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(54) Title: GAS EMPOWERED EXPANDABLE DRUG DELIVERY SYSTEMS

(57) Abstract: An expandable drug delivery system comprising of one or more actives, force generating components, optionally containing one or more absorption modifiers and optionally containing one or more bioadhesive polymers. The active ingredient is entrapped into the nano/microsized particles of a mucoadhesive polymer matrix. The single unit dosage form is optionally coated with a degradable separating and/or enteric coating layer. An expandable drug delivery system for oral delivery consisting of a protein or peptide drug(s), force-generating components, with/with out absorption modifiers, wherein the composition is formulated to increase the residence time drug containing sub-units of the delivery system in the GIT, optionally coated with enteric polymers. An expandable drug delivery system consisting of a peptide drug, expandable polymer matrix, expanding force-generating component, which delivers drug to the absorbing membrane after a lag time followed by a burst release or sustained release.

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GAS EMPOWERED EXPANDABLE DRUG DELIVERY SYSTEMS

FIELD OF INVENTION

The invention relates to a single unit expandable drug delivery system of hydrophilic macromolecular or low molecular active ingredients, one or more force generating components, preferentially achieved by the formation of carbon dioxide bubbles, absorption modifiers and a nano/microsized matrix of mucoadhesive components for oral application. The active ingredient is entrapped into the nano/microsized particles of a mucoadhesive polymer matrix. The single unit dosage form is optionally coated with a degradable separating and/or enteric coating layer. The invention is primarily intended for the delivery of hydrophilic drugs in the intestinal tract and colon.

BACKGROUND OF THE INVENTION

In the past decade, a large number of endogenous peptides and protein drugs are produced in the biotechnological companies for the treatment of chronic diseases. The majority of these drugs are administered by the parenteral injection routes which are inconvenient, time and money consuming as well as dangerous. Oral drug delivery is the most convenient way for self administration of drugs, allowing a wide range of dosage adjustments . Hence, a lot of research is focused on design and development of novel oral drug delivery systems for hydrophilic, large macromolecules such as peptide and protein drugs.

Effective oral delivery of therapeutic peptides and proteins to the small intestine poses a great challenge in drug delivery system design. The harsh environment of the stomach, the presence of proteolytic enzymes in the small intestine, the hydrophilicity of the peptide molecules and its large molecular size as well as the poor membrane permeability have led to an intense investigation for site-specific drug delivery systems . In order to overcome the above obstacles, the ideal oral delivery system must release its contents pH dependently only at the optimal target region, remain in the optimal site long enough for the complete peptide and protein releases to be absorbed across the intestinal epithelium, and have a reproducible therapeutic effect. Thus, site specific delivery is required to deploy the peptides and proteins intactly to specifically targeted parts of the body through a platform that can control their release by means of physiological or chemical triggers.

Therapeutics like protein, peptide and nucleotide are unstable against acidic, alkaline and/or enzymatic degradation upon systemic uptake and additionally they show poor intestinal absorption due to their high hydrophilicity. Therefore, these compounds are administered by parenteral injection, which has the disadvantages of painful application, risk of infections, low patient compliance and the need of trained personnel.

Usually, oral route is the easiest and most preferred way of drug administration for most high molecular weight drugs or active ingredients. In general the oral absorption of peptide drugs like insulin is hampered by the properties of the drug since the peptide molecule is unable to cross the lipophilic enterocyte membrane and also due to the hostile environment of the gastro-intestinal tract (high acid concentration in the stomach and high amount of enzymes (peptidases)) in the lumen of the gut).

The reason for this most probably is the overall presence of soluble mucins in the lumen of the gut where the mucoadhesive drug delivery systems are released and their mucoadhesive properties (which are the essential feature for functioning of the delivery system) are immediately deactivated by the soluble mucins before the micro/nanosized delivery systems have reached the absorbing membrane of the enterocytes.

Most of the published peptide delivery systems for oral application are micro- or nanosized systems based on mucoadhesive and multifunctional polymers which are able to adhere to the enteral mucosa for a certain period of time, interact with the tight junctions protein to reversibly open the tight-junctions, locally de-activate the gut enzymes and finally release the peptide drug at the preferred site in the GI tract. However these micro- or nanosized delivery systems are only capable of inducing substantial blood peptide drug levels in small animals like mice and rats, but unable to be effective in bigger animals like pigs of 25 – 30 kg or humans.

This is mostly due to the overall presence of soluble mucins in the lumen of the gut where the mucoadhesive drug delivery systems are released and their mucoadhesive properties (which are the essential feature for functioning of the delivery system) are immediately

deactivated by the soluble mucins before the micro/nanosized delivery systems have reached the absorbing membrane of the enterocytes.

Attempts employing mucoadhesive polymers have been rather successful in vitro and in vivo (example: H. L. Lueßen et al; Pharm. Res.1995,12: 1293-1298; H. L. Lueßen et al. ; Pharm. Res. 1996,13: 1668-1672). However, the turn-over of intestinal mucus covering the epithelium led to a rapid delocalization of the polymeric delivery system (C.-M. Lehr et al.; Int. J.Pharm. 1991,70: 235-240). It would thus be desirable to have a system that is retained at specific sites in the gut, e.g. by controlled swelling and/or bioadhesion over a predetermined and extended period of time. Such systems would have distinct advantages over other delivery systems in terms of therapeutic effect, patient compliance and manufacturing feasibility.

EP-A-0 873 750 discloses tablets for localized drug delivery of actives. These tablets adhere to biological material by means of a bioadhesive layer that becomes adhesive after impregnation with water or biological fluids. After adhesion, an active ingredient is released. The matrix system consists of polymers such as cellulose derivatives. The drug delivery system in presence of food will not have a desired release pattern.

US 5292518 discloses a prolonged release composition consisting of active, gel forming dietary fiber and mineral salts which release gas upon ingestion. The delivery system described above is not feasible for site-specific drug delivery (small intestine).

EP0542364 discloses a device, which essentially contains an aperture through which the drug is released. The release rate is independent of the environmental pH and can release the drug even in stomach. This sort of a delivery system is a disadvantage for the acid sensitive active agents like peptides and proteins.

Studies have been done to prepare a floating drug delivery systems of the orally active drugs where the investigators attempted to deliver the drug from a floating dosage form in the stomach. The disadvantage is that it is not a suitable site for active agents like peptides or proteins.

WO01/30322 has disclosed the use of superporous hydrogels (SPHs) or SPHs Composites (SPHCs) the latter system also containing a super disintegrant like Ac-Di Sol. These polymers swell up on contact with aqueous fluid up to 200-fold of their dry volume and contain voids filled with drug composition which are sealed and coated. Upon removal of the enteric coating, the polymers swell to mechanically attach to the intestinal wall for a certain period of time at a desired position of the intestine to bring the peptide delivery subunit system in direct contact with the mucosal membrane and further release the drug. Once the SPHs or SPHC carrier systems (shuttle system) are further hydrated and broken down by the peristaltic forces of the gut to be excreted as fine polymer powder. The invivo study in pigs resulted in reproducible absolute octreotide bioavailabilities of 16 ± 3.3%. (F.A. Dorkoosh et.al; J. Control. Release. 2004, 99:199-206)

These SPHs and SPHCs formulations fulfill the requirements bringing the peptide drugs in direct contact with the absorption membrane. However the synthesis and fabrication of the delivery systems is based on SPHs or SPHCs technology, which is difficult and not commercially feasible on production scale. Another disadvantage is their big size (i.e. capsule size 000), which is not easily swallowed.

Hence the present invention aims at developing a modified formulation, which overcomes the demerits associated with the exiting technologies disclosed in the prior art.

OBJECTIVES OF THE INVENTION

The primary objective of the invention is to deliver primarily hydrophilic actives to the intestinal tract and to make their absorption across the intestinal wall possible by fixing multiparticles containing active compounds by direct contact with the absorbing membrane of the gut tissue using mucoadhesive polymer.

Another objective of the invention is to protect the active ingredients from the low pH of the gastric fluid and the digestive enzymes of the GI lumen.

Another objective of the invention is to prepare an expandable drug delivery system, which retains for a longer period of time at the specific site of absorption and delivers the drug at a predetermined rate through the mucus membrane.

Another objective of the invention is to use a delivery platform for the drug carrier nanosized particles or capsules, microsized particles or capsules including liposomes or other similar systems, micro tablets or microcapsules, quantum dots or similar systems.

Another objective of the invention is to prepare an expandable drug delivery system by generating gas bubbles using a simple chemical reaction without involving complex procedures.

Another objective of the invention is the forced transport of the micro/nanosized drug carriers by the gas bubbles to the absorbing membrane simultaneously protecting their mucoadhesive properties through the gas bubbles

Another objective of the invention is to prepare an expandable drug delivery system comprising absorption modifiers to facilitate opening of the tight junctions of the intestinal epithelium.

Another objective of the invention is to deliver the peptide drugs (which are sensitive to the pH and the digestive enzymes of GIT) without exposing the drug to the GIT contents.

Yet another objective of the invention is to release the drug at the specific site after a lag time, which is achieved by enteric coating.

SUMMARY OF THE INVENTION

The present invention relates to the preparation of an Expandable drug delivery system or gas empowered drug delivery system comprising of actives, force generating component, absorption modifiers, optionally coated with enteric coating polymers. The preparation may further include pharmaceutical excipients or carriers.

The present invention also relates to preparation of an expandable drug delivery system, which delivers the drug at a specific site of the intestinal tract by adhering to the mucous membrane using bioadhesive polymers.

The present invention also aims at the preparation of an expandable delivery system whereby the dosage form reaches the desired site of action after administration for imbibes the intestinal fluids into the core. Consequently, it dissolves the absorption modifiers in the core which generates a force to expand the dosage form and adheres firmly to the lumen. The drug present in micro/nano particles diffuses through the polymer matrix and is absorbed across the intestinal wall primarily by the paracellular pathway. The micro/nano particles , which is adhered to the intestinal wall, slides down as the mucous membrane is shed off and reaches the large intestine where the micro/nano particles is degraded or expelled as such.

The dosage form of the present invention may contain carbon dioxide releasing agent (force generating component) that pushes the nano/microsized multiparticles to the absorbing membrane and forms a bubble layer around the nano/microsized multiparticles acting as a protective layer against enzymatic degradation of the drug. The carbon dioxide bubbles formed by the gas generating components, may additionally act as penetration enhancers when reaching the mucosal surface.

As the dosage form enters into the intestine the enteric coating dissolves and the carbon dioxide bubbles are formed due to the gas releasing agent. The bubbles also prevent the hydration of the mucoadhesive polymer off the nano/microsized delivery systems until it reaches the mucosal surface preventing the mucoadhesive polymers in the delivery systems from being de-activated by soluble mucins present in the gut lumen

BRIEF DESCRIPTION OF THE DRAWINGS

The invention can be better understood with reference to the following detailed description together with the appended illustrative drawings.

FIG.1 depicts the schematic description of the behaviour of gas empowered expandable drug delivery system (GEDDS) after oral administration

FIG.2 The effect of the GEDD system on the transport of the insulin across the sheep's intestine.

DETAILED DESCRIPTION OF THE INVENTION

An expandable drug delivery system/ gas empowered expandable drug delivery system is a system, which consists of more than one microparticles . Each microparticles acts as separate delivery system in which the active agent(s) is entrapped. The expandable drug delivery system may be a multiparticulate or single unit system. Multiparticulate is manufactured with any of the techniques known in the prior art or known to the person skilled in the art. Some of the examples of multiparticulate drug delivery system but not limited to these examples are nanoparticles or nanocapsules, micro particles or microcapsules, liposomes or niosomes in unilamellar or multilamellar structure, micro tablets or quantum dots, pellets or all other delivery systems which are filled in the capsules or punched in to mini tablets and filled in to capsule or compressed in to tablets. The single unit drug delivery system is prepared by conventional granulation technique or by hot melt technique where in the non-multiparticulate is a monolithic tablet prepared by hot melt technique.

The term "Absorption modifiers" is defined as the substances that influence absorption of a drug in the gastrointestinal tract by an increase in the rate and/or the extent of absorption of the drugs that are known or suspected of having poor bioavailability. It is believed that such increase can rise from one or all of the following mechanisms:

1. reducing the thickness and/or the viscosity of the mucus layer which is adjacent to the gastrointestinal mucosa.
2. alteration of the tight junctions between cells, thus promoting absorption through the paracellular route.

3. inducing a change in the cell membrane structure, thus promoting transcellular absorption.
4. increasing the hydrophobic environment within the cellular membrane.

"Bioadhesion" is defined as the ability of a material to adhere to a biological tissue for an extended period of time. Bioadhesion is one solution to the problem of inadequate residence time resulting from stomach emptying and intestinal peristalsis, and from displacement by ciliary movement. For sufficient bioadhesion to occur, an intimate contact must exist between the bioadhesive and the mucosal tissue. the bioadhesive must penetrate into the crevice of the tissue surface and/or mucus, to form mechanical, electrostatic, or chemical bonds. Bioadhesive properties of polymers are affected by both the nature of the polymer as well as the surrounding media.
The terms bioadhesive and mucoadhesive can be used interchangeably.

The term "multilayered dosage form" is a dosage form which is made up of one or more layers. If it is more than on layer the layers can be laminated horizontally, vertically or by concentric layered (where in the core has a coated layer).
"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

The term "Carrier or excipients" comprises of a material that is not biologically or otherwise undesirable. The carriers or excipients may include any biologically inactive substance known in prior art used for the preparation of any pharmaceutical dosage form.

The formulation will, in general comprise of one or more excipients. Examples of excipients include, but are not limited to, diluents, disintegrants, lubricant, glident, binders, fillers, surfactant, solubilizers, and wetting agents. A combination of excipients may also be used. Such excipients will include diluents such as mannitol, dextrose, xylitol, sorbitol, gelatin, acacia, sucrose, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, lactose, starches, vinyl polymers and the likes. Disintegrants referred to in the present invention include one or more of microcrystalline

cellulose, croscarmellose sodium, crospovidone, carboxymethyl starch sodium, sodium starch glycolate and the likes. Binders referred to in the present invention include one or more celluloses such as hydroxypropyl cellulose, hydroxy ethyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose or mixtures thereof, acrylates, methacrylates, povidone, sucrose, corn or maize starch, pregelatinized starch and the like, coloring agents such as ferric oxide, FD&C dyes, lakes and the likes and flavoring agent. Examples of glidents include but are not limited to silica, sodium benzoate, magnesium trisilicate, powdered cellulose, talc, and starch.

The term "force-generating component" is defined as the component that is responsible for generating force for expanding the drug delivery system and give sufficient strength or pushing power to transport the drug to the absorbing membrane for the time period sufficient to release the drug. The force generating component comprises of gas generating components like carbon dioxide releasing agents e.g. acid base mixtures, carbonates and bicarbonate, swelling polymers, osmogens and the like the force generating component can be a swellable or a non swellable substance.

The term "expandable drug delivery system" is a delivery system which can expand or swell, which is fabricated in combination of gas forming compounds, swellable polymers and/or mucoadhesive polymers and the latter two components are able to adhere to the mucous membrane and expand at the site of the lumen after being pushed there by the force generating components.

The delivery system can release sub unit delivery (multi particles) platforms, which are driven either by the swellable polymers and/or by the gas to the absorbing membrane. These sub-units delivery system can consist of nanoparticles or nanocapsules, micro particles or microcapsules, liposomes or niosomes in unilamellar or multilamellar structure, micro tablets or quantum dots or all other delivery systems sized from 4 mm down to nanometer size, with or without mucoadhesive properties using mucoadhesive polymers as described below with or without substances which allow endocytosis or transcytosis of the particles across the enterocyctes of the intestine (like invasins and other similar particles

across or along the enterocytes of the intestine (like invasins and other similar substances), with or with out enzyme inhibitors.

Active agents suitable for use in the present invention include biologically active agents (actives) and chemically active agents (high and low molecular weight), including, but not limited to, pharmacological agents, and therapeutic agents. Suitable active agents include those that are rendered less effective, ineffective or are destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes and the like. Also included as suitable active agents are those macromolecular agents that their physiochemical characteristics such as: size, structure or charge, prohibit or impede absorption when dosed orally.

Moreover, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, proteins, polypeptides, peptides, hormones, polysaccharides, mixtures of muco-polysaccharides; carbohydrates, lipids, organic compounds and finally compounds which do not pass or only a fraction of their administered dose can pass through the intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; or any combination thereof.

Further examples include, but are not limited to, the following: synthetic, natural or recombinant sources such as: growth hormones, including human growth hormones (hGH), recombinant human growth hormones (rhGH), bovine growth hormones, and porcine growth hormones; growth hormone releasing hormones; growth hormone releasing factor, interferons, including [alpha] (e.g., interferon alfacon-1), [beta] and [gamma]; interleukin-1; interleukin-2; glucagon; insulin, including porcine, bovine, human, and human recombinant, optionally having counter ions including zinc, sodium, calcium and ammonium; insulin-like growth factor, including IGF-I; heparin, including un-fractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin and ultra low molecular weight heparin; calcitonin, including salmon, eel, porcine and human; erythropoietin; atrial naturetic factor; antigens; monoclonal antibodies; somatostatin; protease inhibitors; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; luteinizing-hormone-releasing-hormone; follicle stimulating hormone; glucocerebrosidase; thrombopoietin; filgrastim; prostaglandins; cyclosporin; vasopressin; cromolyn sodium

(sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); bisphosphonates, including alendronate, tiludronate, etidronate, clodronate, pamidronate, olpadronate, and incadronate; parathyroid hormone (PTH), including its fragments; anti-migraine agents such as BIBN-4096BS and other calcitonin gene-related proteins antagonists; glucagon-like peptide 1 (GLP-I); antimicrobials, including antibiotics, anti-bacterials and anti-fungal agents; vitamins; analogs, fragments, mimetics or polyethylene glycol (PEG)-modified derivatives of these compounds; or any combination thereof and the like. Non-limiting examples of antibiotics include gram-positive acting, bacteriocidal, lipopeptidal and cyclic peptidal antibiotics, such as daptomycin, Aliskerin and analogs thereof.

In the present invention the term swellable polymer can encompass other polymers like mucoadhesive polymers and the like.

A swellable polymer/mucoadhesive is a polymer that expands upon ingestion such that the pharmaceutical composition is retained in the stomach for 30 minutes, 90 minutes, 4 hours, 6 hours, 12 hours, 24 hours or more post administration. For example, the swellable polymer may cause the pharmaceutical composition to increase in size 10%, 15%, 50%, 100% or 200% or more as compared to its pre-ingested volume.

Generally higher molecular weights of the polymers are more desirable since they provide a larger swollen size and stronger mechanical strength. In one embodiment of the present invention, the swellable polymers have a molecular weight in excess of 50,000 Daltons. In another embodiment, the swellable polymer has a molecular weight in excess of 200,000 Daltons. In another embodiment, the swellable polymer has a molecular weight in excess of 7,000,000 Daltons.

Swellable polymers include, but are not limited to, cross linked poly(acrylic acid), poly (alkylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone); polyurethane hydrogel, maleic anhydride polymer, such as a maleic anhydride copolymer, a cellulose polymer, polysaccharide, starch, and starch based polymers.

Examples of poly (alkylene oxides) include, but are not limited to, polymers, which contain as a unit, ethylene oxide, propylene oxide, ethylene oxide, or propylene oxide. These polymers may consist entirely of any of the above units (as a monomer), combinations of any of the above units, such as a copolymer. In one embodiment, the swellable polymer is a block copolymer in which one of the repeating units consists of ethylene oxide, propylene oxide, ethylene oxide, or propylene oxide or combination thereof.

Examples of cellulose polymers include, but are not limited to, cellulose, hydroxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxy propyl methylcellulose (also known as hypromellose), and carboxymethyl cellulose or combination thereof.

Examples of polysaccharides include, but are not limited to, dextran, xanthan gum, gellan gum, welan gum, rhamsan gum, sodium alginate, calcium alginate, chitosan, gelatin, and maltodextrin. Examples of starch-based polymers include, but are not limited to, hydrolyzed starch polyacrylonitrile graft copolymers, starch-acrylate-acrylamide copolymers or combination thereof.

Commercially available swellable polymers include Polyox 303(TM) (Polyethylene oxide, molecular weight 7,000,000); Polyox WSR N-12K (Polyethylene oxide, molecular weight 1,000,000), Polyox WSR N-60K (Polyethylene oxide, molecular weight 2,000,000), Polyox WSR 301 (Polyethylene oxide, molecular weight 4,000,000), Polyox WSR Coagulant, PolyoxWSR 303, Polyox WSR 308, NFgrade(TM) (Poly(ethylene oxide molecular weight 1,000,000) or combination thereof.

Swellable polymers can also be used as rate controlling polymers. Release controlling polymers are often selected from the same class as swellable polymers. Examples of release controlling polymers include, for example, poly(ethylene oxide), poly(acrylic acid), polyvinyl alcohol, alginate, chitosan and chitosan derivatives like trimethyl chitosan (TMC), polyvinylpyrrolidone, cellulose polymers and polysaccharides and the like.

Addition of hydro-attractants can improve the swelling properties of a dosage form significantly, and hence can constitute a swellable polymer. Examples of hydro-attractants, which can be incorporated into pharmaceutical compositions of the present invention include crosslinked poly(acrylic acid), crosslinked poly(vinyl pyrrolidone), microcrystalline cellulose, crosslinked carboxymethyl cellulose, starch granules, sodium carboxymethyl starch, alginates, low substituted hydroxypropyl cellulose (L-HPC, 10-13% substitution by weight, Shin-Etsu Chemical Company, Ltd, distributed by Biddle Sawyer), Croscarmellose Sodium (Primellose) (Avebe, distributed by Generichem), Sodium Starch Glycolate (Avebe, distributed by Generichem) sodium phosphates, such as disodium phosphate, sodium chloride, sodium citrate, sodium acetate, succinic acid, fumaric acid, tartaric acid, tannic acid, sugars (e.g. mannitol, sucrose, lactose, fructose, sorbitol) and natural amino acids. Amino acids can also be used as permeation enhancers.

An orally ingested product swells and adheres to either the epithelial surface or the mucus lining of the gastrointestinal tract. For the delivery of bioactive substances, it can be advantageous to have a polymeric drug delivery device adhering to the epithelium or to the mucous layer. Bioadhesion in the gastrointestinal tract proceeds in two stages: (1) viscoelastic deformation at the point of contact of the synthetic material into the mucus substrate, and (2) formation of bonds between the adhesive synthetic material and the mucus or the epithelial cells. In general, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds, and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, consist of depressive interactions (i.e., Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups primarily responsible for forming hydrogen bonds are the hydroxyl and the carboxylic acid groups.

Duchene et al, in Drug Dev. Ind. Pharm., 14:283-318 (1988), reviewed the pharmaceutical and medical aspects of bioadhesive systems for drug delivery. Polycarbophils and acrylic acid polymers were noted as having the best adhesive properties. Others have explored the use of bioadhesive polymers; however, the extent of bioadhesion achieved in these studies

has been limited. In addition, these studies do not demonstrate how to prepare larger bioadhesive drug delivery devices, such as tablets. WO 93/21906 discloses methods for fabricating bioadhesive microspheres and for measuring bioadhesive forces between microspheres and selected segments of the gastrointestinal tract in vitro.

Separately or in addition to the need to control the location at which a drug is released, there is also a need to control the duration over which a drug is released from a pharmaceutical formulation. In particular, certain drugs, especially peptide drugs are inactivated by the highly acidic environment or enzymatic degradation if released in the stomach.

In a preferred embodiment, the present invention is a tablet for oral delivery of a drug, comprising a core containing the drug to be delivered intestinally, and optionally a polymeric coating, which is not bioadhesive.

The present invention is not limited to tablets, it may contain capsules, pellets, mini-tablets, granules, monolithic tablets, spherules and the like, known to a person skilled in the art at the time of invention. Also these dosage forms can be prepared by any l method known in the prior art. Another embodiment of the present invention wherein the expandable drug delivery system is in the form of mini-tables filled into the capsules.

The dosage form of the present invention may contain and release carbon dioxide releasing agent that forms a bubble layer around the micro/nanoparticles which acts as a protective layer against enzymatic degradation. The bubble layer formed by gas generating component will remain intact around the nano/microsized particles until it reaches the intestinal wall and adheres to the intestinal mucosa. The gas generating component is the transport medium bringing the drug compartment to the absorbing mucosal surface.

As the dosage form enters the intestine, the enteric coating dissolves and the carbon dioxide gas bubbles are formed preventing the hydration of the mucoadhesive polymers before reaching the absorbing membrane.

The present invention provides methods for improving the bioadhesive properties of drug delivery systems such as tablets, capsules and drug-eluting devices. The invention also provides methods for improving the adhesion of drug delivery systems to mucosal membranes including membranes of the gastrointestinal tract. The polymeric drug delivery systems of the invention have an improved ability to bind to mucosal membranes, and thus can be used to deliver a wide range of drugs or diagnostic agents in a wide variety of therapeutic applications, and/or improve uptake of the active agent across the intestinal mucosa.

In embodiments of the present invention, the pharmaceutical composition includes a mucoadhesives/ bioadhesives. The mucoadhesive facilitates retention in the GIT by binding to the mucosal surface of the GIT, or by association with the mucus layer.

Examples of mucoadhesives include, but are not limited to, a polyacrylic acid or polyacrylate optionally cross-linked with allyl sucrose, allyl ethers of sucrose, allylpentaerythritol, pentaerythritol or divinyl glycol; carboxylvinyl polymer; polyvinyl pyrrolidone (PVP); polyvinyl alcohol; chitosan and its quaternary derivatives sodium carboxymethylcellulose (CMC); dextran polymer; copolymer of polymethyl vinyl ether and maleic anhydride; hydroxymethylcellulose; methylcellulose; tragacanth; alginic acid; gelatin; gum arabic; and polysaccharide optionally interrupted with a [beta]-(l-4)-linked D-glucosamine unit and/or a N-acetyl-D-glucosamine unit, and mixtures thereof.

The preferred embodiment of the present invention involves the preparation of an expandable delivery system in which the dosage form reaches the desired site of action and will adhere to the mucous surface followed by imbibing the fluids of the intestinal environment in to the core, where it activates the force generating material in the core which creates a force to expand the dosage form and carries it for adhesion to the luminal surface without losing its mucoadhesive properties. The drug present in the polymer matrix diffuses across the intestinal wall by the paracellular route. Once the delivery system is adherered to the intestinal wall, it slides down as the mucous membrane is shed off due to the mucus turnover and reaches the large intestine and colon to be excreted.

The preferred embodiment of the present invention may include other excipients such as absorption enhancers and enzyme inhibitors. Also and intestinal motility modifiers can be integrated in the polymer matrix.

In order to increase epithelial permeability, all compounds that are used as permeation enhancers can be integrated in the matrix.

Examples of such compounds are EDTA, polyacrylates (Carbomer), chitosans and their derivatives such as TMC, anionic surfactants such as sodium lauryl sulfate, nonionic surfactants such as polyoxyethylene ethers and esters, fatty acids such as sodium caprate, trihydroxy bile salts such as taurocholate, dihydroxy bile salts such as taurodeoxycholate, acyl carnitines such as palmitoyl carnitine and salicylates such as sodium salicylate, carbon dioxide and the like.

In order to reduce enzymatic activity all known classes of protease inhibitors and other enzyme inhibiting substances can be added in the swellable polymer matrix. Enzyme inhibitors increase the absorption of macromolecular drugs. Compounds, which increase epithelial permeability and reduce enzymatic activity simultaneously, can also be added. Suitable enzyme inhibitors are aprotinin, cystatin, amino acid and its derivates, soybean trypsin inhibitor, leupeptin, bestatin and small inhibitors based on boron compounds, such ASA- aminoboronic acid derivatives.

Another application possibility is the use of ketoconazole and levamisol as enzyme inhibitors for cytochromes such as cytochrome P450 and especially for cytochrome P3A4 and for other drug transporters such as P-glycoproteins within the gut wall to overcome multidrug resistance of drugs especially anti-cancer drugs.

Further, optional ingredients are compounds that can control the intestinal motility; either decreases the motility for prolonged retention time of the dosage form at the site of action or increase the motility for easier excretion of the dosage form. These compounds can influence the transition of the system through specific parts of the intestine. Examples of

such compounds are loperamide.HCl, papaverine.HCl, opiate receptor stimulators and acetylcholine antagonists.

Other Excipients

The pharmaceutical composition may also contain other conventional pharmaceutical excipients, for example, water soluble diluents such as lactose, dextrose, mannitol, sorbitol, and the like; water insoluble diluents such as starch, microcrystalline cellulose, powdered cellulose, and the like; or lubricants such as talc, stearic acid or its salt, magnesium stearate, sodium benzoate and the like. The invention is not limited to the examples given in the specification it may include other excipients, which are known in the field of invention.

The delivery system was prepared by granulation technique with the citric acid, Na-bicarbonate and lactose. TMC (Trimethyl chitosan), PEO, Avicel, drug and the Na-benzoate were then added step-wise to the obtained granules and mixed. The granules were then pressed to tablets. The variables were: the percent of polyethylene oxide (PEO) as mucoadhesive polymer, percent of citric acid and Na-bicarbonate (CO_2 gas production), and Ac-Di-Sol as super-disintegrant. The response was the CO_2 gas production, tablet disintegration as well as a mucoadhesive mass response. The variables were set as low and high values of 50 and 70%, 2.5 and 5.0% a s well as 5.0-10% of the total weight for the amount of acid-base, Ac-Di-Sol and the PEO, respectively. The prepared tables were optinally coated with separating layer consisting of polymer in order to generate a smooth surface around the tablet for homogenous coating then the dosage form is again coated with enteric coating polymer. The polymers, which are used for the sepearting layer, are well known in the art.

The enteric coating of the present invention is obtained by coating of the delivery system with one or more polymer which protect the delivery from the acids of the stomach. The entric polymer coat may contain a water insoluble polymer alone or in combination with water soluble substance with may be a polymer

Suitable water-soluble polymers include, but are not limited to, polyvinyl alcohol, polyvinylpyrrolidone,methylcellulose,hydroxypropylcellulose,hdroxypropylmethylcellulose or polyethylene glycol, and/or mixtures thereof.

Suitable water-insoluble polymers also include, but are not limited to, ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly (methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), and poly (hexyl methacrylate), poly (isodecyl methacrylate), poly (lauryl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), poly (ethylene), poly (ethylene) low density, poly (ethylene) high density, poly (ethylene oxide), poly (ethylene terephthalate), poly (vinyl isobutyl ether), poly (vinyl acetate), poly (vinyl chloride) or polyurethane, and/or mixtures thereof.

Matrix-based dosage form can comprise the drug or pro-drug, a filler, such as starch, lactose, or microcrystalline cellulose ; a binder, /controlled-release polymer, such as hydroxypropyl methylcellulose; a disintegrant,; a lubricant,; a surfactant, such as sodium lauryl sulfate or polysorbates; and a glidant, such as colloidal silicon dioxide or talc.

The amounts and types of polymers, and the ratio of water-soluble polymers to water-insoluble polymers in the inventive formulations are generally selected to achieve a desired release profile of the drug or pro-drug, as described below.

Amino methacrylate co-polymers such as Eudragit RS and Eudragit RL (Rohm Pharma) are suitable for use in the modified-release formulations of the present invention. These polymers are insoluble in pure water, dilute acids, buffer solutions, or digestive fluids over the entire physiological pH range. The polymers swell in water and digestive fluids independently of pH. In the swollen state they are then permeable to water and dissolved actives. The permeability of the polymers depends on the ratio of ethylacrylate (EA), methyl methacrylate (MMA), and trimethylammonioethyl methacrylate chloride (TAMCl) groups in the polymer. Those polymers having EA:MMA:TAMCl ratios of 1:2:0.2 (Eudragit RL) are more permeable than those with ratios of 1:2:0.1 (Eudragit RS). Polymers of Eudragit RL are

insoluble polymers of high permeability. Polymers of Eudragit RS are insoluble films of low permeability.

The amino methacrylate co-polymers can be combined in any desired ratio. For example, a ratio of Eudragit RS:Eudragit RL (90:10) can be used. The ratios can furthermore be adjusted to provide a delay in release of the drug or pro-drug. For example, the ratio of Eudragit RS:Eudragit RL can be about 100:0 to about 80:20, about 100:0 to about 90:10, or any ratio in between. In such formulations, the less permeable polymer Eudragit RS would generally comprise the majority of the polymeric material.

The amino methacrylate co-polymers can be combined with the methacrylic acid co-polymers within the polymeric material in order to achieve the desired delay in release of the drug or pro-drug. Ratios of ammonio methacrylate co-polymer (e.g., Eudragit RS) to methacrylic acid co-polymer in the range of about 99:1 to about 20:80 can be used. The two types of polymers can also be combined into the same polymeric material, or provided as separate coats that are applied to the core.

In addition to the Eudragit polymers described above, a number of other such copolymers can be used to control drug release. These include methacrylate ester co-polymers (e.g., Eudragit NE 30D). Further information on the Eudragit polymers can be found in "Chemistry and Application Properties of Polymethacrylate Coating Systems," in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (ed. James McGinity, Marcel Dekker Inc., New York, pg 109-114).

Methyl acrylate copolymers and amino methacrylate copolymers of the type such as can be obtained under the tradename Eudragit.RTM. RS/RL/NE are particularly preferred. As functional groups, these polymers have ester groups (Eudragit.RTM. NE) or ammonium groups (Eudragit.RTM. RL/RS). Poly(ethyl acrylate, methyl methacrylate) and poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) are preferred. These polymers are obtainable, for example, as poly(ethyl acrylate, methyl methacrylate) 2:1 in 40% strength aqueous dispersion as Eudragit.RTM. NE 40 D and as poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1 in

12.5% strength isopropanolic solution as Eudragit.RTM. RS 12.5 and in the composition 1:2:0.2 as Eudragit.RTM. RL 12.5. The most preferred is Eudragit.RTM. NE 40 D

In one of the present embodiment the use of the Co_2 and the TMC had shown a synergist effect on the permeability of the insulin across ex-vivo isolated sheep's intestine. The apparent permeability for insulin using the expandable drug delivery system in the presence of TMC has shown a highest value of 27 $x10^{-7}$ (cm/sec) as shown in figure 1.

The comparative study of insulin permeability

Formulation	**Papp of insulin x 10^{-7} (cm/sec)**
Free insulin	2.1 ± 0.03
Free insulin + TMC	4.1 ± 0.65
Expandable drug delivery system containing Insulin	4.4 ± 0.83
Expandable drug delivery system containing Insulin + TMC	27 ± 1.89

Examples:

This example illustrates the present invention when the active ingredient is peptide drug. Peptide drug is an example of a drug, which is absorbed, only from the upper part of the intestine. The pharmaceutical composition is given in Table 1.

Ingredient	(mg/tablet)
Peptide drugs (Insulin)	
Polyethylene oxide	20.00
Sodium bicarbonate	15.00
Microcrystalline cellulose	16.00
Citric Acid	20.0
Sodium carboxymethylcellulose	110.00
Magnesium Stearate	20.00

Aerosil	10.00
Enteric coating	
Methacrylic acid Copolymer,	65
Triethyl Citrate USPNF	10
Talc USP	5

Example 2

Ingredient	**(mg/tablet)**
Insulin	
Polyethylene oxide	20.00
Microcrystalline cellulose	16.00
Trimethyl chitosan	10
Sodium Chloride	25.0
Cross-linked polyacrylic acid	110.00
Magnesium Stearate	20.00
Aerosil	10.00
Enteric coating	
Methacrylic acid Copolymer,	65
Triethyl Citrate USPNF	10
Talc USP	5

Example 3

Ingredient	**% w/w**
Acetaminophen	5.0
Citric acid	46.7
Microcrystalline cellulose	10
Sodium bicarbonate	23.3
Lactose	1.0
Acdisol	5.0
Polyethylene oxide	4.0
Sodium benzoate	5.0

Example 4

Ingredient	% w/w
Insulin	20.0
Citric acid	46.7
Microcrystalline cellulose	10.0
Sodium bicarbonate	23.3
Acdisol	5.0
Polyethylene oxide	10.0
Sodium benzoate	5.0

DETERMINATION OF MUCOADHESION

The mucoadhesive properties of the system were evaluated in a piece of sheep's intestine (Jejunum). The experiment was performed according to the method described by Smart et al (Int. J. Pharm. 116 (1995) 223-230). with some modifications. Briefly, a small section of fresh sheep's intestine was removed, quickly frozen and was cut into pieces of 3 cm lengths, opened longitudinally to expose the mucous surface and gently washed with PBS buffer pH 6.0. A preliminary histological study indicated the absence of any major damage to the tissue caused by the freeze-thawing process. A layer of mucus was shown to be present on the inner surface of the intestine. The sections of intestine were mounted on a platform and secured using a plastic cap, exposing an 11mm diameter of the test surface. The exposed surface was equilibrated in PBS buffer of pH 6.8 for 1 min at 37^{0}C. The cap was elongated at one side to allow sufficient distance for the tablet to be detached. Using a cyanoacrylate adhesive, the gas empowered expandable drug delivery tablets were individually attached to 1.5 g weight, lowered into PBS buffer pH 6.8 and placed in contact with the adhesive surface for 2 minutes. Subsequently, a brass ring was placed over the 1.5g weight. The ring was connected to the force and position sensor of the rheometer via a pulley system (diagram 1). After 2 min the contact platform was lowered at a rate of 2mm/min and the maximum detachment force was calculated.

CLAIMS

1. An expandable drug delivery system comprising of one or more actives, force generating components, optionally containing one or more absorption modifiers and optionally containing one or more bioadhesive polymers.

2. An expandable drug delivery system of claim 1 where in the force generating component is selected from the group consisting of gas generating components, swelling polymers and osmogens.

3. An expandable drug delivery system of claim 2 in which the generated gas forces the multiparticular nano/microsized drug delivery systems containing the active API to attach to the mucosal surface

4. An expandable drug delivery system of claim 1 where in the swelling polymers polymer is selected from the group consisting of cellulose and its derivatives, PEO, gums, PVP, cross linked PVP, sodium starch glycolate, cross linked cellulose, polysaccharides, cross linked polyacrylic acids, polyalkyl oxides, polyurethane hydrogels, maleic anhydrate polymers and chitosan and its derivatives

5. An expandable drug delivery system for oral delivery consisting of macromolecular active, force generating component, with/with out absorption modifiers

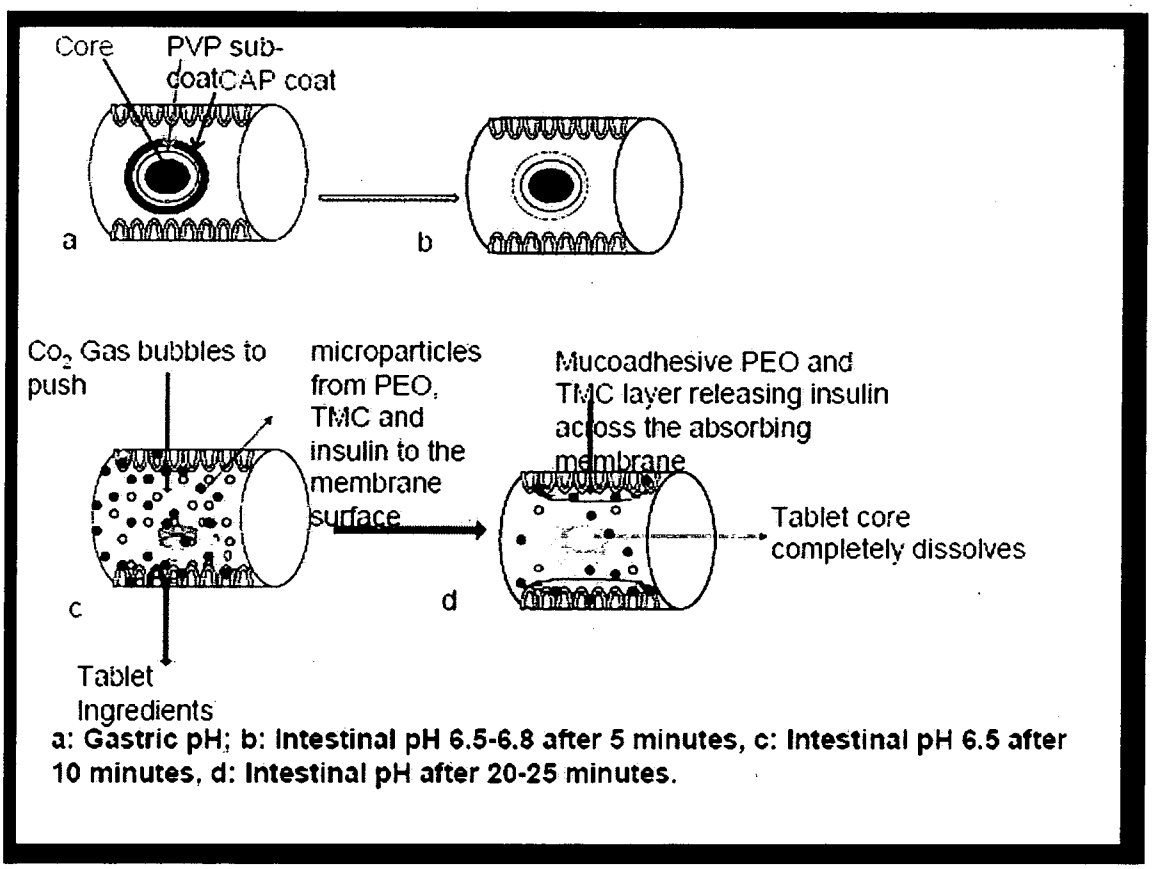
6. An expandable drug delivery system of claim 3 where in the macromolecular actives selected from the group consisting of proteins; polypeptides; peptides; hormones; polysaccharides, and particularly mixtures of muco-polysaccharides; carbohydrates; lipids; small polar organic molecules

7. An expandable drug delivery system for oral delivery consisting of a protein or peptide drug(s), force-generating components, with/with out absorption modifiers, wherein the composition is formulated to increase the residence time drug containing sub-units of the delivery system in the GIT, optionally coated with enteric polymers.

8. An expandable drug delivery system according to any preceding claims the increase in the gastric and intestinal retention is achieved by the use of mucoadhesion or bioadhesion

9. An expandable drug delivery system according to claim 8 the coating polymer is a hydrophilic or hydrophobic polymers.

10. An expandable drug delivery system consisting of a peptide drug, expandable polymer matrix, expanding force-generating component, which delivers drug to the absorbing membrane after a lag time followed by a burst release or sustained release.



a: Gastric pH; b: Intestinal pH 6.5-6.8 after 5 minutes, c: Intestinal pH 6.5 after 10 minutes, d: Intestinal pH after 20-25 minutes.

Figure 1

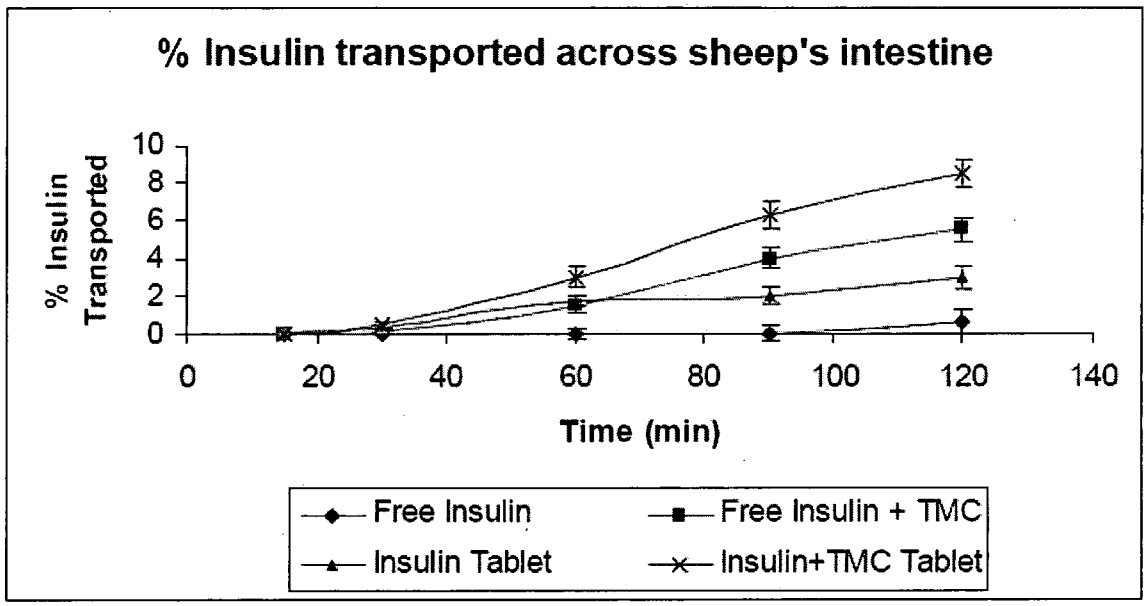

% Insulin transported across sheep's intestine
% Insulin Transported
10
8
6
4
2
0
0
20
40
60
80
100
120
140
Time (min)
Free Insulin
Free Insulin + TMC
Insulin Tablet
Insulin+TMC Tablet

Figure 2