ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

GASTRO - RETENTIVE DRUG DELIVERY SYSTEMS: A REVIEW WITH FOCUS ON FLOATING DRUG DELIVERY SYSTEMS

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ARTICLE INFO

Key words:
GRDDS, migrating motor complex, floating drug delivery systems

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Gastro-retentive drug delivery systems (GRDDS) attributes to gastric retention time coupled with the drug release for extended time has significantly improved patient compliance. In this current review physiology of stomach along with its motility pattern usually called migrating motor complex (MMC) was discussed. Various approaches to GRDDS with focus on floating drug delivery systems (FDDS) were reviewed. Further the Advantages, limitations, suitable drug candidates, factors effecting and Future challenges of FDDS were discussed.

INTRODUCTION

Among all the various marketed formulations the highly recommended formulations are oral drug delivery systems (ODDS).[1] Whereas the limited success of conventional dosage form is due to the faster gastric emptying rate and it can be overcome by the current technological advancements in which gastro-retentive drug delivery system-GRDDS is one of the example, where gastric retention time coupled with the extended drug release significantly improved the patient compliance. Drugs which are having low solubility in intestine or prone to degradation in colon when formulated through ODDS can be effectively delivered by increasing the gastric retention time.[2] Also better bioavailability for the drugs with less half - lives can be easily achieved through GRDDS.[3]

Others infections including gastric ulcers, duodenal ulcers, oesophagitis, *H. pylori* infections etc. can be treated effectively using GRDDS.[4] Many reviews on GRDDS were made in recent times mainly focussing on *in vitro* studies, formulation parameters but the number of marketed formulations were still not significant. Hence the main aim of this study is to summarize GRDDS with focus on floating drug delivery system (FDDS).

Stomach physiology:

The main role for successful design of GRDDS is studying the physiology and emptying process of stomach. It is divided into three parts which are fundus, body and pylorus with average volume of 1.5 L after a food intake and 250 to 500 mL during the inter-digestive phases. The main function of fundus and body of stomach is it acts as

reservoir and mixing of food is performed by pylorus. Along with mixing it also plays an important role in maintaining gastric residence time through propeller action. The migrating motor complex (MMC) which is the motility pattern of stomach varies for fed state and fasting state. The entire cycle is of 90-120 min and it has four of 4 phases (Figure 1).[5]

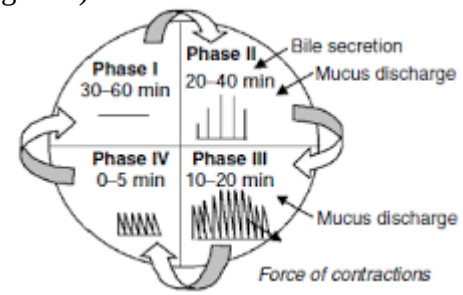

Figure 1: Different phases of MMC cycle

Approaches to GRDDS:

Various approaches to GRDDS are

High density systems: The density of these systems ranges from 2.5 to 3.0 g/mL. These help the formulation to withstand gastric disturbances and peristaltic movements. Titanium oxide, iron powder, barium sulphate, zinc oxide etc. are used to increase the density of the dosage forms. But the main drawback of the system is raised dose size to attain high density. GRDDS based on high density is depicted in (Figure 2).[5]

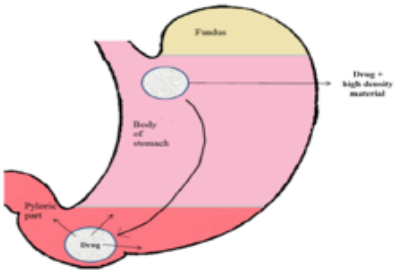

Figure 2: GRDDS based on high density

Magnetic systems: The dosage form was retained within the stomach by the application of external magnetic field and contains magnetically active elements. To retain the administered dosage for within the place a magnetic stirrer is placed externally on the stomach and lack of patient compliance is the major drawback of the system. GRDDS based on application of magnetic force is shown in (Figure 3).[5]

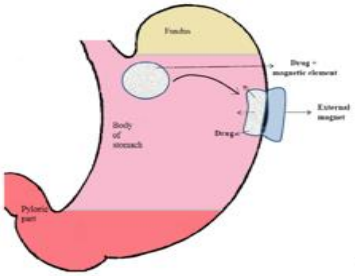

Figure 3: GRDDS based on application of magnetic force

Modified shape and swelling systems: With these swelling and expanding systems the *in vivo* and *in vitro* systems were succeeded in retaining the dosage form within the stomach. These are otherwise called as plug type systems because these are facilitated with increased size of the system above the diameter of pyloric sphincter. The polymer gets swelled once it gets in contact with the gastro intestinal fluid and hence type of polymer used and its viscosity affects the sustained delivery of drug. Super porous polymers with swelling ratio 1:100 (rapid swelling nature) increases the efficiency of the system. GRDDS based on polymer swelling is shown in (Figure 4).[5-7]

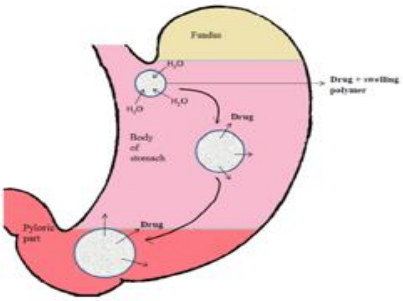

Figure 4: GRDDS based on polymer swelling

Bioadhesive/mucoadhesive systems: These systems resist the gastric emptying time for long period by attaching to the mucosal lining of the stomach wall and hence named as bioadhesive or mucoadhesive systems. It also facilitates local drug delivery. Pectin, lectin, carbopol, gliadin, carboxymethylcellulose, polycarbophil, chitosan etc. are some of the bioadhesive polymers. GRDDS based on mucoadhesion is shown in (Figure 5).[8-9]

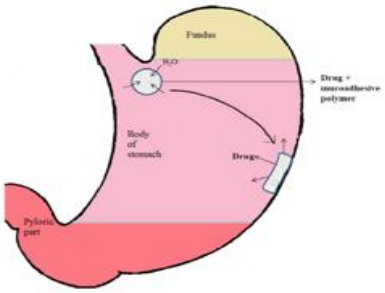

Figure 5: GRDDS based on mucoadhesion

Raft forming systems: These are the formed by the process of carbon dioxide bubble entrapment with *in situ* gelling mechanism. A solution containing sodium alginate as in situ gel former and bicarbonates or carbonates which acts as effervescent agents is formed initially. The insitu gel former swells soon it gets in contact with the gastro intestinal fluid and forms a cohesive gel which entraps carbon dioxide make it to float. These are used for the treatment of gastroesophageal reflux. GRDDS based on raft forming systems is shown in (Figure 6).[10]

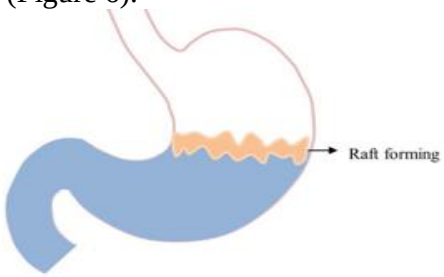

Figure 6: GRDDS based on raft forming systems

Floating drug delivery systems (FDDS): The main concept of these FDDS is to maintain less density than that of GIF so that they can float for certain time (lag time). The nature and type of polymer used effects the lag time and also determines the drug release pattern and rate within the formulation. Other factors such as disease condition of the patient, their fasting or fed state, amount of gastric fluid etc. influences the buoyancy of the formulation. FDDS are further divided into two categories namely effervescent and non-effervescent systems based on the principle of buoyancy.[11-13]

a. **Non-effervescent systems:** In this type of FDDS, the early exit of the dosage form from the stomach is prevented as it swells soon it comes into contact with the GIF. The type of polymer used influences the appropriate action of dosage form. A polymer which has swelling property (when it gets in contact with the GIF), low bulk density when compared with GIF etc. have to be selected. Sodium alginate, Hydroxypropyl methyl cellulose (HPMC), carbopol, polyvinyl acetate, polycarbonates etc. are some of the polymers used in preparation of FDDS. The following are the subtypes of non-effervescent systems.[14, 15]

Colloidal gel barrier systems: Combination of drug with gel-forming hydrocolloids gives these systems. This aid in increasing the absorption of drug at its side by prolonging the gastro retention time.

Microporous compartment system: In this type the drug is entrapped within the drug reservoir system which is encapsulated and it contains micro porous compartment with pores which allows the GIF to pass through and allows drug absorption. It also contains sealed peripheral walls which involves in prevention of immediate contact of GIF with the formulation there by increasing the lag time.

Alginate beads: These are spherical in shape with a diameter of 2.5 mm. These are prepared by calcium alginate precipitation which occurs when sodium alginate solution is added drop wise into the calcium chloride aqueous solution. Thus formed beads are filtered and dried. The formed beads are capable of maintaining bouncy for 5-6 h.

Hollow microspheres / Microballons: These are prepared by a novel emulsion solvent diffusion method. These are prepared when ethanol solution of drug and an enteric acrylic polymer was added into agitated poly vinyl alcohol solution at 40 ^{0}C. The micro spheres with internal cavity were form when gas is generated in the dispersed polymer due to the evaporation of ethanol. The gastro retentive time of these microspheres is more than 12 h.

b. Effervescent systems: In these systems carbon dioxide is liberated when it comes into contact with the GIF and thus formed CO_2 is trapped in the microspheres of the system decreases the overall density which aids in the buoyancy. These are generally formed using sodium bicarbonate, tartaric

acid and citric acid. These are classified into two types.[16, 17]

Volatile liquid containing systems: An inflatable chamber is present within the system and it contains volatile liquid such as ether, cyclopentane. This liquid gets converted into gases and the chamber gets inflated at normal body temperature which makes them to float over the gastric fluids. The gas from the chamber can be removed by providing bioerodable plugs to the system which releases the gas after certain time so that the drug can be absorbed. GRDDS based on volatile liquid containing system is depicted in (Figure 7).

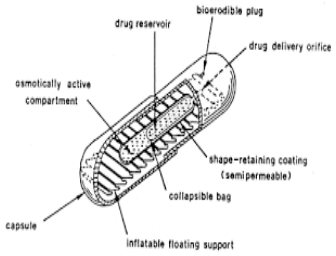

Figure 7: GRDDS based on volatile liquid containing system

Gas-generating systems: These systems generate CO_2which decreases the density of the formulation facilitating buoyancy. The CO_2 gas is produced due to effervescent reactions that takes place between citric acid and carbonate or bicarbonate salt. The ratio of citric acid and sodium bicarbonate must be 0.76:1 for required gas generation. Various polymers used in preparation of gas generating systems are sodium alginate, chitosan, HPMC etc. GRDDS based on combination of polymer swelling and effervescence is shown in (Figure 8).

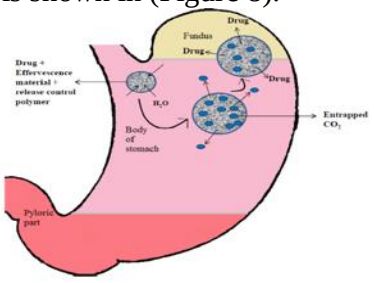

Figure 8: GRDDS based on combination of polymer swelling and effervescence

Advantages of FDDS: These play a main role in increasing the bioavailability of certain drugs like levodopa, riboflavin etc.[18, 19] The presystemic metabolism of the drug can be decreased.[20, 21] The dosage frequency of drugs with less bioavailability can be reduced as the sustained release can be achieved through these systems.[22, 23] Dose dependent adverse effects and changes in plasma drug concentration can be decreased. Degradation of drug within the colon can be prevented as drug stays for more hours in the stomach. FDDS is more convenient for drugs with lesser absorption sites in upper small intestine.[24]

Limitations of FDDS: To obtain desired effect of FDDS, high volume of stomach fluid which facilitate floating is necessary. Drugs with stability and solubility problems in the gastric region are not suitable to be taken as FDDS**.** Due to the increased gastric retention time there may be chances of occurrence of first pass metabolism. Some drugs when given through FDDS can cause gastric irritation. FDDS have to be given with considerable amount of water which is not possible in case of unconscious patients.[18-24]

Drugs which are suitable for FDDS: Locally active drugs within the stomach such as misroprostol, antacids. Drugs which have narrow absorption window in stomach and intestine (L-DOPA, PABA, riboflavin, furosemide).[25] Drugs which are not stable in colon or intestine (captopril, ranitidine, metronidazole).[26] Drugs which causes instabilities in normal colonic microbes such as tetracycline, clarithromycin, amoxicillin etc. Drugs which are less soluble at alkaline environment (diazepam, chlordiazepoxide, verapamil).[27]

Factors effecting FDDS:

Density: It should be less than gastric fluids (g/mL).

Size and shape: Are the parameters to be considered while formulating FDDS such that increased gastric retention time can be achieved.

Diameter: Dosage form with diameter 7.5 mm or more experience buoyancy for longer time when compared to those with diameter 9.9 mm.

Size and Shape: the formulation with tetrahedron and ring shapes with modulus of 48 and 22.5 kilopond per square inch (KSI) show increased GRT that those with other shapes.[28]

Fed or unfed state: During fasting state, the gastro intestinal motility is more or the myoelectric complexes occur at every 1.5 to 2 h when the contents in stomach gets emptied and move into intestine and the dosage form when administered at that time moves into intestine along with GIF and the GRT is reduced, where in case of fed state the MMC gets delayed increasing the GRT.[29]

Nature of meal: Food containing indigestible polymers of fatty acids decreases the gastric motility which makes the drug to stay in stomach for long time there by facilitating the prolonged drug release

Caloric content:

protein rich food causes increased GRT for 4 to 10 h.[30]

Applications of FDDS:

FDDS mainly facilitates effective formulation and delivery of drugs with low bioavailability but increases the gastric retention time of the drug. Other applications include increased absorption, sustained drug release, site-specific drug release etc.[31-33]

Future challenges of FDDS:

The main requirements for the success of FDDS are decreased FLT and raised gastric retention time (GRT), whereas the main challenge faced by FDDS is to allow the prolonged release of the drug with in the stomach or the anterior part of the GIT.[34, 35] Other physiological parameters that effect the gastro retention time are age, sex, amount and type of food intake along with its calorific value.[36] The gastro retention time process is prolonged by fatty meals (meals with high calorific value).[37, 38] The particle size and diameter must be considered as particles with diameter less than 5 mm pass through the pylorus (2 to 3 mm diameter in digestive phase and 12 to 13 mm diameter at inter-digestive phase) into the duodenum.[39, 40] Some other factors on which gastro retention time depends are shape of the dosage form, size, patients disease state, body mass index etc. It is also shown that multiple unit FDDS have predictable and improved drug release than single unit FDDS because single unit exits earlier before it becomes functional.[41] Therefore all the problems associated with FDDS, along with proper monitoring of drug release patterns have to be followed in such a way that a fully functional FDDS can be developed.[42]

Evaluation tests for FDDS:

The following are the few evaluation tests to be performed on floating tablets.

Pre compression parameters:

These include tapped density, angle of repose, bulk density, Hausner's ratio, Carr's index etc. were measured on powdered mixture or granules depending on the granulation process.[43]

Pre compression parameters:

Diameter and thickness:

10 tablets of each batch were randomly selected and tested for their thickness and diameter using hardness tester or Vernier callipers. The standard deviation of both thickness and diameter and average values were calculated.

Weight variation: 20 tablets were randomly selected from each batch and weighed to determine average weight and deviations.

Friability test:

10 tablets of each batch were selected, weighed and individual weights were noted. The weighed tablets were then transferred into friabilator which for set 25 rpm for 4 min. Later they were removed, dedusted and weighed and the percentage of weight difference is calculated.[44]

$$Friability\ (\%) = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

Where: W initial = weight of tablets before friability test and W Final = weight of tablets after friability test

Hardness test:

6 tablets of each batch were selected and kept in hardness tester and tested for the force required to break the tablet into pieces and the values are noted. The average value is calculated and expresses as Kg/cm^2.[45]

Floating behaviour:

This test is performed to calculate the time required by the tablet to float over the gastric fluids. It is determined to calculate total floating duration and buoyancy lag time. The tablets were placed in 100 mL of 0.1 N HCl and the entire system is maintained at

37 ^{0}C and the time taken by the tablet to sink into the fluids is noted.[46, 47]

In vitro release of drug:

The amount of drug released from the tablet at certain time period is calculated using disintegration test apparatus. 6 tablets were selected and placed in 6 baskets in the disintegration apparatus which is maintained at 37 ^{0}C. The solution was withdrawn after the complete disintegration of tablet and the amount of drug released is calculated using UV Spectrophotometer.[48, 49] To understand the pharmacokinetics of drug, the above occurred results were analysed using certain kinetic equations like zero order, first order equations etc.[50]

Differential Scanning calorimetry (DSC):

The variations that occur within the drug characteristics after they get combined with excipients can be easily identified using DSC. The pure drug sample and drug excipient sample were heated to certain temperature and the thermal behaviour of both drug and drug excipient mixture were investigated using differential scanning calorimeter.[51, 52]

Marketed drug products of FDDS are mentioned in (Table 1)[53-56]

Table 1: Marketed drug products of FDDS

Brand name	Drug	Type of formulation
Madopar	Levodopa & Benserazide	Floating CR capsule
Valrelease	Diazepam	Floating capsule
Liquid Gaviscon	Al-Mg antacid	Effervescent floating liquid alginate preparation
Topalkan	Al-Mg antacid	Floating liquid alginate preparation
Amalgate flot coat	Al-Mg antacid	Floating dosage form
Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin	Gas generating floating form
Cytotec	Misoprostal	Bilayer floating capsule

Some of the patents on FDDS are mentioned in (Table 2)

Table 2: Patents on FDDS

Type of formulation	Patent No.	Reference No.
Floating capsule	US4126672	57
Gastro retentive dosage form	US3418999	58
Floating device	US4055178	59
Floating tablet	US3786813	60
Multiple unit floating dosage form	WO2007106957	61
Bilayer tablet	WO2004002445	62
Microspheres	US6207197	63
3-layer tablet	US5780057	64
Foams or hollow bodies	US5626876	65
Floating tablets	US5169639	66
Granule	US4844905	67
Floating capsules	US4814178 US4814179	68
Tiny pills	US4434153	69
Empty globular cells	US3976164	70

CONCLUSION:

Among the various GRDDS, FDDS have become more successful and commercialized. However, several advantages of FDDS for patients have been noticed in majority of cases. Dose and the manufacturing process are to be monitored by case to case for a drug or combinations in designing FDDS. Selection of a Polymer or their combinations remains critical for the success of the FDDS, a minimum quantity that provides a maximum GRT with a significant minimum FLT and sufficient controlled release of drug from the matrix is preferred. Currently use of matrix forming polymer(s) together with effervescence is highly applying technology in the design of FDDS and even various patented technologies were even been established. In terms of systemic delivery of drugs along with enhanced effectiveness, FDDS is expected to become more popular in the near future. However, due to complexity in pharmacokinetic and pharmacodynamic parameters it is essential to establish *in vivo and in vivo* studies.

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