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Novel Approaches of Gastro Retentive Drug Delivery System: A Review

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Abstract---Oral route of drug administration is the most convenient route and accepted route of drug delivery. It is probable that at least 90% of all the drugs given by oral route. There are different drug deliveries to cure the diseases through oral route. Among them Gastroretentive drug delivery system plays an important and significant role in novel drug delivery systems. The floating systems, bioadhesive drug delivery system, expandable drug delivery system, high density systems, effervescent systems (Gas Generating systems), non-effervescent systems etc are various approaches. The wide applications can be achieved through this delivery system are enhanced bioavailability, sustained drug delivery, site-specific drug delivery, absorption enhancement, mitigating adversity at colon etc. In addition to specified above, the advantages and disadvantages, drugs and polymers used and the method of evaluation is also summarized in this review.

Keywords---Gastroretentive Drug Delivery system (GRDDS), Floating systems, site specific drug delivery, absorption enhancement.

Introduction

The oral route is leading way for the administration of drugs for single-dose systems and it is convenient for usage and cost-effective for formulating a single dose controlled release or extended or sustained release dosage form the massive research has been designed for getting the better patient compliance and minimising of repeated administration of the drug the highly soluble drug at acidic pH condition and lower solubility at pH higher than 7 resulted as a lower absorption window drug from intestine. The fundamental advantages of GRDDS

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3464

are to ameliorate the bioavailability and they having site-specific drug delivery for curing GI disorder when the active ingredient bioavailability is enhanced then mitigating the dosing usage and leads to lowering GI disorder the demerits of the GRDDS is incompatible with those drugs that irritate the gastric mucosa in contrast to conventional dosage form (Patil et al., 2016).

Formulation is to static in the stomach region for an indefinite time by offering a product material to the top part of the GI tract. There is the numerous methods for enhancing the gastric retention time in the stomach could include as floating systems which are the low density in that gas generating system, swelling systems in these systems the drug administered form is buoyant in the gastric fluid because of density of the formulation product is less than the density of the stomach (Ghosh & Ghosh 2013).

In the bio adhesive system the administered dosage form adheres to the mucosal surface and several explanations are illustrated in this category systems in the high-density system dosage form they remain in the distal section of the stomach because of the mass of dosage form are higher than gastric fluid. In the super porous hydrogel system, the dosage form is swelled due to water uptake through the porous by a capillary wetting mechanism. In the raft forming systems contains polymers they swell and form the in situ gel layer and they are floated above the gastric fluid called raft forming systems. In the expandable techniques, systems is swell and unfold and it occurs by diffusion (Streubel et al., 2006).

Basic Gastrointestinal Tract Physiology

The stomach basically intends at digesting and carrying food materials. The stomach offers for short term food reservation and rapid consumption of relatively large meal. The chief substantial metabolism of enzymes is enriched in stomach of proteins. The peristalsis of stomach mixes and break down consumed food with the natural secretions of the stomach, converting food in normal liquid form. The liquefied volume is passed to the small intestine for further digestive process (Wilson & Washington et al., 1989)

The anatomy of stomach is divided into three major parts: the fundus part, body and antrum (pylorus). The proximal area named to as fundus and the body functions as storage for undigested food. The antrum available for the major site for mixing movements and acts as gastric emptying pump by propeller actions (Desai.,1984). The fasting and fed states cause the gastric emptying. These states are changed upon pattern of motility. In this phenomenon, series of electric events takes place in cycles via stomach and intestine every 2 to 3hours (Prajapati S & Dharamsi 2013). There occurs a phenomenon of interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is divided in 4 phases as given by Wilson and Washington.

Table 1: Four phases of migrating myoelectric cycle

Phase	Name of the Phase	Duration
Phase I	Basal phase	30 to 60 minutes
Phase II	Preburst phase	20 to 40 minutes
Phase III	Burst phase	10 to 20 minutes

Phase IV	Transition period between Phases III and I	0 to 5 minutes
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After the food material being ingested, the stomach movement changes from fasted to fed state. It's described as digestive motility pattern and constitutes regular peristalsis as in phase II of the state of fast. This decreases food size (to lower than 1mm), transporting the food towards pylorus. The gastric emptying rate is minimized during fed state onset of MMC, causing slowdown of gastric emptying rate (Sharma et al., 2011).

Anatomical and physiological features of GIT

In oral cavity, stomach, colon, duodenum, jejunum, ileum, caecum and rectum passive diffusion in absorption occurs. In addition to this mechanism active transport occurs in duodenum, jejunum, ileum, caecum (Ravindra Pal Singh & Devendra Singh Rathore 2012).

Factors Affecting the Gastro retentive System

There are various factors influencing the GRDDS, such as dosage form density, size and shape of dosage form, the fed and fasting state, meal or food ingested nature, caloric value and composition, feed or food taken gap, the gender such as male and female, age which of adult elderly people especially above 65 lower GRT, the posture state and disease nature, and the drug administration.

Why there is need of GRDDS?

The occurrence of a rapid elimination of certain drugs, that have been absorbed from the gastrointestinal tract (usually having short half-lives), from circulatory system results in administration of frequent dosing. In order to overcome this the novel path gastroretentive drug delivery systems are used.

They have efficacious drug concentration in plasma so that mitigating the dosing frequency. Most escalated aspect of this system is that it effectively reduces variations in plasma drug concentration by delivering the active ingredient in a controlled and reproducible way (Swetha., et al 2012 & Kawatra., et al 2012).

Table 2: Rationale for the use of GRDDS

S.NO	RATIONALE FOR THE USE OF GRDDS
1	Enhancement of bioavailability
2	Increase in half life
3	Patient compliance
4	Promotes dosage form stability
5	Mitigated frequency dosing
6	Rises solubility
7	Sustained/prolonged release
8	Elimination of drug waste
9	More GRT
10	Promotes therapeutic efficiency

Main types of gastro retentive drug delivery systems

Gastro retentive drug delivery systems are designed to retain drug or dosage form in the stomach for a maximum time and release their active ingredients and thereby enhances sustained and prolonged uptake of the drug in the upper part of the gastrointestinal (GI) tract. The advanced system has developed great attention over the last few decades owing to its potential application to maximize the oral drug 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. Gastro retentive delivery system can be classified as follows.

- a. Bio adhesive Drug Delivery System
- b. Expandable Drug Delivery System
- c. Floating Drug Delivery System and
- d. High density systems

Bio adhesive systems

Bio adhesive drug delivery systems are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial surface in the stomach (Mahesh et al., 2006). Bio adhesive systems adhere to gastric epithelial cells or mucous and extend the gastric retention by increasing the intimacy and duration of contact between gastro retentive drug delivery system (GRDDS) and the biological membrane. Some of the most promising excipients that have been used commonly in these systems include polycarboxophil, carbopol, lectins, chitosan and gliadin and alginate etc. Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastric residence time of drug delivery system in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bioadhesive polymers. The ability to provide adhesion of a drug to the mucous layer provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Expandable systems

Expandable gastric retentive delivery systems are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (Klausner et al., 2003). 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. Narrow absorption window drugs compounded in such systems have improved *in vivo* absorption properties. Expansion mechanism of this system is swelling to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “*plug type system*”, since

they exhibit the tendency to remain lodged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

Floating drug delivery systems

Floating drug delivery systems 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 (Singh & Kim 2000). 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 gastric retention time and a better control of the fluctuations in plasma drug concentration. Floating drug delivery system can be divided into (i) Non-effervescent and (ii) Gas-generating system (Arora & Ahuja 2005).

Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibitions 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 (Desai & Bolton 1993). 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.

a. Colloidal gel barrier system

Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. 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.

b. 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. 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.

c. Alginate beads

Multi-unit floating dosage forms have been developed from dried calcium alginate complex.¹⁵ Spherical beads of approximately 2.5mm 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°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

Hollow microspheres/Microballons

(Kawashima et al., 1992) was developed hollow microspheres loaded with drug in their outer polymer shell 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 40°C. 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.

a. 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 (Choi & Park 2000, Hilton & Deasy 1992). 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. These mini capsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO₂ release in gastric fluid and resides in the stomach for prolonged period (Bhowmik et al., 2009).

b. High density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture (David et al., 1986). Dense pellets (approx. 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³.

c. Multiple unit type floating system

Multiple unit type floating system is sustained release pills, known as 'seeds', which are surrounded by two layers. The outer layer is of swellable membrane layer and inner layer consists of effervescent agents. This system sinks at once

and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density of the system is due to generation and entrapment of CO₂ within the system (Bechgaard & Ladefoged 1978).

Ion exchange resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems

It is comprised of an osmotic pressure-controlled drug delivery device and an inflatable floating support in a bio erodible capsule (Seth & Tossounian 1984). The osmotic controlled drug delivery device consists of two components– drug reservoir compartment and osmotically active compartment. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag.

Gastro retentive drug delivery system desirable characters

- Drugs that act locally in the stomach e.g., Antacids and Misoprostol (Nayak et al., 2010 & Sarojin & Manavalan 2012).
- Drugs that are primarily absorbed in the stomach. e.g. Calcium supplements, Chlordiazepoxide and Cinnarazine.
- Drugs those are poorly soluble at an alkaline pH.
- Drugs that have a narrow window of absorption. e.g., Riboflavin and Levodopa.
- If the drugs disturb normal colonic microbes.
- Drugs that is unstable in the intestinal or colonic environment. e.g. Ranitidine and Metronidazole.
- Drugs with variable bioavailability. E.g. Sotalol HCl

Advantages of Gastro retentive drug delivery system (Badoni et al., 2012 & Bhalla et al., 2012).

- Enhanced drug absorption.
- Controlled drug delivery.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to slow and controlled rate.
- Highly suitable for the treatment of gastrointestinal disorders such as gastro-esophageal reflux.

- Simple and conventional equipment is enough for formulate.
- Site-specific drug delivery.

Disadvantages of gastroretentive drug delivery systems (Badoni et al., 2012 & Sarojini & Manavalan 2012).

- Unsuitable for drugs with limited acid solubility.
- Unsuitable for drugs that are unstable in acidic environment.
- Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's
- Unsuitable drugs that absorb selectively in colon.
- Floating drug delivery systems require high fluid level in stomach to float and work effectively.

Commonly used drug in formulation of gastro retentive dosages forms

(Arrora et al., 2005 & Vyas et al., 2006 & More et al., 2018).

The most convenient, cheap and oral dosage form i.e, Floating tablets, capsules, microspheres, granules and powders, eg- Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerrzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p- Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil Chlordiazepoxide HCl, Diazepam, Antihypertensive drugs such as Losartan, Eprosartan mesylate, verapamil, captopril, nimodipine, quinapril, amlodipine, atenolol, metaprolol, furosemide, nicorandil, quinapril etc are used in this method of approach.

Table 3: Gastroretentive products available in the market (Arrora et al., 2005 & Chawla et al., 2004)

Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoat ®	Aluminum -magnesium antacid
Liquid Gavison ®	Aluminium hydroxide,
Conviron	Ferrous sulphate
Cytotec®	Misoprostal

Polymers

The polymers used in the delivery system to attain the drug delivery in the stomach. Both the natural from various sources such as Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate, Tara gum, karaya gum, locust beam gum are available. The synthetic could include Poly ethylene oxide like WSR 301, 301, N10, Coagulants, methylcellulose, ethylcellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl ethyl cellulose, sodium carboxy methylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly

(hydroxyl ethyl methyl acrylate), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).
(Singh & Kumar 2012, Ramdas)

Evaluation of gastro-retentive dosage form (Thaherabanu Shaik. et al., 2014)

***In Vitro* Evaluation**

i) Floating systems

a) Buoyancy Lag Time

This evaluation parameter is performed to know the time taken by the dosage form to float on the top of the dissolution medium, after being placed in the medium.

b) Floating Time

The total time or duration of dosage form continuously floats on the dissolution media at 37° C.

c) Specific Gravity / Density

This test be assessed by the displacement method using Benzene as displacement medium.

ii) Swelling systems

a) Swelling Index: After being contact of swellable dosage form into Simulated Gastric Fluid at 37°C, the dosage form is taken out at regular time interval and changes in dimensions are measured in terms of increase in tablet thickness / diameter with proportion to time.

b) Water Uptake: It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time.

$$\text{Water uptake} = \text{WU} = (\text{Wt} - \text{Wo}) * 100 / \text{Wo}$$

Where, Wt = weight of dosage form at time t.

Wo = initial weight of dosage form.

***In vitro* Evaluation Test**

This test is generally performed by using USP dissolution apparatus with paddle and GRDDs is introduced normally as for other conventional tablets. The various types of dissolution test apparatus are available.

- To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.
- Floating unit can be made fully submerged, by attaching some small, loose, nonreacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
- Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.
- Other method suggests placing dosage form between 2 ring/meshes.
- Change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

- In spite of the various modifications done to get the reproducible results. Dissolution test apparatus with modification of Rosette-Rice test Apparatus was proposed.

***In vivo* Evaluation Test**

- **Radiology:** Barium sulphate is used as radio opaque marker and X-ray is widely used for examination of internal body systems.
- **Scintigraphy:** Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is ^{99}Tc (Nayak et al., 2010).
- **Gastroscopy:** Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach (Sarojini & Manavalan 2012).
- **Magnetic Marker Monitoring:** In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.
- **Ultrasonography:** Used sometimes, not used generally because it is not traceable at intestine.
- **^{13}C Octanoic Acid Breath Test:** ^{13}C Octanoic acid is incorporated into GRDDs. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with ^{13}C isotope. So time up to which $^{13}\text{CO}_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO_2 release. So this method is cheaper than other.

Application of Gastro-Retentive Drug Delivery System

Enhance bioavailability

The bioavailability of Controlled Release –Gastro Retentive Dosage Form is significantly more in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Sustained drug delivery

The Gastroretentive drug delivery system is used for dosage form retained in the stomach for longer period for the drug released in stomach or intestine.

Site-specific drug delivery systems

These systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

Absorption enhancement

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

Minimize adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Reduce fluctuations of drug concentration

Continuous input of the drug following controlled release gastro-retentive dosage form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Conclusion

Gastroretentive drug delivery system have emerged as an efficient means of prolonged retaining ability in stomach and thereby increase gastric residence time of drugs and also improves bioavailability, achieves sustained drug delivery, site-specific drug delivery system, enhancement of absorption. GRDDS also offers maximum benefit to patient so that maximum patient compliance associated with it.

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