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ADVANCEMENT IN GASTRO-RETENTIVE DRUG DELIVERY SYSTEM: A SYSTEMATIC REVIEW

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ABSTRACT

The aim of the present review was to bring together various approaches, advancements and literatures on gastroretentive drug delivery system. Gastro-retentive drug delivery system is mostly preferred drug delivery system with their better compliance, flexibility and duration of action. The system is useful for drugs with narrow absorption window. Recent development in approaches leads to increase residence in gastrointestinal tract and slow release of drug for longer period of time, like floating system, muco-adhesion, swelling system, magnetic system etc. Various in-vitro and in-vivo techniques are employed for determination of drug release and residence of dosage form in the gastrointestinal tract Gama scintigraphy, X-rays and Magnetic Resonance Imaging are the best suitable techniques for determination the of gastric residence of dosage form.

Keywords *– Gastroretention, Muco-adhesion, Floating system*

1. INTRODUCTION

Oral drug delivery system is most preferred system in the administration of drug due to flexibility and ease of administration. These drugs are absorbed mostly form stomach and intestinal part of GIT. There are various factors which affects the absorption of drug like

1. Stomach pH
2. Enzymatic degradation.
3. Food presence in GIT.
4. Gastric emptying time, etc.

Therefore, drug absorption from GI tract is variable in different situations. Drugs with short half-life from GIT are excreted quickly. In such cases, repeated doses required to be given to attain the required concentration of drug in the blood plasma, in order to attain steady state concentration for longer period of time in blood plasma.

For developing GRDDS release drug delivery following characteristics are required to be known [(1)].

1. Physiochemical properties of drugs.
2. Anatomy & Physiology of GIT

3. Characteristics of dosage form.

GRDDS release drug in sustained/controlled manner for longer period of time as depicted in fig.no.1

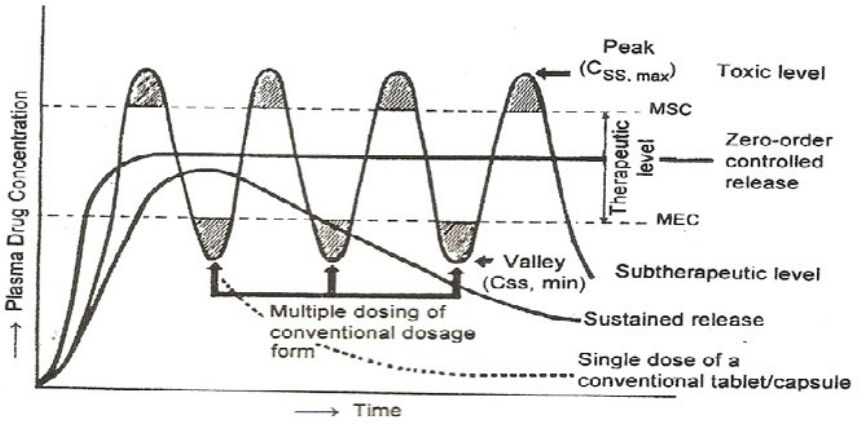


Fig. 1: Plasma concentration versus time curve

Gastro-retentive drug delivery system is that system where drug is aimed to release in upper part of stomach/& intestine. This is most advantageous because maximum benefit of drug in the form of plasma concentration and prolonging the release of drug from dosage form can be achieved. Over the past years, various models were developed for achieving the real goal of gastro-retentive drug delivery system, like high density where dosage form is sinked, low density where the dosage form is floated on the gastric fluid [2, 3], Mucoadhesive, swellable, hydrogel, magnetic, etc. The aim of the present review was to bring together various approaches, advancements and literatures on gastroretentive drug delivery system.

2. FACTOR RESPONSIBLE FOR GASTRIC RETENTION

To retain the dosage form for longer period of time in the stomach, the dosage form must be buoyant and this can be achieved by reducing the density of dosage form without changing the gastric emptying rate. During floating the drug is released slowly from dosage form. There are various factors responsible for slow release of drug from system as discussed below:

2.1. Density: This is the main factor responsible for increasing the gastric residence time of dosage form. A buoyant dosage form having density less than that of the gastric fluid floats, since it is away from the pyloric sphincter [1]. A density of 1.0 g/ml less than that of gastric content has been reported by Vyas S. P. [3]

2.2. Shape and size: Shape and size of dosage form is one of the important formulation factor responsible for determining the gastric residence. Larger the dosage form, the greater will be the gastric residence time. Larger size of the dosage form does not allow it to pass quickly though the pyloric antrum into intestine [4]. A dosage form having diameter of more than 7.5mm shows better gastric retention then 9.9mm [5]. A tetrahedron and ring-shaped device with a flexural modulus of 48 and 22.5 kilo pound per square inch (KSI) are reported to exhibit a better gastric residence and 90%-100% retention far 24 hrs compared with other shapes [6].

2.3. Viscosity of Polymers: Floating time and drug release is measurably affected by the viscosity of polymers. Low viscosity polymers are found to be more beneficial than high viscosity polymers in improving floating properties [1].

2.4. Gender: Mostly female have slower gastric emptying rate than male. Mean ambulatory gastric retention time in male (3.4±0.6hrs) compared to female (4.6±1.2hrs) [6].

2.5. Age: People with age above 70 have a longer GRT [7].

2.6. Posture: GRT can vary between supine and upright ambulatory status of the patients.

2.7. Caloric content: GRT can be increased by 4 to 10 hours with meal that is high in protein and fats [8].

2.8. Nature of meal: consumption of indigestible polymers or fatty acids salt can change the motility of stomach to fed state, thus reducing the pattern of the gastric emptying rate [8].

2.9. Disease Condition: Disease like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying, while partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote it [9].

3. ADVANTAGES GRDDS [1, 4, 6,7, 9, 10, 11, 12]:

- **Bioavailability:** Bioavailability in the upper GIT is improved for those drugs which are metabolized in upper GIT.
- **Absorption:** Drugs absorbed from stomach are best suited for this system.
- **Delivery of drug:** Delivery of drug can be controlled at upper part of stomach by using various approaches of floating.
- **Disease associated with GIT:** GRDDS spend most of its time in the stomach so it's very useful for treating the disease associated with stomach and also it helps in treating the disease of intestine.
- **Site specific:** GRDDS deliver the drug at target site for its local action even though are mostly utilized for systemic action.
- **Adverse Activity:** Adverse activity of drug in colon is minimized.
- **Administration:** Gastro retentive drugs are easy to administer as these are designed similar to tablet, capsule**,** etc.
- **Patient compliance:** reduced frequency of administration of drug thereby improves patient compliance.

4. DISADVANTAGES GRDDS [1, 4, 6,7, 9, 10, 11, 12, 13]:

- **Stability:** GRDDS is not accepted for drug degraded in acidic pH or gastric enzymes.
- **Solubility:** GRDDS is not useful for drugs which are not absorbed from stomach.
- **Gastric irritation:** Drugs having irritant effect on gastric mucosa are not suitable for gastro retentive drug delivery system.
- **First pass metabolism:** Drug like nifedipine which undergo first pass metabolism is not the best choice of drug for gastro retentive drug delivery system.
- **Fluid in stomach:** The high volume of fluid is required in stomach for dosage form to float and work effectively.

5. SUITABLE DRUG CANDIDATE FOR GRDDS

Drug delivery need to be slow, steady and controlled to minimize the side effects and to improve its efficacy without repeated dosing. Sustained release is the best suited for the drugs which are not readily absorbed from stomach, since it prolong the drug release and increase the contact time in upper part of intestine.

Specific candidate for GRDDS selected depending on following characteristics:

1. Drug with narrow absorption window in gastrointestinal tract e.g. Levodopa and Riboflavin.
2. Drugs which are only absorbed in stomach e.g. Cinnarazine and Chlordiazepoxide.
3. Drugs that disturb normal colonic bacteria e.g. Amoxicillin trihydrate.
4. Drugs active in stomach e.g. Antacid and Misoprostol.
5. Drugs that gets degraded in colonic environment e.g. Ranitidine HCl and Metronidazole.
6. Drugs those are poorly absorbed at alkaline pH.

6. UNSUITABLE DRUG CANDIDATE FOR GRDDS [4]:

1. Drugs with limited solubility in acidic environment.

2. Drugs get degraded in gastric pH.
3. Drugs release required in colon e.g. 5-amino salicylic acid and corticosteroid.

7. DIFFERENT APPROACHES FOR RETENTION OF DRUG IN GIT

Different approaches are available for retaining the drug in GIT are discussed as follows;

7.1 High Density

This method involves formulating the dosage form with density higher than the water because the density of stomach content is approximately similar to water. So, when density is high dosage form sink at bottom of the stomach near pyloric region. This dosage form restrains against peristaltic movement and do not gets emptied from stomach early. These formulations are prepared by coating the drugs on a heavy core or mixed with inert material such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. [3]. A density close to 2.5 gm/cm^3 has significant prolongation of stomach residence [14].

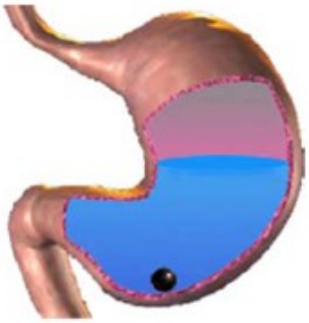
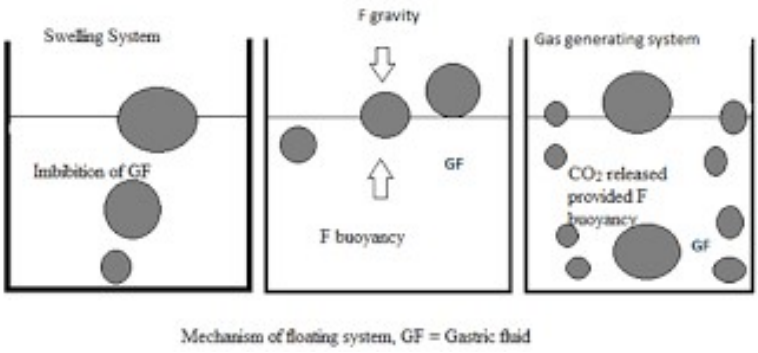


Fig. 2: High density dosage form

7.2 Floating

To achieve maximum retention and sufficient bioavailability floating drug delivery is the most useful system of drug deliver. This type of delivery system is of great value for drugs which are get absorbed from upper part of stomach i.e. their absorption window resides in upper part of stomach [15].

Though, immediately floating of the delivery system can only be achieved if the density of the delivery system is on lower side [16]. Delivery system with higher density, initially settle down in stomach and then tend to float with decrease in the density of the system. But with such system, there may be possibility of gastric emptying of system, before floating start. Low density of system, which leads to floating, render either by incorporation of low density excipients or by providing a mechanism which leads to air entrapment within the system. [17, 18].



Mechanism of floating system, GF = Gastric fluid

Fig. 3: Mechanism of floating system.

Different approaches have been developed to attain the floating: -

7.2.1 Hydrodynamically balanced system

In this system, floating is achieved by the use of hydrophilic gel forming polymers like Hydroxy propyl methyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, agar, alginic acid etc. and mixing them with drug along with excipients and encapsulating in gelatin shell.

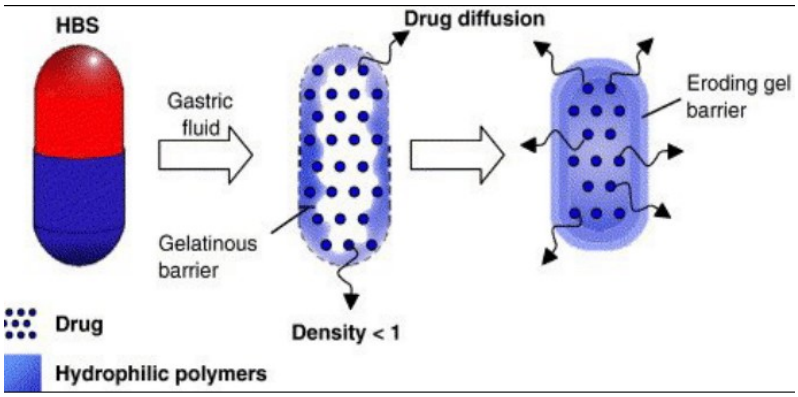


Fig. 4: hydrophilic polymers involved in floating.

7.2.1 Gas-generating system/effervescent drug delivery system:

Bubbles are generated for floating of this system using sodium bicarbonate, citric or tartaric acid mixed with swellable polymer like methocel, chitosan etc. the reaction between sodium bicarbonate and acid takes place forming carbon dioxide gas in the form of effervescence leaving the system to float.

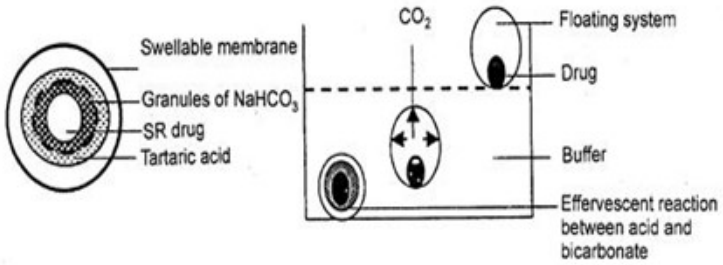


Fig. 5: gas generating effervescent system.

7.2.2. Raft-forming system [19]

In this system raft like layer of gel is formed which resembles to raft in river and it float on the gastric content due to generation of carbon dioxide within the system. This system is prepared by the use of gel forming polymers and gas generating agents like sodium bicarbonates, citric acid or tartaric acid which when come in contact with gastric content by reacting together gas is formed which help in floating of system.

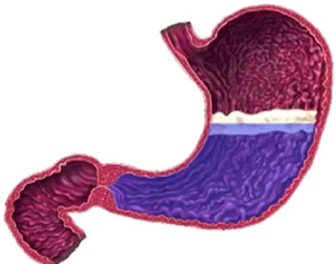


Fig. 6: Raft forming system

7.2.3. Low density System [15]

Major limitation of gas generation effervescent system is the time lag before floating on the gastric contents. In this period, it may be possible that the delivery system may get evacuated before floating and drug release. In order to overcome this limitation, low density system (lesser 1000mg /cm^3) have been developed, which shows immediate floating and release of drug on gastric content surface. System basically consists of low density materials which entraps oils or air.

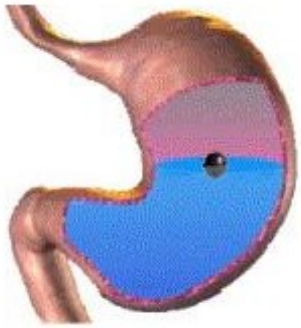


Fig. 7: low density system.

7.3 Expandable, Unfoldable and swellable:

A dosage form with bigger size than pyloric sphincter withstands the gastric transit, but its limitation is that the dosage form should be swalloweble and should not cause gastric obstruction. Therefore, an expandable system has developed to prolong drug gastric retention. Gadtroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of stomach [4]. Unfoldable and swellable systems were developed for effective gastric retention. Unfoldable system was made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4-label disc or 4-limbed cross form) of bioerodible polymer compressed within a capsule which extend in stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually result from osmotic absorption of water and the dosage form is small enough to be swallowed by gastric fluid Fig No.08 Expandable systems have some limitations that biodegradable polymers easily undergo hydrolysis, they are in the shape for very short time and they are not cost effective.

Fig. 8: Different geometric forms of Unfoldable system.

7.4 Super Porous Hydrogel System

These are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states [20] during which the premature evacuation of the dosage form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size with in minutes, due to

rapid intake of water by capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol [21].

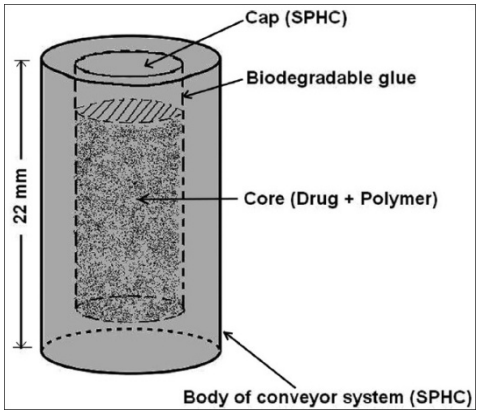


Fig 9: super porous hydrogel system.

7.5 Mucoadhesive or bioadhesive

Bioadhesive drug delivery dosage form is placed within the lumen thereby rate of absorption can be increased at that site. In this system bioadhesive polymers are used which can adhere to the epithelial surface in the stomach. The mechanisms of adhesion to the mucosal surface are as follows [22]:

1. Wetting mechanism: Based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layer.
2. Diffusion mechanism: This proposes physical entanglement of mucin strands the flexible polymer chain, or an interpenetration of mucin strands into porous structure of the polymer substrate.
3. Absorption mechanism, suggest that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. Electron mechanism, which proposes attractive electrostatic forces between the glycoprotein mucin network and the biadhesive material.

Polymers used for bioadhesion are chitosan, sodium alginate, acrylic acid, cholestyramine, hydroxyl propyl methyl cellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acid etc.

Fig. 11. Bioadhesion

7.6 Magnetic system

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [23].

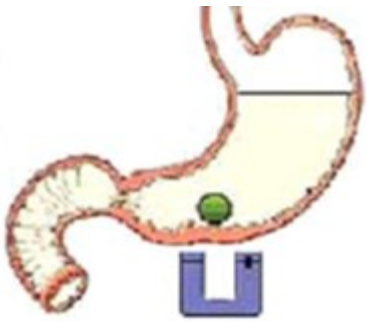


Fig 12: Magnetic system.

8. EVALUATION OF GRDDS

The evaluation parameters vary with the types of dosage form formulated. Generally, tablet dosage form is evaluated for following parameters.

***In-Vitro* Evaluation**

- **Size and shape**

Vernier caliper is used to measure the shape and size of the tablets.

- **Content uniformity**

The amount of drug present in dosage form can be determined by suitable analytical technique such as HPLC, UV, etc.

- **Hardness**

Ten to twenty tablets are selected for determine the hardness using Monsanto hardness tester or any other suitable hardness tester.

- **Friability**

Ten tablets weight before and after friability is calculated and variation should not be more than 1%.

- **Floating lag time** [24]

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

- **Dissolution** [24]

It is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±2^{O}C in simulated gastric fluid of pH 1.2. Aliquots of the samples are collected and analyzed for the drug content. The time for which the drug remains floating on the surface of the medium is the duration of the floating time.

***In-Vivo* Evaluation** [15]

- **X-Ray Method**

This method helps to predict and correlate gastric emptying time and passage of dosage form. In this method radio-opaque material used to visualize dosage for.

- **Gama-scintigraphy**

The inclusion of a gama emitting radio-nuclide in a formulation allows indirect external observation using a gama camera or scintiscanner. In case of gama sentigraphy, the gama rays emitted by the radio-nuclide are focused on the camera, which help to monitor the location of the dosage form in the GI tract.

- **Gastroscopy**

It comprises of peroral endoscopy, used with a fibereoptic and video system. It is suggested that gastroscopy may be used to

inspect visually the effect of prolonged stay in the stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.

- **Ultrasonography**

This method involves the assessment of intragastric location of the hydrogels, solvent penetration in to the gel and interactions between gastric wall and FDDS during peristalsis.

Literature survey revealed that many dosage forms are available for retaining the API in the GIT. Some of the dosage form & their API's are summarized in table no. 1. [21, 23, 25]

Table-1: Summary of dosage forms and their API

S. No.	Dosage Forms	Drugs
1.	Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p- Aminobenzoic acid
2.	Capsules	Furosemide, L-DOPA, Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
3.	Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
4.	Granules	Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate, Isosorbide dinitrate.
5.	Powders	Riboflavin,phosphate, Sotalol, Theophylline.
6.	Films	Cinnerzine, P-Aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate.
7.	Multiple unit	Clarithromycin, *p*-aminobenzoic acid)
8.	Bilayer tablet	Misoprostal
9.	Foams/hollow bodies	Ibuprofen
10.	Controlled release capsule	Levodopa, Benserazide
11.	Effervescent floating liquid alginate preparation	Aluminium hydroxide, Magnesium carbonate
12.	Floating liquid alginate preparation	Aluminium-Magnesium antacid
13.	Colloidal gel forming FDDS	Ferrous sulphate

9. CONCLUSION

Gastro retentive drug delivery system is most useful system to improve bioavailability of drugs in the proximal part of gastrointestinal tract (GIT) and to deliver the drug with maximum efficiency rather than complexity in their pharmacokinetics and pharmacodynamics parameters. To develop an effective gastroretentive drug delivery system is a challenge for researchers because dosage form needs to be present in stomach for longer period of time which is very difficult to achieve due to normal physiology of GIT. there are various approaches can be used to achieve the goal but still there is a lot scope for improvement in dosage form.

10. ACKNOWLEDGEMENT

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