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GASTRORETENTIVE SYSTEM IMPROVES THE PROBLEMS OF ORAL DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT:

Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Dosage forms with a prolonged gastric residence time, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options. GRDFs extend significantly the period of time over which the drug may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. A number of approaches have been used to increase the GRT of a dosage form in a variety of concepts. These include Floating drug delivery systems, Bioadhesive systems, Swelling and expanding systems, Modified shape systems and High density drug delivery systems. This review also discusses the recent advances in the field of gastroretentive drug delivery systems.

KEYWORDS: *Delivery System, Gastroretentive, Gastric Residence Time, Bioavailability.*

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INTRODUCTION:

Gastroretentive Drug Delivery Systems

Recent scientific patent literature reveals an increased number of information data on novel dosage forms which possess not only a mechanism for controlled release of the drug and also controlled GI transit [1]. Among novel drug delivery systems, rate controlled oral drug delivery systems forms an important avenue. Extensive research has directed towards overcoming physiological adversities such as short gastric residence time (GIT) and unpredictable gastric emptying times [2].It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such dosage form would be retained in the stomach and release the drug in a controlled manner, so that drug could be supplied continuously to its absorption sites in upper GIT. These dosage forms provide a means to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for such drugs [3]. Retention of drug delivery systems in the stomach prolong overall GI transit time, thereby resulting in improved bioavailability for some drugs [4].

Pharmacokinetic and Pharmacodynamic Aspects

Incorporation of the drug in a controlled release gastroretentive dosage forms can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors as shown in Table 1 [5].

Table 1: Pharmacokinetic and Pharmacodynamic aspects of gastroretentive [5]

Pharmacokinetic aspects	Pharmacodynamic aspects
Absorption window-validation that drug is within the category of narrow absorption window	Reduced fluctuations of drug concentration
Enhanced bioavailability	Improved selectivity in receptor action
Enhanced first pass biotransformation	Reduced counter activity of the body
Reduced dose frequency of dosing	Extended time over critical effective concentration
Site specific therapy for local ailments in the upper GIT	Minimized adverse activity at the colon

Biological Aspects of Gasric Retention

To comprehend the considerations taken in the design of gastric retentive dosage form and to evaluate their performance the relevant anatomy and physiology of the GI tract must be fully understood [6]. The extent of drug absorption in a segment the GI tract depends generally on the rate of absorption as well as on the exposed surface area and time available for drug absorption.

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [7]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states.

Table 2: Salient features of upper gastrointestinal tract

Section	Length (m)	Transit time (h)	pH	Microbial count [a]	Absorbing surface(m^2)	Absorption pathways
Stomach	0.2	Variable	1-4	$< 10^3$	0.1	P,C,A
Small intestine	6-10	3±1	5-7.5	10^3-10^{10}	120-200	P,C,A,F,I,E,CM

During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours [8].This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington [9].

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate [10].

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

[a] –Number of microorganisms per gram of GI contents

[b] P-passive diffusion; C: connective or aqueous channel transport; A: active transport;

F: facilitated transport; I: ion pair transport; E: entero-or pinocytosis; CM: carrier mediated transport [11].

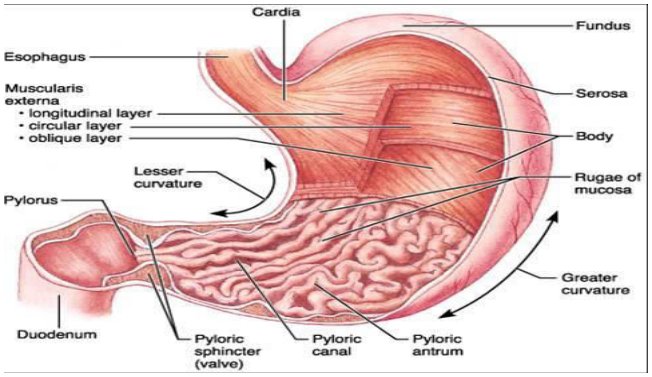

Fig.1: Anatomy of stomach [11]

Factors Affecting Gasric Retention

There are several factors that can affect gastric emptying and hence gastric retention time (GRT) of oral dosage form.

To pass through the pyloric valve into small intestine the particle size should be in the range of 1 or 2 mm [7]. The most significant parameters controlling the GRT of oral dosage forms include density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake etc. as described in the following text: [7, 12, 13, 14, 15].

Approaches to Gastric Retention

A number of approaches have been used to increase the GRT of a dosage form in a variety of concepts. These include:

Types of FDDS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non-effervescent system.

Effervescent system

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate) and other organic acid (citric acid and tartaric acid) to produce carbon dioxide (CO_2), thus reducing the density of the system and making it to float on the gastric fluid [18]. These effervescent systems further classified into two types:

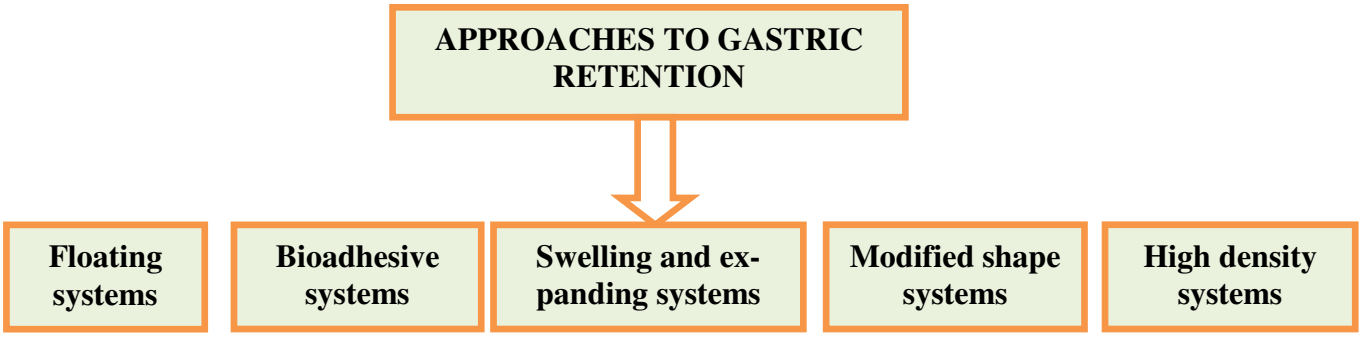

Fig.2: Approaches to gastric retention [17]

Floating drug delivery systems

FDDS have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system [16]. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are [17]:

• It should release contents slowly to serve as a reservoir.

• It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm^3).

• It must form a cohesive gel barrier.

Gas generating systems

These are matrix types of systems prepared with swellable polymers such as methylcellulose and chitosan and various effervescent compounds e.g. sodium bicarbonate, tartaric acid and citric acid [19].The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 [18].They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. A decrease in specific gravity causes the dosage form to float on the chyme [20]. The carbondioxide generating components may be intimately mixed within the tablet ma-

trix, in which case an single-layered tablet is produced [21], or an bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a SR effect [22].

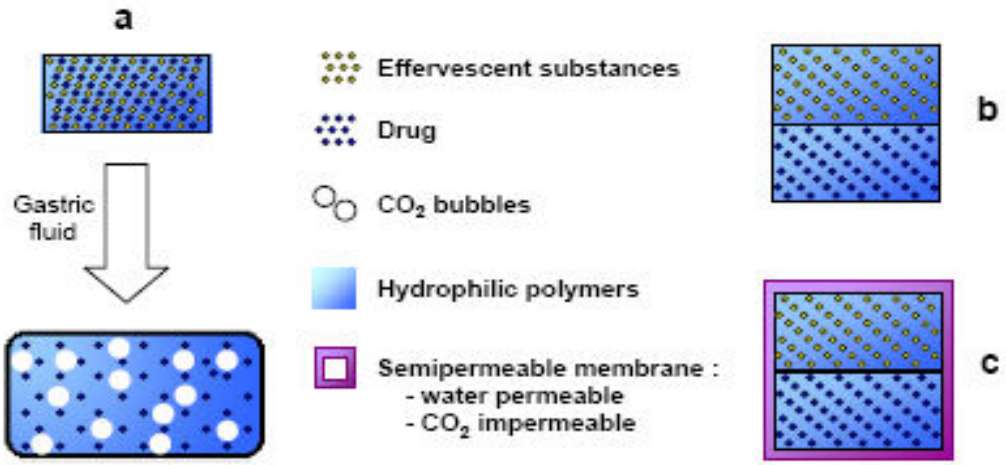

Fig.3: Gas generating systems [22]

a) Ingastric single layer floating tablet or hydro dynamically balanced system (HBS)

b) Ingastric bilayer tablets

c) Multiple unit type floating pills

❖ **Volatile liquid containing system**

The gastric retention time of drug delivery system can be sustained by incorporating floatable chamber, which contains a liquid e.g. ether, cyclopentane that gasify at body temperature to cause inflation of chamber in the stomach. These devices are osmotically controlled floating system [23]. When the device reaches the stomach, bioerodible chamber disintegrate to release the drug delivery system. . The floating supports made up of deformable hollow polymeric bag containing a liquid that gassify at body temperature to inflate the bag. In stomach water is absorbed through the semipermeable membrane into the osmotic compartment to dissolve the salt. An osmotic pressure is thus created, which acts on the collapsible bag, and in turn forces the drug reservoir compartment to reduce its volume and release the drug solution [12].

Non-Effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [24]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [14].

- Colloidal gel barrier systems(HBS)
- Microporous Compartment System
- Alginate beads
- Microbaloons /Hollow microsphere

Bioadhesive /Mucoadhesive systems

The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane [11]. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems [25]. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated [26]. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral.

Swelling and Expanding systems

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as "plug type system" since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. A balance between the extent and duration of swelling is maintained by degree of cross-linking between the polymeric chains. A high degree cross-linking retards the selling ability and maintains its physical integrity for prolonged period [27,28].

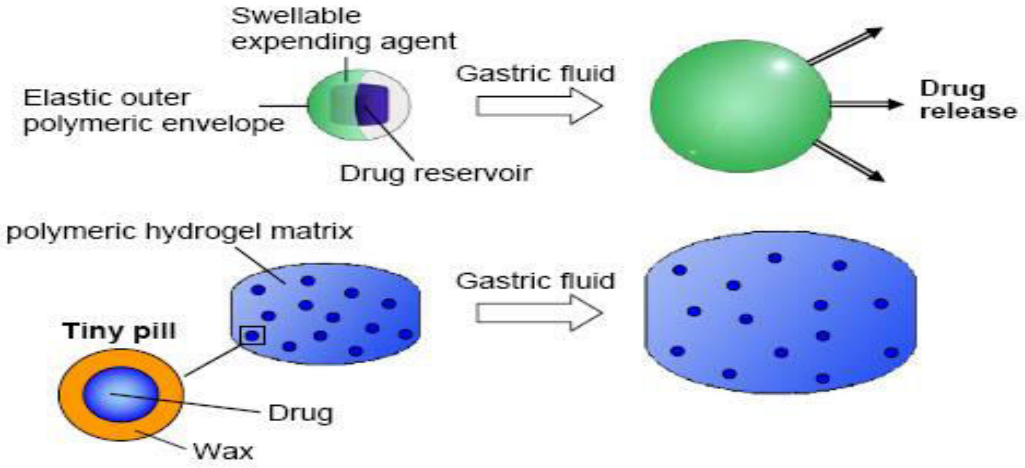

Fig.4: Swellable and Expandable System [27]

High density (sinking) system or Non- Floating drug delivery system

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. [17].The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time [29]. But, effectiveness of this system in human beings was not observed [30] and no system has been marketed.

Modified shape systems

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of the

drug delivery system [31]. Unfolding takes place due to mechanical shape memory i.e. the gastroretentive dosage for (GRDF) is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrier dissolves and the GRDF unfolds or opens out, to achieve extended configuration. The unfolding occurs when polymeric matrices, known or designed to have suitable mechanical properties, are used with some emphasis on appropriate storage conditions of the GRDF. The storage should maintain unfoldable properties for extended time span.

APPLICATIONS [32,33,34]

- **Sustained drug delivery**

HBS system can remain in the stomach for long periods and hence can release the drug over a period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of Nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) [32].

Similarly a comparative study [17] between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case. Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

- **Site specific drug delivery**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. misoprostil, riboflavin and Furosemide.

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional Furosemide tablets [33].

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E, used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced [34].

- **Absorption Enhancement**

Drugs that have poor bioavailability because of sits specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and

enteric coated LASIX-long product (29.5%) [33].

- **Maintenance of constant blood level**

These systems provide an easy way of maintain constant blood level with an ease of administration and better patient compliance.

LIMITATIONS [35]

The floating system requires a sufficiently high level of fluid in the stomach for the system to float. This problem can be overcome by coating the dosage form with bioadhesive polymer which adhere to gastric mucosa or administering dosage form with a glass full of water (200-250 ml) [36].

These systems require the presence of food for delaying their gastric emptying.

Floating systems are not suitable for drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa. Drugs which have multiple absorption site or which undergo first pass metabolism were not desirable candidate for FDDS.

The single unit floating dosage form is associated with "all or none concept". This problem can be overcome by formulating multiple unit system like floating microsphere or microballons. Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.

MARKETED PRODUCTS OF GRDDS [37]

Table 2: Some of the marketed products are as follows

MARKETED PRODUCTS OF GRDDS			
Brand name	**Delivery system**	**Drug (dose)**	**Company name**
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	Glaxo Smithkline, India
Topalkan®	Floatingliquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flot coat®	Floating dosage form	Al – Mg antacid	
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Any drug product must be evaluated to ensure its performance characteristics and to control batch-to batch quality. In addition to routine tests for general appearance, hardness, friability, drug content disintegration time, and drug release, various other tests i.e. floating/buoyancy time, specific gravity, floating forces, for bio/mucoadhesive systems; bioadhesive strength, for swelling systems; weight gain and water uptake studies should be evaluated. In vivo visualization is a crucial parameter for evaluating the GI retention characteristics of the dosage form. To characterize GRDFs, some of the techniques have been recently introduced for pharmaceutical applications such as:γ-scintigraphy, radiology, magnetic marker monitoring.

CONCLUSION:

The objective of present study was to preclude the problem of poor dissolution of relatively water insoluble and poorly permeable drug by gastroretentive drug delivery system. After oral administration, such dosage form would be retained in the stomach and release the drug in a controlled manner, so that drug could be supplied continuously to its absorption sites in upper GIT. These dosage forms provide a means to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for such drugs.

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