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e215p32
Abstract

Patent, once seen as a technical matter for legal experts, has today become a central concern for governments, businesses, civil society, scientists and innovators. In a world where the economic growth of nations is driven increasingly by creativity and knowledge of their people, effective intellectual property (IP) systems, which create incentives for innovation and structures for sharing the results, are key to unlocking the human potentials. Recent pharmaceutical patented literature has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. This review on GRDDS attempts to compile the available patented literature with all the possible mechanisms used to achieve gastric retention.

Keywords: Gastric Retention, Mechanism, Patents, Drugs, Polymers, Evaluation Method.
Introduction

Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success.\(^1\) Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications.\(^2\) The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and, thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems, with a prolonged residence time in the stomach, can be used.\(^3\) Incorporation of the drug into a CR-delivery system, which releases its payload in the stomach over a prolonged time period, can lead to significant therapeutic advantages owing to various pharmacokinetic (PK) and pharmacodynamic aspects.

Gastroretentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome.\(^2\)

The challenge to develop efficient gastroretentive dosage forms began near about 20 years ago, following the discovery of \textit{Helicobacter pylori} by Warren and Marshall.\(^4\) Many attempts have been made to devise an extended release GRDDS where the dosage form is small enough to ingest and then retained in the GI area for a long enough time for the active agent to be dissolved and eventually absorbed. For example, many swelling and expanding systems have been attempted. There are dosage forms that swell and change their size thereby floating to the surface.\(^5\) It is also reported that oral treatment of gastric disorders with an $\mathrm{H}_2$-receptor antagonist like ranitidine or famotidine, used in combination with antacids, promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion.\(^6\)

Suitable Drug Candidates for Gastroretention

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hours.\(^5\) In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
Dehghan & Khan

Gastricretentive Drug Delivery Systems

• Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
• Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

Types of Gastroretentive Dosage Forms

A. Expandable systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention (GRT). After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro-retentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties. Patented literature on this mechanism of GRDDDS has been outlined in Table 1.

B. Bio/Mucoadhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc. Patented literature on this mechanism of GRDDS has been outlined in Table 2.

C. Floating drug delivery systems

Floating drug delivery systems (FDDS) have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system.

(a) Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types:
(i) Colloidal gel barrier system

Sheth and Tossounian first designated this ‘hydrodynamically balanced system’. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv) Hollow microspheres / Microballons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

(b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc. Patented literature on this mechanism of GRDDS has been outlined in Table 3.
D. Combination of floating, mucoadhesion and swellable systems

These systems combine floating, mucoadhesion and swelling mechanism for gastric retention of dosage forms. A preferred formulation comprises a mixture of a high or medium viscosity (HPMC) and a high or medium viscosity (HEC). The formulations optionally may comprise a low viscosity HPMC. It also includes a salt being capable of releasing gaseous carbon dioxide alkaline metal carbonates can be used, an acid may be added, such as citric acid and maleic acid. Patented literature on this mechanism of GRDDS has been outlined in Table 4.

Conclusion

It is evident from the patents that there are many means to achieve retention of the dosage form in the gastrointestinal tract and a systematic study of the available patents will help in development of newer non patent infringing GRDDS, as the first step in design and development of any new dosage form is the systematic study of prior art i.e previous available patents, to prevent others from making, using, or selling the invention.

Table 1: Drugs, Dosage form, polymers and Evaluation method reported in patents for swelling and expanding systems:

<table>
<thead>
<tr>
<th>S/N</th>
<th>DRUGS/DOSAGE FORMS</th>
<th>POLYMERS</th>
<th>EVALUATION METHOD</th>
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<tbody>
<tr>
<td>1.</td>
<td>A CR oral tablet composition of acyclovir was prepared. Other examples given are Azithromycin, Simvastatin, Carbamazepine.</td>
<td>Stearyl macrogol glyceride Polyethylene oxide, Crosspovidone, Polyvinyl pyrrolidone K30, Magnesium stearate.</td>
<td>Swelling studies: Rate of swelling was determined in 0.1N HCl combination of a swelling enhancer and polymer results in faster rate of swelling, as desired for gastro-retention. Comparative oral bioavailability study under non-fasting conditions indicate significant increase in the bioavailability of the formulation compared to the reference product Zovirax &amp; commat. Dissolution study done in O. 1N HCL: 900 ml Temp 37 °C.</td>
</tr>
<tr>
<td>2.</td>
<td>A coated tablet having prolonged gastric retention. Two or more compositions in the form of compressed layers, Coating with a coat rupturing system.</td>
<td>One layer of active ingredient, a coat rupturing system of Ethyl Cellulose. Swelling excipient as croscarmellose. A second layer of methacrylates and its derivatives for ex. polymethacrylate like Eudragit L and S.</td>
<td>Dissolution done in simulated GF (0.01 N HCL) at 100 rpm and 37 °C using Type I USP apparatus.</td>
</tr>
</tbody>
</table>
### 3. Solid monolithic matrix tablet of defined size, being non-circular in shape and having first and second orthogonal axes of unequal length. Examples of active ingredients are lisinopril, acyclovir, metformin HCL, baclofen, ciprofloxacin, furosemide, cyclosporin, sertraline HCL, and Calcium Carbonate.

Water-swellable polymer used is Poly (ethylene oxide) having a viscosity-average molecular weight within the range of about 200,000 to about 2,000,000.

Not mentioned

### 4. A CR oral dosage form of rosiglitazone in the form of pellets dispersed in a solid polymeric matrix, wherein the solid polymeric matrix swells upon imbibition of water, and retains greater than or equal to about 40 weight percent of the rosiglitazone within 1 hour after immersion in simulated gastric fluid, and wherein the solid polymeric matrix remains substantially intact until substantially all of the rosiglitazone is released.

Polymeric matrix is HMC, HEC, HPC, HPMC, a CMC, or a combination of alkyl celluloses, is poly (ethylene oxide) has a MW of greater than or equal to about 4,000,000. Polycrylic acid is a crosslinked polycrylic acid. Polysaccharide gum is xantham gum

Not mentioned

### 5. A bilayered SR tablet or caplet composition of heparin and insulin, consisting of two layers. One layer contains the active agent, the delivery agent and a release-controlling polymer. The second layer contains a swellable polymer.

Delivery agent compound is SNAC (N-(6-[2-hydroxybenzoyl]- amino) caprylic acid), and 4-CNAB (4-[2-hydroxy-4-chlorobenzoyl]amino)butanoate). Release-controlling polymer (e.g., polyethylene oxide, having a molecular weight of about 200,000). Swellable polymer (e.g. polyethylene oxide having a molecular weight of about 200,000).

Dissolution of both SNAC and heparin in Simulated Intestinal Fluid (SIF) was measured. Gastric retention, Heparin/SNAC absorption and pH of the stomach fluid study in rats were checked through necropsy. A primate study on monkeys with baso beads-embedded caplets to study the gastric retention of the caplets with X-ray monitoring was done. Swelling tests were performed on various swellable
<table>
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<th>Description</th>
<th>Details</th>
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<tr>
<td>6.</td>
<td>A gastro-retentive tablet dosage form of levodopa and carbidopa, a binder,</td>
<td>Membrane made of polyvinyl alcohol of about 40% and 85%, gas-generating agent is sodium bicarbonate, binder is from the group of Myrj 52, Lutrol F68, PEG 3350, methylcellulose and a polyvinyl pyrrolidone.</td>
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<td></td>
<td>a gas-generating agent, surrounding the tablet with an expandable, hydrophilic, water-permeable and substantially gas-impermeable membrane, and, sealing the membrane to retard the escape of gas from within the sealed membrane.</td>
<td>Gastrointestinal transit of the dosage form were measured in human volunteers, using Samarium Oxide, a radionucleotide by scintigraphy. Relative expansion of pouches containing the tablet formulation, based on visual inspection in simulated gastric fluid on a scale of 0 to 3 is done. A rating of 0 indicates the pouch is not inflated, 1 indicates beginning to inflate, 2 indicate almost inflated and 3 indicate fully inflated.</td>
</tr>
<tr>
<td>7.</td>
<td>Matrix type CR tablet dosage form of Bupropion HBr.</td>
<td>Combination of polymers used, one polymer shows stronger tendency of hydrophobicity Ethyl Cellulose and the other towards hydrophilicity Hydroxyethylcellulose, Hydroxypropylmethylcellulose. Dissolution of Formulations in different USP-3 Media, i.e., SGF pH 1.2, Acetate Buffer pH 4.5 and Phosphate Buffer pH 6.8 over a period of 16 hours is done.</td>
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<td>8.</td>
<td>Bi-layer oval matrix tablet of Valsartan. The gastro-retentive portion is greater than 1 cm upon hydration.</td>
<td>Layer I (SR portion) - active agent, Avicel, Methocel, Sodium Chloride, and magnesium stearate. Layer II (Gastroretentive portion) - Avicel, Methocel (one or more grade), coloring agents such as Yellow Iron oxide and Sodium Chloride, magnesium stearate. Dissolution studies done in USP type II apparatus at 50 RPM in suitable buffer.</td>
</tr>
<tr>
<td>9.</td>
<td>Gabapentin SR matrix tablets, and alternate drug</td>
<td>Combination of hydroxypropylcellulose and hydroxypropylmethylcellulose, Dissolution study in USP apparatus II (paddles) RPM - 50 Medium - 0. IN HCl. Alternate dissolution</td>
</tr>
</tbody>
</table>
| 10. | CR matrix tablets, caplets, vegecaps, and capsules of one of the active agents from the group of Clarithromycin, metformin, azidotimidine, orlistat, ciprofloxacin, and levodopa.  
Polymers consist of Gellan gum and one or more hydrophilic polymers such as guar gum, HPMC, CMC sodium salt, and xanthan gum. | The resulting tablets produce, after wetting, a dense and stable gel for more than 24 hrs in Simulated gastric fluid. |
|---|---|---|
| 11. | Oral CR matrix tablet formulation of active beta-adrenergic inverse agonist such as nadolol, and in another formulation plurality of solid particles of initially about 3-9 mm in diameter in maximum dimension, each particle containing a solid-state active beta-adrenergic Metoprolol.  
First component Polyvinylalcohol combined with Polyvinylpyrrolidine, a second component of a cellulose ether polymer; CR formulation wherein the cellulose ether polymer is methylcellulose polymer and a HPMC polymer. Superporous hydrogel is formed by polymerization of one or more monomers of acrylic acid, acrylamide, vinylpyrrolidone, sulfopropyl acetate, etc. Cross- linker consisting of N'-methylenebis-acrylamide, polyethylene glycol diacrylate, etc. Enteric polymer is esters of cellulose, polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methylmethacrylate copolymers, shellac and derivatives. | Acute Reduction in Airway Function, (FEV₁) was measured in Subjects with Mild Asthma with the first 10 mg dose of Once-Daily Corgard (Nadolol) Subjects with mild asthma, baseline FEVi >80% predicted, were enrolled in a clinical study. Peak serum levels of nadolol occur in 3.5 hours, on average, after administration as advised in the Corgard product insert (Monarch Pharmaceuticals, Inc.), |
| 12. | Pill or capsule to reduce the volume of stomach, esophagus or intestine without interfering with food through the GIT.  
Synthetic polymer blocks include polyphosphazenes, poly (vinyl alcohols), polyamides, polyester amides, poly (amino acid) s, synthetic poly (amino acids). | Not mentioned |
|   | polyanhydrides, polycarbonates, polyacrylates  
Synthetically modified natural polymers ex MC, EC, HPC, HPMC |
|---|---|
| 13. | **A bilayer tablet formulation of Acyclovir ganciclovir, Ritonavir, minocycline, ranitidine, captopril, methyldopa, selegiline, fexofenadine metformin, bupropion, orlistat and metformin.**<sup>20</sup>  
Water soluble polymers are Polyethylene oxide, HPC, HPMC, HEC, sodium CMC, methyl cellulose, polyacrylic acid, most preferably high molecular weight PEO. A hydroattractant selected from low-substituted HPC, MCC, cross-linked sodium or calcium CMC, cellulose fiber, cross-linked PVP, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginites etc.  
In vivo study was done on dogs in the fed state. Plasma samples are collected periodically over the 48-hour period post dosing. The concentration of the minocycline hydrochloride in the samples is then measured by high pressure liquid chromatography. |
| 14. | **Polymeric matrix tablet dosage form of Metformin HCL, vancomycin HCL, captopril, erythromycin lactobionate, ranitidine HCL, sertraline HCL, and ticlopidine HCL.**<sup>21</sup>  
Polymers used are Xanthan gum, cellulose, crosslinked polyacrylic acids. HMC, HEC, HPC, HPMC, and CMC. PEO at a MW of about 4,500,000, 4,500,000 to about 10,000,000, 5,000,000 to about 8,000,000  
Dissolution study in USP Apparatus II, modified to include a stainless steel cone (7/8 inch in height and 7/8 inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4°C modified simulated gastric fluid (7 ml of HCL and 2 g of NaCl, in 100 ml of deionized water; the enzyme pepsin was omitted). |
| 15. | **Gastro retentive drug Delivery system enclosed in a capsule consisting of Parathyroid hormone (PTH), For treatment of osteoporosis.**<sup>22</sup>  
Composed of three layers, a core containing a matrix for peptide; polymer strips (in a frame shape) of enforcing polymeric composition affixed to the core matrix, and two enveloping layers each covering one side of the matrix affixed with the strips, the enveloped layers comprising cross-linked hydrolyzed gelatin. Polymer strips comprising Eudragit L100, Ethylcellulose, triacetin were affixed to the peptide-carrying film, and two enveloping layers comprising crosslinked enzymatically hydrolyzed gelatin.  
It was found that PTH is stable over a wide range of pH values. The results of the stability study in various buffer solutions show that, the peptide showed decreased stability at pH < 7 and at pH=1.2. Thus, for further in vitro release tests, a KC1/HCl buffer pH=2.2 was selected. (peptide is stable at this pH over 24 hr)  
The results show that for macromolecules there is a need to provide (or induce) apertures in the cross-linked gelatin containing enveloping layer in order to enable release of the macromolecule from the GRDA. It is believed that this requirement will be relevant for any
| 16. | Gastrorretentive oval tablet, for immediate release of a vitamin D derivative that stimulates calcium absorption from the intestine, like calcitriol, combined with delayed release of a bis-phosphonate calcium resorption inhibitor such as alendronic acid and its salts and hydrates.  
|  | The polymers for hydrogel comprises of hydroxypropyl methylcellulose and hydroxypropyl cellulose in a weight ratio of from about 1: 3 to about 5: 3. HPMC K-15M, Tannic acid, HPC klucel HF, Crosscarmellose sodium. Magnesium stearate. | Bioavailability study was done in beagle dogs. |
|  | Strips of enforcing polymeric composition were prepared by casting a solution of methylmethacrylate-methacrylic acid copolymer (Eudragit L100), ethylcellulose, and triacetin in ethanol. The shielding sheet was prepared by casting a solution consisting of enzymatically hydrolyzed gelatin (average molecular weight 10,000- 12,000) methylmethacrylate-methacrylic acid copolymer (Eudragit S) and glycerin. Glutaraldehyde, added cross linking and evaporation. A preferred type of paramagnetic contrasting agents for use in MRI includes the superparamagnetic iron oxide (SPIO) based colloids. | Retention of the GRDA capsule in the stomach was assessed by Magnetic Resonance Imaging at various time-points. Imaging of the volunteers was performed in supine position using the General Electric 0.5 T MRI machine (Signa SP/I). Images were taken in axial and coronal planes. The MRI technique was shown to be a suitable method to determine the location of the magnetite-labeled GRDA in the GI tract and to assess the degree of retentivity of the GRDA in the stomach of human volunteers. The use of MRI provided an opportunity to closely follow the administered GRDA without any health hazard to the volunteer. Implementation of the GRDAS in γ-scintigraphy in human subjects The purpose of this study was to investigate the movement of the soluble- polymer |
These substances consist of nonstoichiometric microcrystalline magnetite cores which are coated with dextranes or siloxanes. There are a variety of SPIO reagents available on the market, known by their trademark as Feridex I.V™, Endorem™, Gastromark™, Lumirem™, Sinerem™. Based GRDA and its retention in the stomach (compared to a control tablet), and to verify that the GRDA does not interfere with normal food evacuation. Radioactively-labeled GRDA was followed in the stomach and through the GI tract of healthy subject, using a similarly labeled non-disintegrating tablet as a control.

| 18. | A CR multi-layered tablet of Theophylline with, two barrier layers and one drug layer. All layers are formed from swellable, erodible polymers. | Swellable, erodible polymer comprises First layer consists of polyethylene oxide (MW 7000000), HPMC K4M, Calcium carbonate, Sodium bicarbonate, Citric acid. Second Layer consists of active agent Polyethylene oxide (MW 1000000) Lactose anhydrous, Magnesium stearate. Third Layer of Lactose anhydrous Polyethylene oxide (MW 1000000) Sodium bicarbonate, Magnesium stearate. Dissolution study in 0.1N HCl solution at 50 rpm and at 37°C. The amount of theophylline released at each test point was measured by a Hewlett Packard HP8451A diode array spectrophotometer at 272 nm. For each tablet, a buoyancy lag time was determined, tablets floated for the remainder of the test, until dissolution was complete. The matrix erosion and dissolution was measured by removing individual tablets from the dissolution medium dried at 60°C, under vacuum, the weight loss corresponding to the amount of drug dissolved and fraction eroded was calculated. |

| 19. | The Gastroretentive dosage form of a capsule containing the dried gel (film) with drug such as Hydrochlorothiazide, ranitidine hydrochloride, or amoxicillin & enzymes to facilitate gastric erosion of the gel. | Combination of Xanthan gum and locust bean gum, Expansion agent is sodium lauryl sulfate. Viscosity adjuster is carbopol and polyvinyl pyrrolidone. Plasticizer used in films is polyethylene glycol. Disolution study was done in USP XXII apparatus (paddle method) at 37°C at 75 rpm for 20 hours, medium consisted of 900 ml simulated gastric fluid (without enzymes). An Invivo study was done in dogs to determine gastric residence time, containing radio-opaque threads to visualize the GRDS in the GI tract by x-rays. They also helped in viewing the hydration and disintegration of the gels. |

| 20. | The tablets and/or capsules having permeable polymeric film surface systems capable of rapid | Polymers used in coating of capsules are Gantrez AN, Poly(methylvinylether/maleic anhydride) (PVM/MA), one to one molar ratio of vinyl ether to No failures in swellability of the film coating were noted for the ammonia treated capsules. Capsules prepared without the ammonia treatment swelled |
hydration and swelling, thus providing for controlled drug release under a positive osmotic pressure of the drug Tetracycline hydrochloride.\textsuperscript{27}

Polymers used are Polyvinylpyrrolidone, methacrylic acid polymer having an acidic number between 100 and 1,200 mg of KOH/g of polymer solid substance, optionally a gas-forming additive Sodium bicarbonate, Carbopol 974 P, Copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups:ester groups from 1:1 to 1:2.

Dissolution study: In the course of 7 hours the tablets released 90% of the active compound linearly in 900 ml of 0.1 N HCl at 37\textdegree{}C, with continuous stirring (75 RPM).

Determination of the swelling behaviour: The tablets were incubated in 0.1 N HCl at a temperature of 37\textdegree{}C. The tablets were removed from the incubation medium at specific times, the adhering liquid was removed and the weight of the swollen tablets was determined. The degree of swelling (Qt) at the time t was defined as the quotient of the weight of the tablets at the time t (Wt) and the dry weight of the tablet (Wo).

Table 2: Drugs, dosage form, polymers and Evaluation method reported in patents for mucoadhesive systems:

<table>
<thead>
<tr>
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<th>POLYMERS</th>
<th>EVALUATION METHOD</th>
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<tbody>
<tr>
<td>1.</td>
<td>The formulation comprises of a gastric retention pellet of Metformin Hydrochloride, consisting of an inner layer, of a drug and a pharmaceutically acceptable carrier; and an outer layer, of a polymer having the mucoadhesive and drug release-controlling properties.\textsuperscript{29}</td>
<td>Non-pariel seeds coated with active agent, further coated with mucoadhesive and rate controlling polymers for ex. HPMC, Na-alginate, Na-CMC, carbomer 934, chitosan</td>
<td>To measure the adhesive properties of the prepared pellets, a texture analyzer (Stable Micro Systems, UK) was used. Mucin membrane was prepared and the magnitude of force required for the mucin disc to be detached from the pellet was examined through a graph of time-force correlation. Dissolution tests were conducted by rotating the pellets in 900 ml of artificial gastric juice for about 2 hours and 900 ml of...</td>
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<td>2.</td>
<td>Botulinum toxin type A oral formulation consisting of plurality of polymeric microspheres, a mucoadhesive polymeric matrix.</td>
<td>A carrier polymer of polylactides, polyglycolides and polyanhydrides. Acrylic-based polymers can be used.</td>
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<td></td>
<td>Not mentioned.</td>
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<tr>
<td>3.</td>
<td>CR bioadhesive formulation of an active agent which comprises a microsphere of H₂-antagonist nizatidine, Cimetidine Famotidine.</td>
<td>The cationic polymer is a cationic polysaccharide, a cationic protein, or a synthetic cationic polymer. The inner core contains a gelling hydrocolloid; the water insoluble polymer is ethylcellulose. The cationic bioadhesive agent is chitosan, cationic bioadhesive agent is diethyiaminoethyldextran, and the gelling hydrocolloid is gelatin/clodronate. A composition obtainable by the spray drying of oil-in-water or of water-in-oil-in-water emulsion including the components of the composition.</td>
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<td>Gastroretention in human Subjects was evaluated in healthy fasted subjects. The formulation was labelled with a gamma emitting radionuclide (indiumil) by the addition of a small amount of ion-exchange resin to the formulation. A marker for the gastric emptying of a simple liquid formulation in the form of a techetium-99m labelled diethylenetriaminepentaacetic acid (DTPA) solution was used as a control. The images were recorded and analysed by a standard method (geometric mean calculation) in order to obtain gastric emptying profiles for both the gastroretentive system and the control. An in vitro test was carried out by the dissolution paddle assembly (USP App 2 or BP App II) was used.</td>
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<td>4.</td>
<td>Bioadhesive macrosphere delivery systems (“BDDS”) having prolonged gastric retention time due to bioadhesion active agents</td>
<td>Coated with a bioadhesive membrane including Eudragit, calcium oxide, FAPP (anhydride oligomer), and polymer (polyfumaric)</td>
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<td>In vivo gastric transit was conducted by orally administering the formulation to beagles that had been fasted for 18hrs. The animals were recorded and analysed by a standard method (geometric mean calculation) in order to obtain gastric emptying profiles for both the gastroretentive system and the control. An in vitro test was carried out by the dissolution paddle assembly (USP App 2 or BP App II) was used.</td>
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are Acyclovir, Salicylate, etc.\textsuperscript{32} acid :sebacic acid). Metal compounds which enhance the bioadhesive properties of a polymer preferably are water-insoluble metal compounds, such as metal oxides and hydroxides, including oxides of calcium, iron, copper and zinc. were X-rayed at each time point to track the transit of macrospheres.

**Table 3:** Drugs, dosage form, polymers and evaluation method reported in patents for floating mechanism

<table>
<thead>
<tr>
<th>S/N</th>
<th>DRUGS/DOSAGE FORMS</th>
<th>POLYMERS</th>
<th>EVALUATION METHOD</th>
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<tr>
<td>1.</td>
<td>A buoyant matrix bilayer tablet dosage form of Ciprofloxacin, Acyclovir, and ofloxacin.\textsuperscript{33} Floating layer composed of cellulose derivatives of which density is less than 1. Ethyl Cellulose, alone or in combination with hydrogenated oils, waxes, fatty acids, shellac, polyethylene-oxyde and the likes. Drug release rate controlling layer consists of HPMC, HEC and the like and/or natural polymers or gums such as xanthan gum, gelatin and/or polyethylene oxide or other synthetic polymers such as acrylic acid derivatives, polyvinyl acetate and the likes.</td>
<td>Dissolution study of the coated tablets was conducted in 0.1N HCl using USP Apparatus 1 (basket) at 100 rpm.</td>
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<td>2.</td>
<td>A monolayered SR dosage form of Thrombin inhibitor, optionally encapsulated slugs or capsules containing either a wet or dry powder or granulation optionally loosely compacted. The powder mixture of milled granulation can then be filled into capsules.\textsuperscript{34} Hydroxypropylmethylcellulose, Hydroxypropylcellulose or polyvinylacrylate or mixtures are used.</td>
<td>An intravenous bolus dose pharmacokinetic study in dogs was done. Active agent can be measured by means of a biomarker. The slug capsules increased the aPTT (activated partial thromboplastin time) to the therapeutic range of 1.5 to 2.5 at the 24 hour time point. The activated partial thromboplastin time is a measure the blood coagulation time relative to the baseline. Floatability study in 80ml of 0.1N HCL Soln and a 1.5 inch stirring bar. Disintegration was</td>
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<td>recorded by photographs. At the completion, both capsules were floating on the medium.</td>
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<td>3.</td>
<td>Bouyant biconvex caplets (Size - length 19 mm and width 9 mm Hardness - 120 to 160 N) of Flouroquinolones, amoxicillin, cephalexin, metformin, gliclazide , diltiazem, metoprolol.</td>
<td>Combination of gelling agents: strong gelling agent is methyl cellulose, HPMC, HPC with the exclusion of low-substituted HPC, HEC, EC, sodium CMC, xanthan gum, guar gum, carrageenan gum, locust bean gum, sodium alginate, agar-agar, gelatin, modified starches, co-polymers of carboxyvinyl polymers, co-polymer of acrylates, co-polymers of oxyethylene and oxypropylene. Weak gelling agent is a co-processed material of microcrystalline cellulose and sodium carboxymethylcellulose. The gas generating agent is water soluble carbonates, sulfites and bicarbonates, such as sodium carbonate, sodium bicarbonate, etc.</td>
<td>Dissolution study done in 0.1 N HCL using USP type II apparatus at 100 RPM.</td>
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<td>4.</td>
<td>CR buoyant unit dose composition, of Ofloxacin, Ciprofloxacin, Deltiazem HCL, Acyclovir etc.</td>
<td>Gel forming husk powder obtained from Lepidium sativum seeds, cross-linking enhancer xanthan gum, karaya gum, cellulose ethers like methyl cellulose, HPMC, CMC and their salts, alginates, PVA and EC or a combination are used, gas generating component is Sodium bicarbonate.</td>
<td>Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N hydrochloric acid, 100 RPM, at 37°C</td>
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<td>5.</td>
<td>A multi-unit floating device of a shaped sheet or a roll containing an anti-tumor agent, a histamine (H&lt;sub&gt;2&lt;/sub&gt;) blocker, a synthetic prostaglandin or an antibiotic.</td>
<td>Low glass transition T&lt;sub&gt;G&lt;/sub&gt; polymers with or without plasticizer (eg: Eudragit RSPO, EC, PVA phthalate and other) loaded with drug and extruded as a hollow tubes with two sealed ends.</td>
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<td>6.</td>
<td>Floating bilayer tablet of Fluoroquinolone antibiotic such as ciprofloxacin etc.</td>
<td>Matrix forming gelling agent is HPMC which has a viscosity from 4000cps to 100000cps. Combination of matrix forming gelling agent of Methocel</td>
<td>Dissolution study in 0.1 N HCl using USP apparatus 1 at 100 rpm is done.</td>
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<td>7.</td>
<td>Pellets, beads, granules or capsules which constitutes a gastro-retentive oral drug delivery system that generates a gas to form a highly porous (preferably honeycombed) matrix with good floating characteristics.</td>
<td>The inert oil is partially hydrogenated cottonseed oil, a fully hydrogenated cottonseed oil, castor oil, coconut oil, etc, Sugar is sucrose, glucose syrup, corn syrup, lactose, dextrose, galactose, maltose, maltodextrin, sorbitol, mannitol etc, ammonium bicarbonate, calcium carbonate, sodium bicarbonate etc, The edible organic acid from the group of citric acid, ascorbic acid etc, Release retarding agent is from the group of cellulose ethers, acrylic polymers and natural gums.</td>
<td>The capsules were tested for in-vitro dissolution and floating characteristics, capsules remained floating on the media throughout the test of 24 hours.</td>
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| 8. | A SR gastroretentive amoxicillin composition in a floating capsule dosage form for once or twice daily administration of amoxicillin and clavulanic acid. | The capsule may be a polymer material of HPMC, gelatin and starch. Preferably, HPMC. Suitable coatings may be well soluble, poorly soluble, or slowly dissolving can be applied of HPMC, HPC, HEC, MC or PVP, combinations of Eudragit RL PO, Eudragit RL 100, Eudragit RL30D, Eudragit RS PO, Eudragit RS 100, Eudragit RS30D or combinations of a neutral polymer of methacrylate (e.g., Eudragit NE 30 D, Eudragit NE 40 D. | A pharmacokinetic evaluation of the therapeutic system was done in twelve healthy male volunteers in fed conditions. |

<p>| 9. | A granule of drug consists of a core comprising a pharmaceutically effective ingredient, a foaming layer coated on core and an expansive film coated on layer. Film is expanded like a balloon so that granule | The polymer of the expansive film is one or more of polyvinyl acetate, acrylic resins, shellac, HPMC phthalate, cellulose acetate phthalate, methylcellulose, ethylcellulose and HPMC. Gas-generating layer comprising | Three caps were administered to a healthy male subject of 40 years old before breakfast and granules remaining in the stomach were monitored with the lapse of time by roentgenography. Granules were buoyant in the upper region of the stomach 30 minutes, one |</p>
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<th>Dehghan &amp; Khan</th>
<th>Gastricretentive Drug Delivery Systems</th>
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<tr>
<td>floats on gastric juice and remains floating thereon for at least 5 hours.</td>
<td>sodium bicarbonate and an organic acid.</td>
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<tr>
<td>10. Non-compressed SR floating tablets of Theophylline, Ampicillin and Captopril.</td>
<td>Matrix formed of Gelling agent is one or more agents from agar, carrageenan, locust bean gum, alginic acid, Mineral oil, and Calcium gluconate.</td>
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<td>11. A SR flexible sheet of theophylline for oral administration, that is buoyant in the gastric juices of the stomach.</td>
<td>The Polymeric film consists of Ethyl cellulose, poly(γ-benzyl glutamate), polyvinyl acetate, cellulose acetate phthalate, a copolymer of methyl vinyl ether with maleic anhydride, and the above polymers to which PVP may be added.</td>
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<td>12. SR tablet of hydrodynamically balanced system acquires and maintains a bulk density of less than one. Examples of active agents are Acetylsalicylic acid, Riboflavin, Magnesium oxide, benzodiazepine such as chlor Diazepam, Ferrous fumarate, and Light magnesium oxide.</td>
<td>Hydrocolloids selected from the group of methyl cellulose, HPC, HPMC, HMC and sodium-CMC</td>
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<td>13. Misoprostol bilayer capsule floating dosage form, and Misoprostol in combination with aspirin, diclofenac, piroxicam, ibuprofen or naproxen.</td>
<td>A high viscosity hydrocolloid from HPMC, gums, polysaccharides or gelatin. A low viscosity hydrocolloid from HPMC, gums, polysaccharides or gelatin.</td>
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14. A buoyant CR pharmaceutical powder of a Calcium antagonist such as verapamil hydrochloride, Diltiazem, nicardipine, nifedipine, gallapomil and cinnarizine, formulation being free of carbon dioxide producing material and will float in gastric juices and which will have drug release properties similar to a tablet of similar composition.\(^46\)

A pH-dependent polymer which is a water-soluble salt of a polyuronic acid (salt of alginic acid) from about 4 to about 300 centipoises Hydrocolloid gelling agent is HPMC having a viscosity of from about 50 to about 100,000 centipoises, binder is HPMC having a viscosity of from about 5 to about 15 centipoises. Floating studies have shown that the capsules are capable of floating for up to 5 hours in 0.1 M HCl.

15. Antacid powders, tablets etc., of prolonged gastric residence time. Active agents are Cimetidine, ranitidine and omeprazole.\(^47\)

The internal phase of an antacid is aluminum magnesium hydroxy carbonates and sulphates, surrounded by a solid external phase of a hydrophobic organic means for floating, from the group of hydrogenated mono-, di- and tri-glycerides, a hydroxylated polyalkene having a MW between 950 and 10000, and a non-ionic emulsifier comprising a polyoxyethylene-sorbitan mono-ester of an oleic, lauric, stearic or palmitic acid. ex: Hydrotalcite, Hydrophobic silicon dioxide, Sorbitan monooleate, Polyoxyethylene stearate, Castorwax, Polyvinylpyrrolidone. The floating characteristics and prolonged gastric residence time with sustained acid neutralisation have been demonstrated in human volunteer studies using isotope labelled Almagate (scintigraphy). In normal volunteers the time required for emptying 20% of the labelled antacid from the stomach is almost 3 times longer for coated Almagate than for the uncoated product. The latter empties with the liquid phase of a light standard meal whereas emptying of the former occurs much later with a half-life of 4 hours.

16. A sustained-release composition in capsule form having a specific gravity of not more than 1. Active agents selected are Theophylline, Chlorpheniramine maleate Cephalexin, Isosoride dinitrate, Nifedipine Dioclofenac sodium, Pindolol, Aspirin, Sodium azulenesulfonate, Ifenprodil tartrate, Sulpiride Dried

Polymers selected are HPC, methylcellulose, CMC, HPMC or alpha-starch or a mixture thereof. Stearic acid, palmitic acid, hardened castor oil, beeswax, stearyl alcohol or ethyl alcohol or a mixture of two or more.

Measurement of Floatage, a microload transformer (UT-100GR: manufactured by Shinkoh-Minevea KK) was modified to include an attachment to which the test capsules could be fixed. The force in milligrams required to sink the test capsules in water was measured electrically, below under zero shaking time. Measurement of resistance against shaking and of floatage.
aluminum hydroxide gel, and Riboflavin butyrate.\textsuperscript{48}

was done as described in the pharmacopeia of Japan. The shape was observed and the flotage was measured as in Test 1 each hour. Dissolution test was performed in accordance with the dissolution test as described in pages 725-733 of The Pharmacopoeia of Japan.

<table>
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<th>Table 4: Drugs, dosage form, polymers and Evaluation method reported in patents covering swelling, floating and mucoadhesive mechanisms</th>
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<td>S/N</td>
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or medium viscosity (HPMC) and a high or medium viscosity (HEC), in a ratio HPMC/HEC = 1/0.85 - 1/1.2 and optionally a low viscosity HPMC in a ratio high or medium viscosity HPMC/low viscosity HPMC = 1/0.01 - 1/0.2, sodium bicarbonate and citric acid as gas generating agent, swelling enhancer is alginic acid. Eudragit NE30D® for coating.

tedisamil salt was conducted in healthy male volunteers. Non-coated MR formulations with an in vitro 100% disso in 4-6 hrs of 150 mg tedisamil. Coated MR formulations with an in vitro 100% dissolution in 8-12 hours of 150 mg tedisamil. Conclusion Tedisamil as a salt in the floating expending (FE) tablet is much better tolerated than in the immediate release formulation with regard to the gastro-intestinal adverse effects.

4. Oral SR tablet dosage form in a non-gas generating, floating, swellable and bioadhesive, novel carrier composition, comprising, one or more of solid compatible drugs such as Ofloxacin; Acyclovir; Simvastatin; Carbamazepine; Niacin; Cefixime; Venlafaxine. High viscosity sodium CMC; a swelling bioadhesive; gellan gum; one or more of hydrophilic water soluble polymers Not mentioned.

References

13. Liao J, Liu P, Dinh S et al, inventors; Emisphere Technologies, assignee. Gastric retention and