Acta Chimica & Pharmaceutica Indica

Acta Chim. Pharm. Indica: 3(2), 2013, 149-164
ISSN 2277-288X

A COMPREHENSIVE REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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(*Received : 25.04.2013; Revised : 03.05.2013; Accepted : 06.05.2013*)

ABSTRACT

In recent years several advancements has been made in research and development of oral drug delivery system. Concept of novel drug delivery system arose to overcome certain aspect related to physicochemical properties of drug molecule and the related formulations. Purpose of this review is to compile the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized factors influencing gastric retention and also included various strategies for gastric retention. GRDDS has become leading methodology in site specific orally administered controlled release drug delivery system. Various drugs, which are unstable in alkaline pH, soluble in acidic pH, having narrow absorption window, site of action specific to stomach can be developed by using this technique.

Key words: Gastro-retentive drug delivery system, Gastric resident time, Hydro dynamically balanced systems (HBS), Gastric retention time.

INTRODUCTION

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive system, swelling system and expanding system and floating system. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of gastric emptying.[1] Unfortunately floating devices administered in a single unit form (Hydro dynamically balanced system) HBS are unreliable in prolonging the GRT owing to their 'all - or - nothing' emptying process and, thus they may causes high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.

More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent *in vitro* release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.

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Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

These drugs can be delivered ideally by slow release from the stomach. Many drugs categorised as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

Scope[3]

The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract. Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines.

Need for GRDDS[2]

- Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity.
- Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- Pharmaceutical field is now focusing towards such drugs which require site specificity.
- Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine.

Merits[4]

- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc.
- Patient compliance by making a once a day therapy.
- Improved therapeutic efficacy.
- Improved bioavailability due to reduced
- P-glycoprotein activity in the duodenum.

- Reduces frequency of dosing.
- Targeted therapy for local ailments in the upper GI tract

Demerits[4]

- Floating systems has limitation, that they require high level of fluids in stomachfor floating and working efficiently. So more water intake is prescribed with such dosage form.
- In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

Physiology of the stomach[5]

The Gatrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the Gatrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

The interdigestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organised in cycles of activity and quiescence.

Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the ‘housekeeper wave’ as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions.

The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food (Fig. 1 and 2).

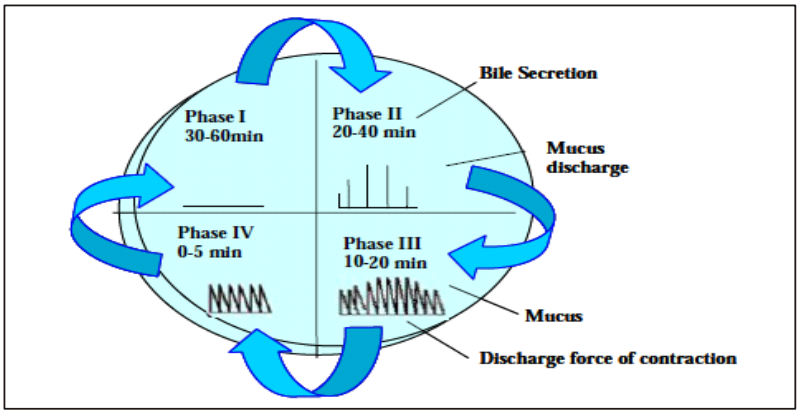

Fig. 1: Phases of gastric cycle

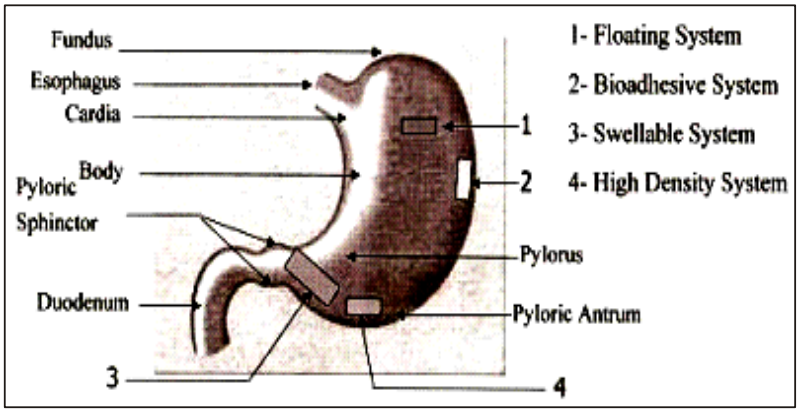

Fig. 2: Physiology of stomach

Different features of stomach

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 mL

Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.

Effect of food on Gastric secretion: About 3 liters of secretions are added to the food. Gastro intestinal transit time.

Factors influencing gastric residence time[6]

(i) Density of dosage form: Dosage forms having density lower than that of gastric fluids experience floating behaviour and greater gastric residence time.

(ii) Size of dosage form: In most cases larger the size greater the gastric residence time because larger size will not allow dosage form to quickly pass through pyloric spincter to intestine.

(iii) Food intake and nature of food: Usually presence of food in stomach increases the GRT of the dosage form and increases drug absorption by allowing it to stay at absorption site for longer time.

(iv) Affect of age, gender, posture and disease state: Elderly persons and females has slow gastric emptying rate. It was found that gastric emptying in women is slower than in men regardless of height, weight, body surface area.

(v) When individual rests on left side floating of dosage form will be towards pyloric antrum. If rests on right side it will be in opposite direction.

(vi) Shape of dosage form: Tetrahedrons (each leg 2 cm long), rings (36 cm diameter) exhibited nearly 100% retention at 24 hrs where as on other hand cloverleaves (2.2-3.3 cms) exhibit (40-67%) retention.

Mechanistic approaches of gastric retentive drug delivery system[7]

A number of systems have been used to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention. Classification of gastro retentive drug delivery system shown in Fig. 3.

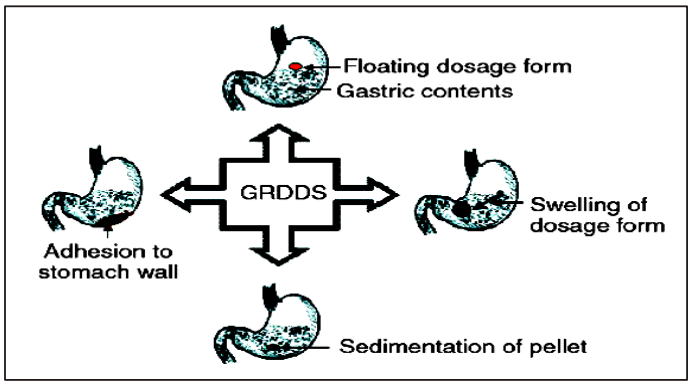

Fig. 3: Classification of gastroretentive drug delivery system

Floating drug delivery system (FDDS)

Floating dosage form is also known as hydrodynamically balanced system (HBS). FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the 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. After release of drug, the residual system is emptied from the stomach.

Classification of FDDS

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories *viz* non-effervescent and effervescent systems.

A. Non-Effervescent systems

(i) Colloidal gel barrier systems: Hydrodynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules (Fig. 4).

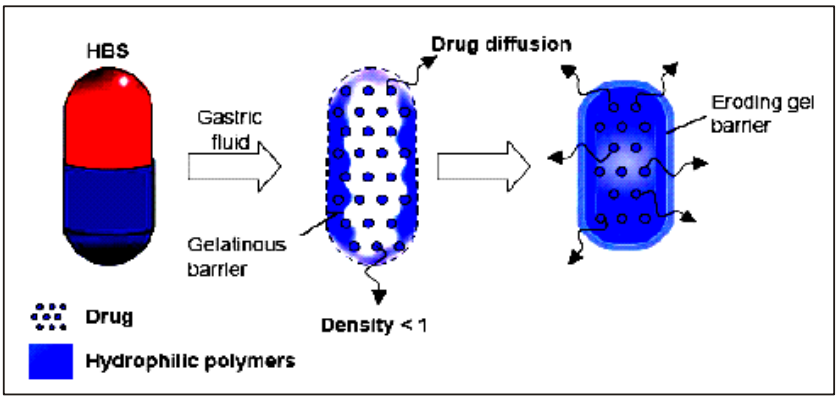

Fig. 4: Hydrodynamically based system (HBS)

(ii) Micro-porous compartment system: This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption (Fig. 5).

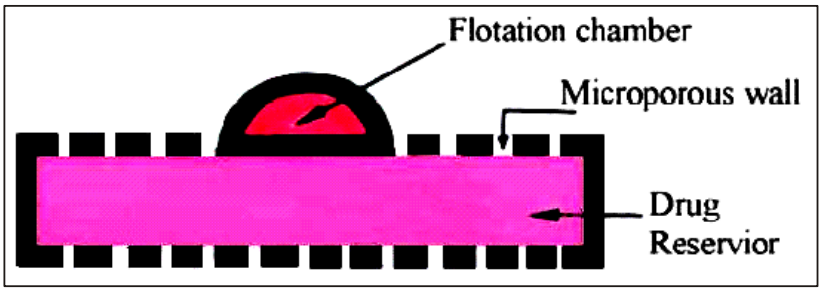

Fig. 5: Floating drug delivery device with microporous membrane andfloatation chamber

(iii) Alginate beads: Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at – 40ºC for 24 hrs. leading to formation of porous system that maintained floating force for over 12 hrs.

(iv) Hollow Microspheres: Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug.

B. Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

Volatile liquid containing systems[8]

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period.

A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach (Fig. 6).

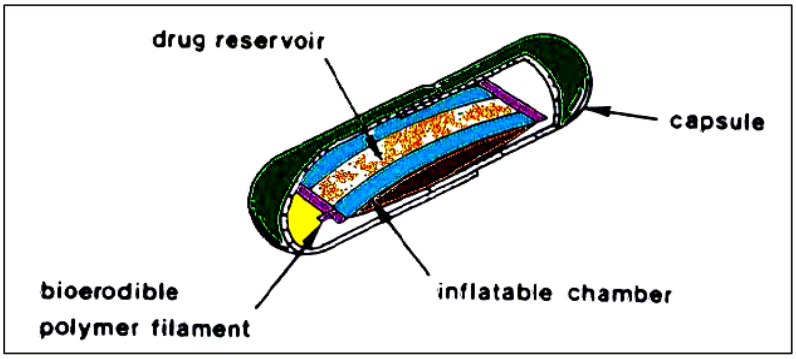

Fig. 6: Gastro inflatable drug delivery device

Gas generating systems

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect. Multiple unit type of floating pills that generates CO_2 have also been developed. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hrs. (Fig. 7).

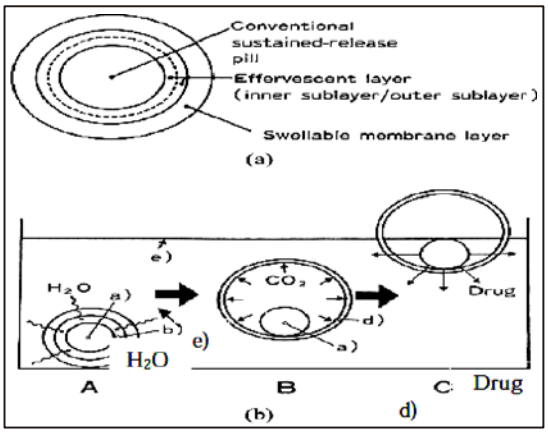

Fig. 7: The multiple units floating drug delivery system using gas generation technique

Bioadhesive DDS

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT2. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material andbiological substrate, such as adhesion between a polymer and a biological membrane.

Swelling and expanding systems

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems may be named as "plug type systems", since they exhibit the tendency to remain lodged at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and hence maintain the physical integrity of the dosage form.[9]

High density systems

These dosage forms have a density (3 g/mL) far exceeding that of normal stomach contents (1 g/mL) and thus retained in region of the stomach and are capable of withstanding its peristaltic movements. High density formulations include coated pellets that have density greater than that of stomach contents (1.004 g/cm^3). This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. The weighted pellet can then be covered with a diffusion-controlling polymer membrane.

Pharmacokinetic aspects

Absorption window- that the drug is within the category of narrows absorption window agents

In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorptionproperties at the upper parts of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of thetransport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non CRmode of administration.

Enhanced bioavailability

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgicalmeans.

Enhanced first pass biotransformation

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is

presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

Table 1: Marketed products of GRDFs[10]

S. No.	Brand name	Drug	Company, Country	Remarks
1	Madopar	Levodopa (100 mg), Benserazide (25 mg)	Roche products, USA	Floating CR capsule
2	Valrelease	Diazepam (15 mg)	Hoffman-Laroche, USA	Floating capsule
3	Liquid gaviscon	Al. Hydroxide (95 mg), Mg. Carbonate (358 mg)	Glaxo smith kline, India	Effervescent floating liquid alginate preparation
4	Topalkan	Al-Mg antacid	Pierre fabre drug, France	Floating liquid alginate preparation
5	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6	Cifran OD	Ciprofloxacin (1 g)	Ranbaxy, India	Gas-generating ® floating tablet
7	Cytotec	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8	Oflin OD	Ofloxacin (400 mg)	Ranbaxy, India	Gas generating floating tablet

Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gpmRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CR-GRDF may elevate absorption compared to the immediate and CR dosage forms.

Reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.[11]

Targeted therapy for local ailments in the upper GI tract

The prolonged and sustained administration of the drug from the GRDF to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

Pharmacodynamics aspects[12]

Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF 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.

Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading tohigher drug efficiency.

Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration.

Minimized adverse activity at the colon

Retention of the drug in the GRDF 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 development of microorganism's resistance.

Suitable drug candidates for gastro retention[13]

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

(i) Narrow absorption window in GI tract, e.g., riboflavin and levodopa.

(ii) Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, chlordiazepoxide and cinnarazine

(iii) Drugs that act locally in the stomach, e.g., antacids and misoprostol

(iv) Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole

(v) Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

Drugs those are unsuitable for gastro retentive drug delivery systems[14]

(i) Drugs that have very limited acid solubility e.g. phenytoin etc.

(ii) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

(iii) Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

Polymers and other ingredients used in the formulation of grdds[15]

Category materials

Polymers: HPMC K4 M, Calcium alginate, Eudragit S100 EudragitRL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Car-bopol

Inert fatty materials (5%-75%)

Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formu-lation and hence increase buoyancy. E.g. Beeswax, Fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Other materials

(i) Effervescent agents:- Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di- Sodium Glycine Carbo-nate, CG (Citroglycine)

(ii) Release rate accelerants (5%-60%):- Lactose, mannitol

(iii) Release rate retardants (5%-60%):- Dicalcium phosphate, talc, magnesium stearate

(iv) Buoyancy increasing agents (upto80%):- Ethyl cellulose

(v) Low density material:- Polypropylene foam powder (Accurel MP 1000®)

Evaluation[16]

(A) *in vitro* evaluation

(i) Floating systems

(a) Buoyancy lag time: It is determined in order to assess the time takenby the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

(b) Floating time: Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 370 C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

(c) Specific gravity/density: Density can be determined by the displacement method using Benzene as displacement medium.

(d) Resultant weight: Now, we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form.

The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form (Fig. 8).

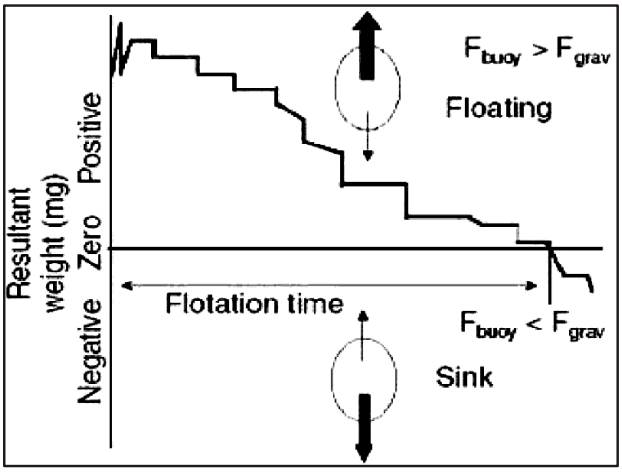

Fig. 8: Swelling systems-water uptake

F = Fbuoy–Fgrav, F = Df g V – Ds g V, F = (Df – Ds) g V, F = (Df – M/V) g V

Where,

F = Resultant weight of object

Df = Density of fluid

Ds = Density of solid object

g = Gravitational force

M = Mass of dosage form

V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

Plot of F vs. Time is drawn and floating time is time when F approaches to zero from positive values.

(ii) Swelling systems

(a) Swelling Index: After immersion of swelling dosage form into SGF at 37^0C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness/diameter with time.

(b) Water Uptake[17]**:** 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. So it is also termed as Weight Gain.

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

Where, Wt = Weight of dosage form at time t

Wo = Initial weight of dosage form

In this assembly concentric circles with various diameters are drawn in computer and print out is laminated to make hydrophobic. This laminated piece is attached with some system which can facilitate up and down movement of assembly.

This assembly is placed in beaker and tablet is placed exactly at center and then there is no disturbance given to tablet.

Tablet is allowed to swell on laminated paper and diameter can be easily noted without removing out.

To determine water uptake/weight gain, whole assembly can bring out. Weighing of assembly done after wiping off water droplets adhered at surface of assembly and then can be placed back as it is without touching to tablet.

Rate of water penetration is also important parameter for swelling matrix, that how fast swelling occurs is determined by equation[18]:

$$\text{Penetration rate} = \left(\frac{\text{Water up take}}{\text{per unit time}}\right) \text{x} \left(\frac{\text{2 x Area of tablet}}{\text{Water density}}\right)$$

(c) Continuous monitoring of water uptake[19]: Although previous method has advantage of un-disturbance of swollen tablet, but for measuring water uptake one has to remove whole assembly out of beaker, so process in not continuous.

Continuous monitoring of water uptake is possible by following apparatus.

In this apparatus, swelling tablet is placed on glass filter as support in one hallow cylinder with smooth surface inside, and one light weight punch is placed on it to prevent floating.

This cylinder is placed pre-heated in dissolution medium.

Another dissolution medium reservoir beaker is placed on digital balance and both are connected with media filled U tube as shown in figure and medium level is kept equal.

As swelling of tablet started, it absorbs water and water level in outer part of cylinder is goes down. The decrease in water level is maintained by importing extra medium via U tube from reservoir beaker.

As medium is transfer from reservoir, amount of water transfer can be determined by observing loss in weight by digital balance.

B) *in vitro* dissolution tests[20]

A. *In vitro* dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results.

In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

B. 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.

C. Floating unit can be made fully submerged, by attaching some small, loose, non-reacting 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.

D. 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.

E. Other method suggests placing dosage form between 2 ring/meshes.

F. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the 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.

G. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the *in vivo* conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

Rossett-Rice test is used for predicting in-vitro evaluation of directly acting antacid (action by chemical neutralization of acid), where HCl is added gradually to mimic the secretion rate of acid from the stomach.[22]

In this modified apparatus as shown in figure, it has side arm from bottom of beaker such that it maintains volume of 70 mL in beaker and fresh SGF is added from burette at 2 mL/min rate. Thus sink condition is maintained. Stirring is done by magnetic stirrer at 70-75 RPM (Fig. 9).

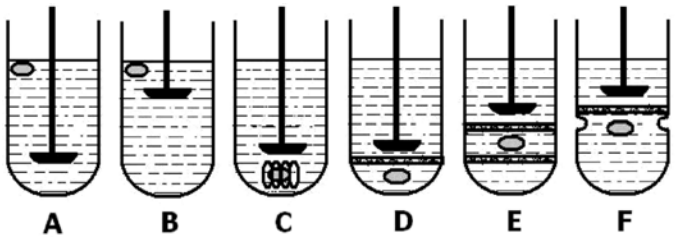

Fig. 9: *In vitro* dissolution tests

(C) *In vivo* evaluation[21]

(a) Radiology: X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

(b) ⊥-Scintigraphy: Similar to X-ray, ⊥-emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used ⊥-emitting material is 99Tc.

(c) Gastroscopy: Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

(d) 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.

(e) Ultrasonography: Used sometimes, not used generally because it is not traceable at intestine.

(f) 13C Octanoic acid breath test: 13C 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 13C isotope. So time upto which $13CO_2$ 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.[23]

Future potential[24]

Offers advantages for drugs with poor bioavailability because their absorption is restricted to upper GI tract and they can be delivered efficiently their absorption and enhancing bioavailability.

In some cases lower bioavailability of drugs could be balanced by clinical advantages of GRDDS.

Example: In patients with advanced parkinson's disease, who experience fluctuations in symptoms while they take levodopa, a HBS dosage form offers better control of motor fluctuations.

GRDDS offer beneficial strategy for treatment of gastric and duodenal ulcers, also being exploited for development of several anti-reflux formulations.[25]

Promising area of research regarding GRDDS is eradication of H. Pylori-causative of chronic gastritis and peptic ulcer. Its complete eradication requires high concentration of anti biotic.

Sustained release of liquid preparation of ampicillin with using sodium alginate- that spreads and adheres to gastric mucosal surface where by drug is released continuously.

CONCLUSION

This study concludes that GRDDS is one of the efficient technique to maintain the sustained release of drug in gastric environment and there by increases its absorption and bioavailability. All these GRDDS are interesting and more feasible when compared to other drug delivery systems and have their own advantages and disadvantages.[26] Now a lot of research program is going on to develop new concepts regarding GRDDS for various drugs by which in the near future we can ultimately lead to improved efficiency of various types of pharmacotherapies. GRDDS is much safer dosage form and have systemic, localized actions as well GRDDS do help in the treatment of chronic diseases like ulcers and carcinoma of GIT, and also reduces dose frequency there by minimize contra indication, systemic toxicity, drug dependence. Ultimately GRDDS is an simple yet effective drug delivery system.[27]

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