

GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A REVIEW ON EXPANDABLE SYSTEM

P. K. Wagh*, S. P. Ahirrao, S. J. Kshirsagar

*Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgoan, Nashik 422 003 (M.S.) India

<p>*For Correspondence: Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgoan, Nashik 422 003 (M.S.) India.</p>	<p>ABSTRACT Gastroretentive drug delivery system (GRDDS) is one of the novel approaches in the area of oral sustained release dosage forms. Gastro retentive dosage forms has received significant interest in the past few decades as they can improve the limitation of conventional and oral controlled release drug delivery system related to fast gastric emptying time. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation require frequent dosing to achieve suitable therapeutic activity. To avoid these limitations, the development of oral sustain release GRDDS is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in controlled manner so, that the drug could be supplied continuously to its absorption sited in the GIT.</p> <p>KEY WORDS: Gastroretentive Dosage Forms, unfolding system, Expandable system, Controlled release.</p>
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INTRODUCTION

Oral drug delivery is the most preferable route for administration of dosage form because it is less invasive than other routes, like intravenous and intramuscular injection. This in turn, increases patient compliance and improves safety compared with other methods. (Sarah and Tejal; 2005 and Lavelle, 2001) Oral controlled drug delivery system have been developed for the past 3 decades due to their therapeutic advantages. (Ruquayya et al. (2014) However, this approach has not been suitable for a variety of important drugs, due to narrow absorption window in the upper part of the gastrointestinal tract. (Permendeet al. (2012) and Etyan et al. (2003) Conventional oral drug delivery shows limited bioavailability because of the fast-gastric emptying time. However, the recent technologies has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. (Uttam et al. (2016) several controlled drug delivery strategies have been developed to overcome these limitations, such as microspheres and nanoparticles, have been used to protect peptides during transport thorough the acidic environment of the stomach.(Sarah and Tejal; 2005 and Saffran et al.(1990) and McClean et al. (1998). Gastro retentive drug delivery system is an approach to prolong the gastric retention time, there by targeting site specific drug release in the upper part of gastrointestinal tract for local or systemic effects. Dosage forms can remain in the gastric region for longer period of time and hence prolong the gastric

retention time of the drugs. Prolonged gastric retention of dosage form improves bioavailability, increases the duration of action, reduces drug waste and could be advantageous for local action in the upper part of the small intestine e.g. treatment in peptic ulcer. The dosage form that are included in the category of narrow absorption window drugs are mostly associated with improved absorption at the jejunum and ileum due to their enhanced absorption properties e.g. large surface area, in comparison to the colon. (Permender et al. 2012 and Hoffman, 1998) In an effort to increase the residence time of drug dosage forms in the GI tract, magnetic systems, gastric retentive units and systems incorporating mucoadhesive properties have been investigated. (Sarah and Tejal; 2005, Groning et al. (1996) and Krauland et al. (2004)

It was suggested that formulating narrow absorption window drugs in a pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such a formulation would be retained in the stomach and release the drug there in a controlled manner, so that the drug could be absorb continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs. (Harshali and Shailesh;2017)

GRDDS are beneficial for such drugs by improving their

- Bioavailability
- Therapeutics efficiency and possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (Meenakshi et al (2015) and Imtiyaz et al. (2015)

ADVANTAGES

- 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.
- Improved bioavailability (Cadwell,1988)
- Patient compliance
- Improved therapeutic efficacy
- Reduces frequency of dosing
- Targeted therapy for local action in the upper GI tract.

DISADVANTAGES

- Floating systems has limitations that they require high level of fluid in the stomach for floating efficiently, so more water intake is prescribed with such dosage form
- 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 gastro retentive drug delivery system.
- Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer and 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. (Pathan et al. (2012) and Rajeev et al. (2013)

CRITERIA FOR GRDDS

1) Drugs acting locally in the stomach e.g., Antacids and drugs for H. pylori

- 2) Drugs that are primarily absorbed in the stomach e.g., Amoxicillin
- 3) Drugs that is poorly soluble at alkaline pH e.g. Furosemide, Diazepam
- 4) Drugs with a narrow absorption window e.g. cyclosporine, Levodopa
- 5) Drugs which are absorbed rapidly from GI tract e.g. metronidazole, Tetracycline
- 6) Drugs that are degrade in colon (Garg and Shringi;2003 and Lahoti et al.(2011) e.g. Ranitidine, metformin, HCl
- 7) Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.(Amit et al. (2010)

Drug	Category	Marketed gastroretentive Formulations
Verapamil	Calcium channel blocker	Sustain release matrix tablet, sustain released solid dispersion,
Nifedipine	Calcium channel blocker	Fast disintegrating tablet, Microemulsion,
Ranitidine	Antacid	Microspheres, immediate release tablet
Atenolol	Antihypertensive	Fast dissolving film, gastroretentive floating tablet
Propranolol	Antihypertensive	Sustain release bilayer tablet, mucoadhesive buccal patch
Diltiazem	Calcium channel blocker	Controlled release pellets, pulsatile release tablet
Lidocaine	Local anaesthetic	Mucoadhesive buccal patch, microspheres
Clarithromycin	Antibiotic	Floating microspheres, nanoparticulate drug delivery system
Ramipril	ACE inhibitor	Microshperes, microballons

Drugs which are used for gastro retentive drug delivery system

PHYSIOLOGY OF STOMACH

There are three main regions according to anatomy of stomach: shown in figure 1.

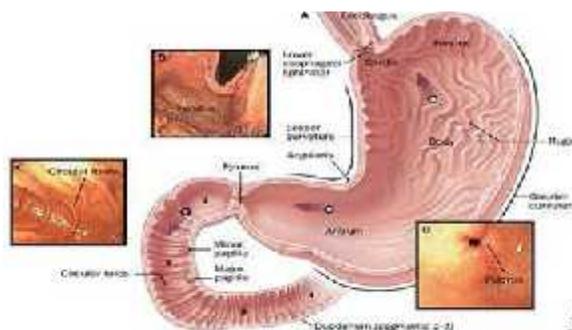
- 1) Fundus: It is proximal part
- 2) Body: It is reservoir for matter that is undigested.
- 3) Antrum: d act as pump during gastric emptying, mixing activity takes place here (Garg and Shringi ;2012 and Cadwell et al. (1988), and Yadav et al. (2016)

Stomach is present in between oesophagus and intestine. Stomach wall is same as that of other portions of gastro intestinal tract, presence of extra coating of smooth muscles inside circular layer is an exception which helps in complicated crushing process. Surface of stomach contains some basic forms of epithelial cells which are secretory in nature. (Mohan,2017).

- 1) Mucous cell: These are secrete mucous.
- 2) Parietal cells: These are secrete Hydrochloric acid
- 3) Chief cells: These are secrete pepsin.
- 4) G cells: These are secrete gastrin (Dr. Singh,2010).

Gastric emptying takes place both in fasting and fed state with distinct form of motility. During fasting condition, here is interdigestive sequence of electrical signalling which takes place is for of cycle along

stomach and intestine as well after every 2-3 hrs. Known as Migrating Myoelectric cycle (MMC) (Dr. Singh,2010).

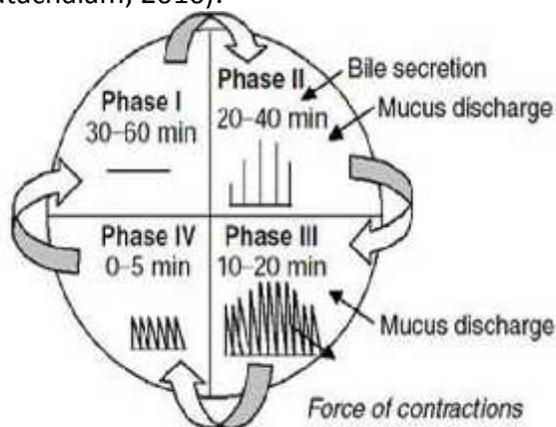


(Ruquayya ,2014 and Dr. Singh,2010)

Fig 1: Physiology of Stomach

This cycle is divided into following 4 Stages:

- 1) Phase I: It is known as Basal phase, it continues from 40-60 min with sparse contraction
- 2) Phase II: It is known as preburst phase, continues from 40-60 min with recurrent action potential and contractions. Gradually intensity and regularity of phase increases.
- 3) Phase III: It is known as Burst phase, it continues for 4-6 min it comprises of severe and consistent contractions for shorter duration.
- 4) Phase IV: It takes place between IIIrd and Ist phase, it continues for 0-5 min. after ingestion of meal contractions change from fasting fed state which termed as digestive motility pattern. Shown in figure 2 (Koelapati and Venkatachalam; 2016).



(Sarojini and Malavanalab;2011)

Fig 2: Stages of Migrating Myoelectric Cycle

FACTORS AFFECTING GASTRIC RETENTION TIME OF THE DOSAGE FORM

density: The density of the dosage form should be less than that of the gastric contents (1.004 g/ml) (Meenakshi et al. (2015)

size: Dosage form having diameter of more than 7.5 mm have more gastric residence time than that of 9.9 mm diameter dosage form.

shape: The tetrahedron shape resided in the stomach for longer period of time.

single or multiple Unit formulation: Multiple unit formulation show a more predictable release profile and in significant impairing or the performance due to failure of the unit, allow co-administration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.

Fed or unfed state: under fasting condition, the GI motility is characterized by periods of strong motar activity that occurs every 1.5-2 hrs. the MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in the fast state MMC is delayed and GRT is longer. (Cadwell, 1988 and Guyton,1997)

nature of meal: feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release.

caloric content: GRT can be increased by 4-10 with a meal that is high in protein and fat.

frequency of feed: The GRT can be increase over 400 min when successive meals given are compared with the single meal due to frequency of MMC.

gender: mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6 hrs.) regardless of height, weight and body surface.

age: people age with more than 70 have a significant longer GRT. (Cadwell,1988 and Guyton,1997)

concomitant drug administration: Anticholinergic like atropine and propantheline, opiates like codeine can prolong GRT.

APPROACHES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

Various approaches have been used for the gastro retentive drug delivery system, these are as floating system, swelling system, effervescent system, gas generating system, high density system, raft system, magnetic system and expandable system. Shown in figure 3.

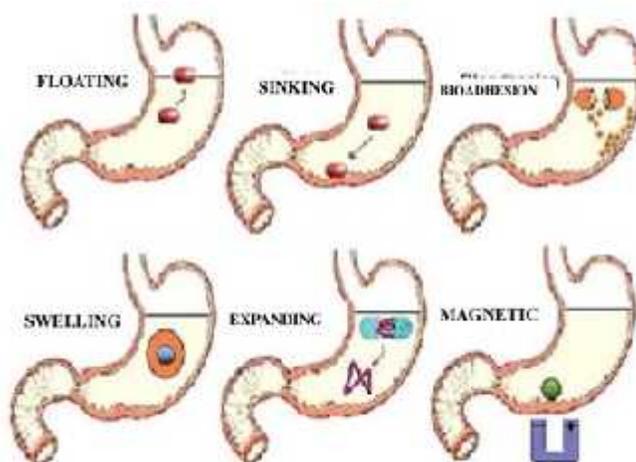


Fig 3: Approaches of GRDDS

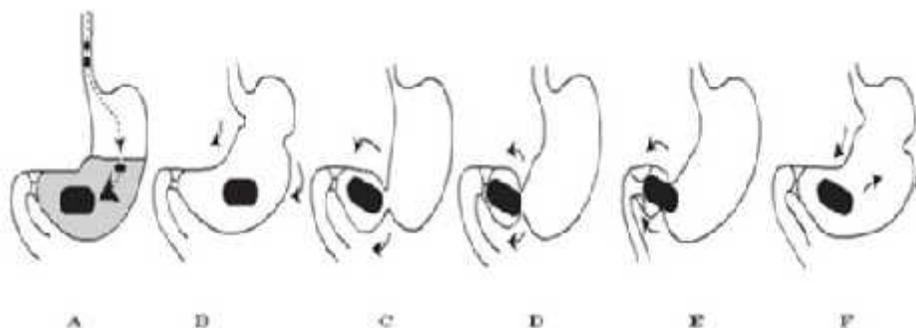
expandable system:

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus their configurations are required to developed an expandable system to prolong gastric retention time. (Paul SD, 2012) The expandable gastro retentive dosage forms are based on three configurations: A) a small configuration which enables convenient oral intake. B) expanded form that is achieved in the stomach and thus prevent passage through the pylori sphincter. C) another small form that is achieved in the stomach when retention is no longer required.(Permender et al. (2012). The expansion can be achieved by swelling or by unfolding in the stomach. Swelling occurs because of osmosis. Unfolding is achieved due to mechanical shape memory. The gastro retentive dosage form is formulate in a large size and is folded into a gelatin capsule for intake. In the stomach the capsule is dissolved and the gastro retentive dosage form unfolds, to achieved extended configuration. (Permender et al. (2012). A study of unfolding devices characterized by different erodibility, mechanical properties, sizes and geometries was conducted by

Caldwell and co-workers. (Dr. Baviskar,2016 and Cadwell,1988) They develop geometric configurations like ring, tetrahedron, planar disc, planar multilobe and string. These devices had the following properties: sufficient resistance to forces applied by the stomach, thus preventing rapid passage through the pylorus, allowance of free passage of food while in residence in the stomach and desired in vivo circumference larger than 5 cm, to ensure gastro retentivity. This system consists of special type of hydrogel polymers with high swelling properties. Their size increases immediately when come in contact with water e.g. super-porous-hydrogel. Figure 4

- A. When dosage form come in contact with gastric fluid marvellous increase in size takes place
- B-E. contractions in stomach pushes it towards pylorus but contractions got miss due to large size.
- F. large size pushes it back into stomach.

It is mostly available as a capsule having inside folded type of dosage form. When these capsules come in contact with gastric content it get dissolve and release its folded part outside and dosage form start expanding. Suitable polymer can provide sustain release characteristics as well. Development of second generation SPH was to enhance mechanical properties. (Ali et al. (2005).

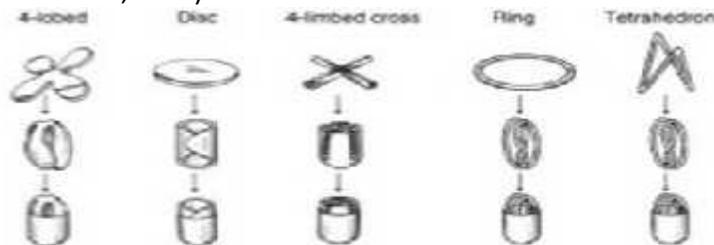


(Ali et al. 2005 and Bardonnnet,2006)

Fig 4: Gastric retention of a highly swellable gastroretentive drug delivery system

unfolding system:

Formulation having various geometrical shapes due to unfolding cause pylorus to create hindrance in its pathway. To properly engulf the dosage form it is delivered as a capsule. Capsule get dissolve in stomach and release it there, where it attains its extended original shape. Following are few shapes which can be packed in form of a capsule. Figure 5. (Cherng,1999). Research has shown that tetrahedron shape has higher gastric retention time as compared to several other shapes such size (Cherng,1999). Ring shape also has higher gastric retention time. Clover - leaf and disk-shaped system have poor GRT. Rapid removal of pellet and string shape was also observed. Unfolding, multilayer film of polymer based on drug with inner layer of shellac matrix was developed by Klausner. (Joseph and Vincent;2009 and Wen and Park;2010).



(Chen,2012, Bardonnnet,2006 Hwang,1998, Cadwell,1988 and Cadwell,1988)

Fig:5 Geometrical shapes of gastroretentive patch

CHARACTERIZATION

Parameters which are used for evaluation of gastro retentive expandable system, are as follows:

1.unfolding time

The film was folded in a zigzag manner and both films were inserted into individual capsule. In each case six capsules were taken for in vitro dissolution study in 900 ml aqueous hydrochloric acid P^H 1.2 at 37± 0.5°C using the USPXXIII Apparatus 1 (Basket) at 100 rpm. Basket were removed after 5, 10, 15, 20, 30, 60,120, 240, 480 and 720 min and the films were examined for their unfolding behavior.(Sharad and Pradeep;2012)

2.uniformity of weight

Each formulation was prepared in triplicate and ten patches each equivalent to 4cm x 2cm was cut from each plate. Their weight was measured using Shimadzu digital balance. The mean ± SD values were calculated for all the formulations.

3.thickness

The thickness of the patches was measured by digital screw gauge. The mean SD values. Were calculated for all the formulations.

4.folding endurance

The number of times the patch could be folded at the same place till it broke gave the value of folding endurance.

5.drug content

Film taken dissolved in 100 ml 0.1 N HCL solution in 100 ml volumetric flask and kept for 24 hrs. with occasional shaking. The filtrate make dilution with 0.1 N Hcl. Then take UV. (Larhed,1997)

6.swelling index

Swelling of films was examined in the triplicate in simulated gastric fluid (PH 1.2). After recording the initial weight of a film (W_1), it was immersed in medium maintained at 37 ± 1°C for 360 min and then weight again (W_2). The swelling ratio was determined as $(W_2-W_1)/W_1$. (Larhed,1997)

7. *in vitro* mucoadhesive force

Mucoadhesion of the film to stomach mucosa was evaluated in triplicate using a double beam physical balance. The moist film was then brought into contact with a film attached to the lower surface of another Teflon cylinder suspended from the left arm of the balance by removing a 5 g weight from the right pan of the balance. The balance was kept in this position for 3 minutes after which weights were added slowly to the right pan until the film separated from the mucosal surface. The excess weight of the pan is the bioadhesive strength required to separate the film from the mucosa. The force of the adhesion was calculated using the formula;

$$\text{Force of adhesion (N)} = (\text{Bio adhesive strength} / 1000) \times 9.81$$

8. *in vitro* mucoadhesive time

The time taken for detachment of film from goat stomach mucosa was measured in 0.1 N hydrochloric acid (pH 1.2). This was evaluated by an in vitro adhesion testing method, by using in vitro dissolution apparatus.

A piece of goat stomach mucosa, (3 cm diameter) was attached inside,0.1 N HCL buffer containing beaker of dissolution apparatus assembly with cyanoacrylate glue and film was attached by applying pressure for 5 m. Suitable rotation speed of dissolution apparatus assembly was maintained at 37 ± 0.5°C and observes the time of detachment of mucoadhesive film from mucous membrane.

9. tensile strength

To determine tensile strength, polymeric film was sandwiched separately by corked linear iron plates. One end of the film was sandwiched separately by corked linear plates. One end of the film kept fixed with the help of an iron screen and other end was connected to a freely movable thread over a pulley.

The weights were added gradually to the pan attached with the hanging end of the tread. A pointer on the tread was used to measure the elongation of the film. The weight just sufficient to break the film was noted. The tensile strength was calculated by using the following equation-

Tensile strength (Kg / mm²) = Force at break (Kg)/ Initial cross sectional area of the sample (mm²)

10. elongation at break

The force and elongation were measured when the films were broken. Results from film samples, which were broken at end and not between the clamps were not included in observations. Measurements were run in six replicates for each formulation. The following equations were used to calculate the mechanical properties of the films.

$$\text{Elongation at break (\%mm-2)} = \frac{\text{Increase in length (mm) } 100}{(\text{Original length}) (\text{Cross sectional area mm}^2)}$$

11. *in vitro* dissolution study

In vitro dissolution studies were carried out employing USP dissolution apparatus (Basket apparatus). 2 cm x 4 cm size films containing 75 mg of equivalent weight of ranitidine was filled into hard gelatin capsule in zigzag manner. Basket was rotated at 100 rpm. 900 ml of 0.1 N HCL pH 1.2 was taken the dissolution medium. 10 ml aliquot were withdrawn at regular time interval until complete drug release and the sample was periodically withdrawn at suitable time interval and the volumes were replaced with fresh dissolution medium to maintain the sink condition. The aliquots were analysed using UV Spectrophotometer at 313 nm. (Shivaneshwari et al. (2017).

CONCLUSION

Based on literature survey, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due to their absorption is restricted to the upper gastro intestinal tract and maximizing their absorption and enhancing absolute bioavailability. This article consists of comprehensive data on GRDDS. It has several advantages and some limitations. Dosage frequency is low so patient compliance and bioavailability is very high. Gastric retention time of this dosage form is higher than conventional dosage form.

GRDDS are used for drugs that, act locally in the stomach, poorly soluble at an alkaline pH, have a narrow absorption window, unstable in the intestinal or colonic environment.

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