for each formulation trial.

Table 2. Floating Lag time and Floating duration of formulations.

Sr No.	Formulation code	Floating lag time [Sec]	Floating Duration[Hrs]
1	G1	16	>20
2	G2	8	>20

3	G3	5	>20
4	G4	18	>20
5	G5	10	>20
6	G6	6	>20
7	G7	20	>20
8	G8	18	>20
9	G9	5	>20

Example 3: *In Vitro* Dissolution study

In Vitro Dissolution study of the sol was carried out using USP dissolution apparatus Type II. The medium used was 500 ml of 0.1N HCl. The testing was carried out at rotation speed of 50 rpm. The temperature of the bath and medium was maintained at 37 ± 0.5 °C throughout the study. 10ml of the insitu gelling solution was transferred in a petriplate (Diameter 2") using a syringe. The plate was then placed on the surface of the medium and plunged in to the medium with the moving paddle. Aliquots of 5ml were withdrawn at hourly interval for duration of 8 hours. These aliquots were then further diluted and analyzed by UV spectrophotometer at 294nm. Further calculations with correction factor were performed by applying the "Hayton and Chein" Equation.

Table 3. Drug Release profile from sol containing 0.5%w/v of gelrite.

Time (hours)	Percent drug release (n=3)		
	G1	G2	G3
1.	26.415	52.037	69.334
2.	35.328	61.772	85.223
3.	50.389	75.721	89.223
4.	55.898	80.993	99.310
5.	79.967	100	
6.	99.098		

Table 4. Drug Release profile from sol containing 0.75%w/v of gelrite.

Time (hours)	Percent drug release (n=3)		
	G4	G5	G6
1.	36.284	38.620	43.227
2.	44.964	40.461	57.532
3.	50.826	49.106	61.336
4.	55.198	54.358	65.203
5.	57.198	64.508	72.224
6.	66.723	79.28	74.379
7.	80.945	83.685	80.266
8.	91.019	99.605	81.921

Table 5. Drug Release profile from sol containing 1 %w/v of gelrite.

Time (hours)	Percent drug release ± Std Deviation (n=3)		
	G7	G8	G9
1.	15.584	6.378	6.047
2.	22.449	6.838	13.543
3.	33.179	8.118	29.682
4.	37.549	16.119	30.947
5.	41.150	32.524	40.062
6.	52.867	38.423	47.001
7.	58.958	45.671	56.431
8.	74.965	52.825	64.011

Example 4: Measurement of gel Strength:

Gel strength is indicative of the tensile strength of the gelled mass. It signifies the ability of the gelled mass to withstand the peristaltic movements *In vivo*. Formulation containing low amount of gellan formed very weak slimy gel.

The degree of rigidness of the gel can thus be attributed to the concentration of the polymer and Ca^{2+} ions. The degree of rigidness of the gel is related to the degree of cross linking of divalent ions with polymer chains.

Table 6. Measured gel strength.

Sr No.	Batch code	Gel strength [Gms]
1	G1	17
2	G2	17
3	G3	18
4	G4	22
5	G5	25
6	G6	24
7	G7	29
8	G8	30
9	G9	30

Example 5: Density measurement of gel:

Density is important parameter as far as the floating properties of the gastro retentive dosage form is concerned. Ideally the density of the dosage form, to float on the gastric content must have density less than or equal to gastric contents (~1.004 gcm^{-3}). The density of all the formulations was recorded and was found that it lesser than above specified value. Table shows the density of all the formulations. All the formulations contain entrapped CO_2 and thus have excellent buoyancy especially those containing higher proportion of polymer and $CaCO_3$.

Table 7. Measured Density of Gelled Formulations.

Sr No.	Batch code	Density [gcm^{-3}]
1	G1	0.992

2	G2	0.992
3	G3	0.979
4	G4	0.998
5	G5	0.992
6	G6	0.993
7	G7	0.992
8	G8	0.996
9	G9	0.995

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. A gastroretentive modified release oral pharmaceutical composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the pharmaceutical composition is in liquid form.

2. The gastroretentive modified release composition as claimed in claim 1, wherein the said solution when administered orally swells in-situ in gastrointestinal tract.

3. The gastroretentive modified release composition as claimed in claim 1, wherein one or more polymers are selected from the group consisting of polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, a fatty acid, a fatty acid ester, an alkyl alcohol, a wax, shellac, rosin, zein (prolamine from corn), povidone, kollidon SR, a poly(meth)acrylate, microcrystalline cellulose or poly(ethylene oxide), polyuronic acid salts, cellulose ethers, xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, ammonium alginate, hydroxypropyl cellulose, hydroxy ethyl cellulose, hydroxypropyl methyl cellulose, carboxyvinyl polymers, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers like methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with

copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS)

4. The gastroretentive modified release composition of claim 3, wherein the one or more polymers are selected from the group consisting of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, and ammonium alginate.

5. The gastroretentive modified release composition of claim 4, wherein the polymer if gellan gum.

6. The gastroretentive modified release composition of claim 1, further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of binders, fillers, disintegrants, glidants, lubricants, surfactants, thickening agents or viscosity modifiers, stabilizing agent, buffering agents, sweeteners, flavors and preservatives.

7. The gastroretentive modified release composition of claim 1, wherein the liquid form is solution, suspension, or emulsion.

8. A process for preparing gastroretentive modified release composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the process comprises a) preparing a dispersion of polymer in a vehicle and b) adding celiprolol or salts thereof to the polymer dispersion optionally along with one or more pharmaceutically acceptable excipients.

9. The process as claimed in claim 8, wherein the vehicle is selected from the group consisting of water, buffer solutions, hydroalcoholic solutions, polyethylene glycols and organic solutions.

10. A method for treating cardiovascular disorder, wherein the method comprises administering a gastroretentive modified release oral pharmaceutical composition comprising pharmaceutically effective amount of Celiprolol or pharmaceutically acceptable salts thereof with one or more polymers, wherein the pharmaceutical composition is in liquid form to a patient in need thereof.

Dated this 2nd day of October 2013

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