

(REVIEW ARTICLE)



## Gastro-retentive drug delivery system: A better approach of drug delivery system

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### Abstract

The oral route is the best and most popular route for the administration of drugs in the systemic circulation. There are number of drugs which are given through the oral route. Gastro-retentive drug delivery system is very important system for the drug delivery system. The gastro-retentive drugs prolonged the drug time in the git and also improve their their bioavailability. These are widely used for site specific for the treatment of git disorders and diseases. There are number of approaches for gastro retentive drug delivery system such as floating system, mucoadhesive system, swelling system, high density system etc. In this review we discussed about approaches and various perspectives of gastro retentive drug delivery system.

**Keywords:** Gastroretentive drug delivery system; Floating system; Gastric residence time; Mucoadhesive system; Swelling system

### 1. Introduction

The most popular route for drug administration is oral route for systemic action .About 90% of the drugs are given by oral route. The oral route is the most prescribed route because it is easy to administer, easy to handling and versatile for various types of drugs. The short gastric retention time and unpredictable short gastric emptying time are the two problems of drug delivery systems. Decrease response of dose Due to incomplete drug release from the dosage form in the absorption zone [1-3].

However some of the drugs have poor bioavailability due to incomplete absorption or degradation in GIT .Therefore to overcome this problem we use Gastroretentive Drug Delivery System(GRDDS) which are use to prolong the gastric retention time of the drugs which are:

- Locally active in stomach.
- Unstable in the intestinal environment.
- Have low solubility in high pH regions.
- Have narrow absorption window in the git.

Over the last two decades, the number of GRDDS have be designed to prolonged GRT . The main aim of preparing GRDDS is to minimize the problems associated with existing oral sustained release dosage form and to develop patient benefited drug delivery [4, 5].

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### 1.1. Drugs suitable for the gastroretentive drug delivery system

- Drugs that are primarily absorbed in the stomach. eg: Amoxicillin.
- Drugs that are narrow absorption window. eg: Levodopa, Methotrexate.
- Drugs that are poorly soluble in alkaline pH. eg: Furosemide, Diazepam.
- Drugs that are degrade in the colon. eg: Ranitidine, Metformin.
- Drugs rapidly absorbed from GIT tract. eg: Tetracyclin
- Drugs acting normally in the stomach [6].

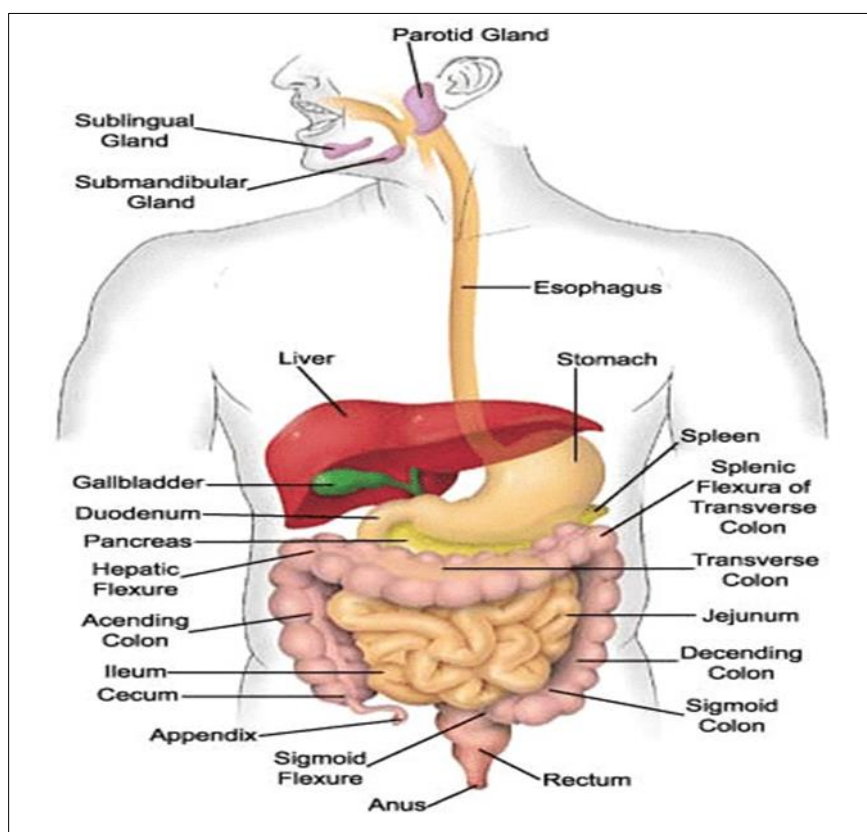
### 1.2. Advantages of GRDDS

- It can improved drug absorption.
- It has control drug delivery system.
- It can minimize the mucosal irritation.
- It is used for the treatment gastrointestinal diseases.
- It is easy to administration and better patient compliance.
- This site specific drug delivery reduce undesirable site effects.
- Ease to administration & better patient compliance.

### 1.3. Disadvantages of GRDDS

- GRDDS is not suitable for drugs with stability or solubility problems in the stomach.
- Drugs that show irritant effect on gastric mucosa are not suitable for GRDDS.
- Drugs that are absorbed along the entire GIT, that undergo first pass metabolism may not be desirable [7].

### 1.4. Anatomy of the GIT tract



**Figure 1** Gastrointestinal tract of human body

The gastrointestinal tract can be divided into 3 main regions:

- Stomach

- Small intestine
- ❖ Duodenum
- ❖ Jejunum
- ❖ Ileum
- Large intestine

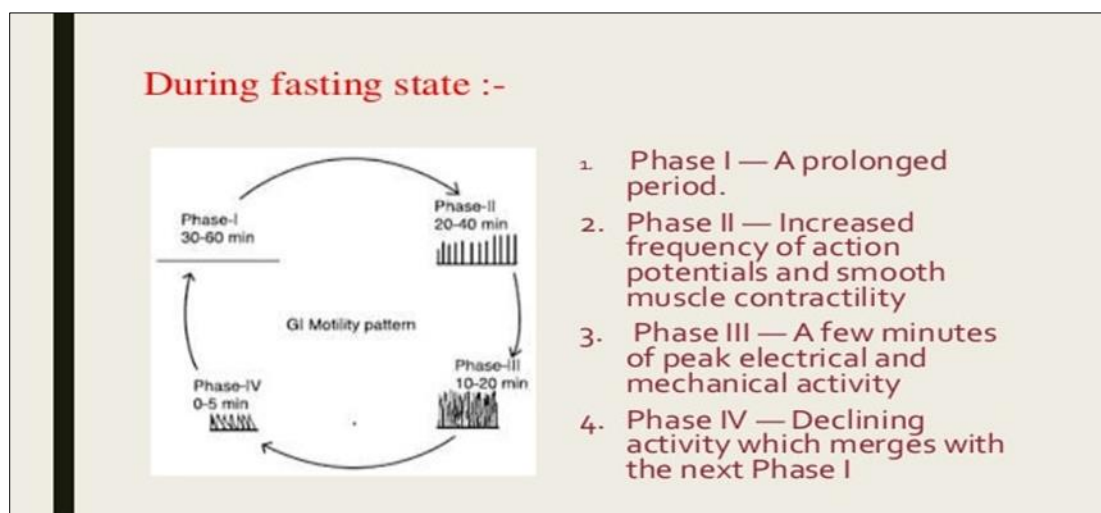
The gastrointestinal tract is a muscular tube of about 9m long which extends from mouth to anus (Figure 1). Its function is to take nutrients and eliminate out the waste products by the different processes such as digestion, absorption, secretion and excretion. The stomach has three muscle layers called as oblique muscle and it is situated in the proximal part of the stomach, branching over the fundus and higher region of the gastric body [8].

## 2. Gastric mortality and gastric empty rate

Two distinct patterns of GIT mortality and secretion exist fasted and fed state. The bioavailability of the orally administered drug is depend upon the state of feeding. In the fasted state , it is characterized by an interdigestive series of electric event called interdigestive myoelectric cycle or migrating motar complex (Figure 2).

It is divided into 4 phases:

- Phase 1(basal phase )
- Phase 2 (preburst phase )
- Phase 3(burst phase )
- Phase 4



**Figure 2** Gastric mortality and gastric empty rate

After the ingestion of the meal the pattern of contraction changes from fed to that of fasted state , this is known as digestive motility pattern , these contractions reduces the size of the food particles, after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate [9, 10].

## 3. Factors affecting the Gastroretentive system

There are various factors which affect the GRDDS :

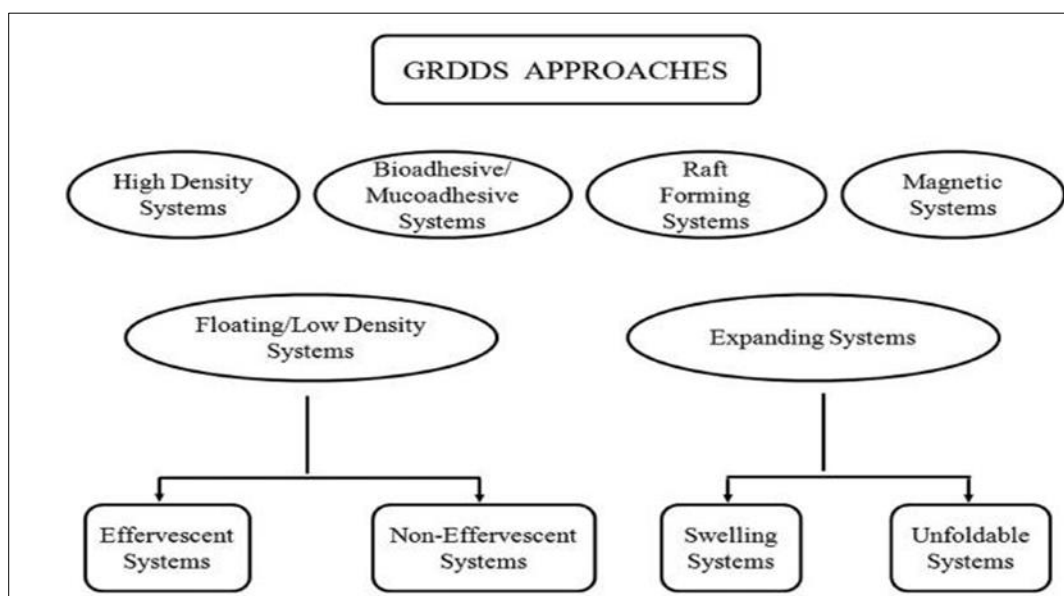
- Density – Gastric retention time of drug is depend on the density. The density is always less than that of gastric content.
- Size - The drugs which have diameter of more than 7.5 mm have more gastric resistance time as compared to drugs of diameter 9.5 mm
- Shape of dosage form – The tetrahedron and ring shaped dosage foam have longer period than other dosage foam of same size.

- Nature of meal - Presence of food in the stomach affects the gastroretentive drug delivery system. Feeding of indigestible polymers or fatty acid salts can change the mortality pattern of the stomach to the fed state, thus decreasing the gastric emptying rate and prolong drug release.
- Caloric content - The GRT can be increased with meal contain high protein and fats upto 4 to 10 hours.
- Frequency of feed – the GRT can increased over 400 minutes when successive meal are given as compared with a single meal due to the low frequency of MMC (migrating motor complex).
- Age – The GRT can be longer to the elderly people , mostly over the of 70.
- Posture – GRT can vary between supine and upright ambulatory states of the patients.
- Biological factors - Diabetes and Crohn’s disease , etc.
- Concomitant drug administration - Floating time is affected by antichilonegics drugs such as atropine and propantheline ,opiates like codein etc [11-14].

#### 4. Approaches to achieve gastric retention

Different approaches have been used to achieve or to increase the gastric retention of oral dosage forms in the stomach. Some of the drugs are formulated as single dosage or some are formulated as multi-component dosage forms. GRDDS can be classified in following approaches (Figure 3):

- High density system
- Bioadhesive/mucoadhesive system
- Raft forming system
- Magnetic system
- Floating/low density system
- ❖ Effervescent system
- ❖ Non effervscent system
- Expanding system
- ❖ Swelling system
- ❖ Unfoldable system

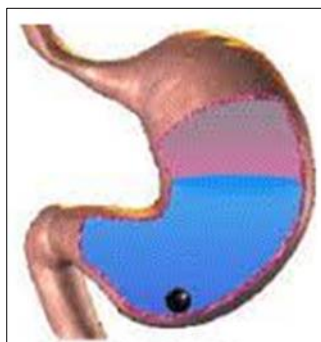


**Figure 3** Approaches to gastric retention delivery system

#### 5. High density system

In this dosage forms the density of formulation is higher than the density of the normal stomach content (Figure 4). These dosage forms are prepared by coating the drug with the heavy core or mixed with heavy inert material such as zinc powder, iron oxide , titanium dioxide etc.

These system have some drawbacks like difficult to manufacture in large amount due to interact with gastric fluid to release its drug content and also this system is not available in the market [15].



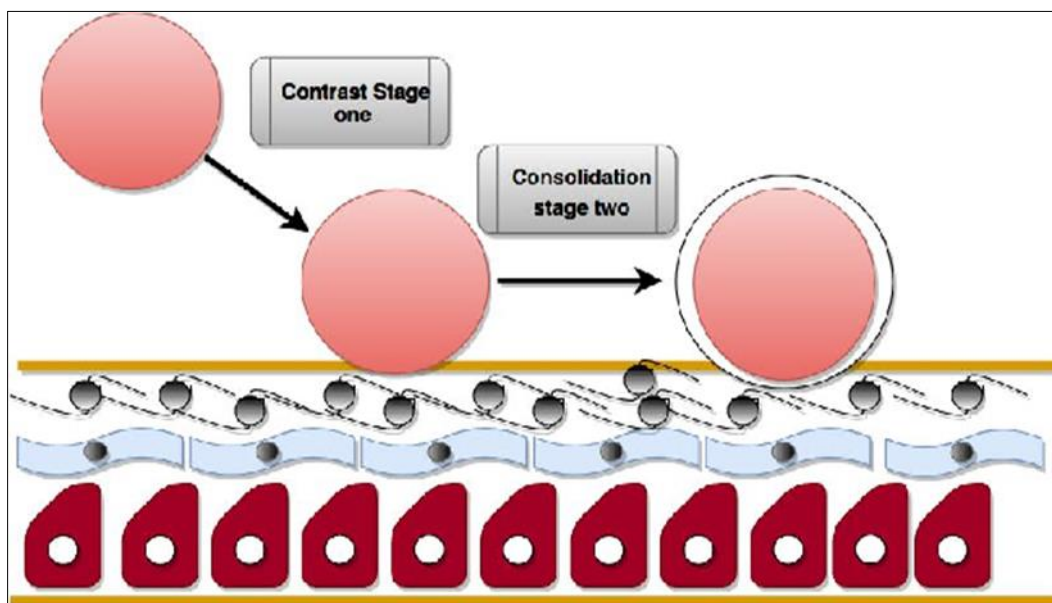
**Figure 4** High density system

## 6. Bioadhesive/mucoadhesive system

In mucoadhesive system, drugs contain mucoadhesive polymers which binds to the gastric mucosal surface and increases its GRT in the git (Figure 5). The mucoadhesive polymers are very useful excipient in the GRDDS. These polymers can be natural or can be synthetic.

Natural polymers are sodium alginate, gelatin, guar gum, tara gum, karaya gum .

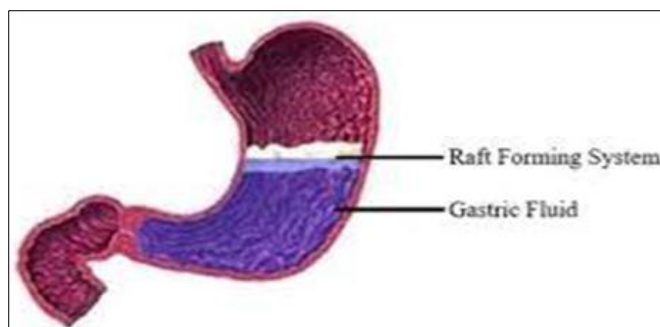
Synthetic polymers are HPMC, carbopol, vinyl pyrrolidone, sodium carboxyl methylcellulose [16].



**Figure 5** Bioadhesive/mucoadhesive system

## 7. Raft forming system

Raft forming system is not only helpful for sustained release drug but also useful for pediatric and geriatric patients. This system is also used in the liquid dosage form. Sustained and prolonged release of drug , good stability and bioavailability makes the raft forming system very suitable for gastric retention of the drug (Figure 6). Nowadays raft forming system have received much attention for the delivery of antacids and drug delivery for GIT infections and disorders [17].

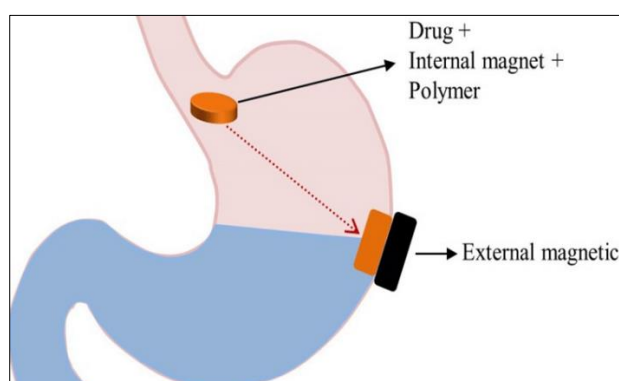


**Figure 6** Raft forming system

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## 8. Magnetic system

In the magnetic system, the dosage form contains a small internal magnet or a magnet placed on the abdomen over the position of the stomach (Figure 7). They guided them to the oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours [18, 19].

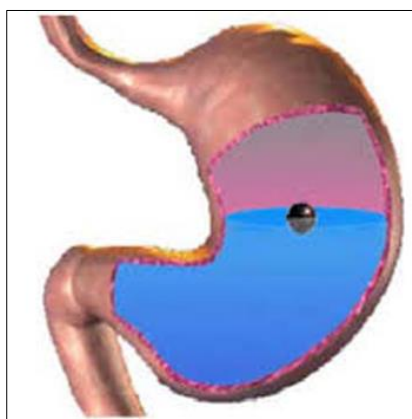


**Figure 7** Magnetic system

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## 9. Floating/ low density system

By the name low density system, these drugs remain float above the gastric contents for a prolonged period of time and provide continuous release of the drug (Figure 8). These systems are broadly used due to less or no adverse effect in the GI. These dosage forms are also known as gas-powered systems, which can float in the contents of the stomach and release the drug in a controlled manner for a prolonged period of time. This system is also known as hypodynamically balanced systems [20, 21, 22].



**Figure 8** Floating or low density system

Floating system are of two types:

- Effervescent system
- Non- effervescent system

### 9.1. Effervescent system

When these drugs come in contact with gastric juice of stomach, carbondioxide gas is released .This provide buoyancy to the dosage form that float on the gastric fluid. These effervescent system have further divided into different types:

### 9.2. Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber , which contain a liquid. eg. Ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. the device made up of Polyvinyl alcohol, Polyethylene 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.

### 9.3. Gas generating system

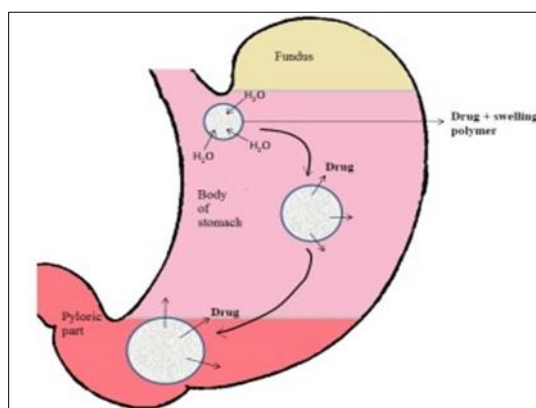
These system utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO<sub>2</sub>, which gets intrapper in the jellified layer of the system thus decreasing its specific gravity and making it float over gastric content.

### 9.4. Non effervescent system

The non effervescent system is based on the mechanism of swelling of polymer to mucosal layer in GIT. The most commonly used excipients are hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacryate, as well as bioadhesive molecule such as Chitosan [23-25].

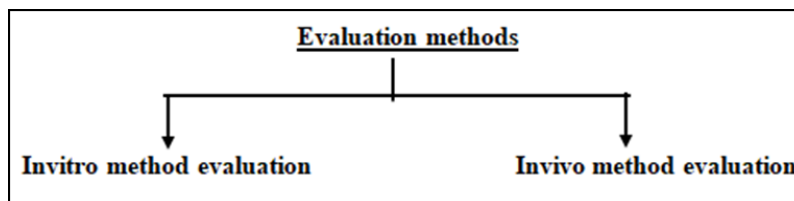
## 10. Expanding/swelling system

These dosage form after administrated to such an extent that it prevents to passage through the pyrolus, as a result the dosage form is remained in the stomach for a prolong period of time (Figure 9). These system are also called as plug type system because they remain have the tendency to lodged at the pyrolic sphincter. These formulations are designed for gastric retention and controlled delivery system for drugs in gastric cavity . Sustained and controlled release drug may be achieved by selecting a polymer with proper molecule weight and swelling property. When it comes in contact with gastric fluid the polymer imbibes water ad swell . The extensive swelling of these polymers is a result of the presence of physical-chemical crosslinks in the hydrophilic polymer network [26, 27].



**Figure 9** Expanding /swelling system

## 11. Evaluation parameter of GRDDS



### 11.1. *In vitro* method of evaluation

#### 11.1.1. Fourier transform infrared analysis

This technique is mostly used to identify organic, polymeric, functional group, and some inorganic material. By this technique we used to measure the drug purity, polymer and drug loaded formulations. The pellets are prepared under hydraulic press of 150kg/cm<sup>2</sup> and the spectra are scanned over the wavenumber range of 3600-400cm<sup>-1</sup> at ambient temperature [28, 29].

#### 11.1.2. Particle size analysis and surface characteristics

The particle size and size distribution of beads or microspheres are determined in the dry state using optical microscopy method. The external morphology is done by scanning electron microscope [30].

#### 11.1.3. Swelling studies

Swelling of tablets occurs by the absorption of liquid resulting increase in weight and volume. The liquid enters in the particles through pores and bind to the larger molecules which break the hydrogen bond resulting swelling of tablet particles. Tablet is weighted and placed in a beaker containing 200ml of 0.1N HCL, after a time interval the tablet is taken out from the beaker, soaked by the filter paper and weighed again [31, 32].

#### 11.1.4. Determination of drug content

Drug content determines that the how much amount of drug is present in the formulation. The amount should not exceed the limit given in the monograph. The drug content is determined by HPTLC, HPLC and by various spectroscopy techniques [33].

### 11.2. *In vivo* method of evaluation

#### 11.2.1. X rays/gamma scintigraphy

It helps to locate dosage form in GIT which can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. The inclusion of a radio opaque material into solid form which enables to visualize by X-rays. The inclusion of a gamma emitted radionuclide in the formulation allows indirect external observation using gamma camera, the gamma rays emitted by radionuclide is focused on camera which help to monitor the location of the dosage form [34, 35].

#### 11.2.2. Gastroscopy

Gastroscopy is a peroral endoscopy used with fibre optics or video system. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS [36].

## 12. Conclusion

Based on the literature, we concluded that the GRDDS is one of the efficient technique to maintain the sustained release of drug in gastric environment and increases its absorption and bioavailability. All the GRDDS approaches are convenient and reliable when compared to the other drug delivery system. A controlled drug delivery system with prolonged gastric retention may have great practical importance for the drugs which have narrow absorption window in upper small intestine. Ciprofloxacin, levodopa, furosemide are example of such drugs. GRDDS have systemic, localized and specific action. It helps in the treatment of various gastrointestinal diseases. From over last two decades various gastroretentive dosage forms have been designed to increase the gastric retention time. GRDDS is effective and simple drug delivery system.



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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declare no conflict of interest, financial or otherwise.

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