REVIEW ARTICLE

Floating Drug delivery System: A Novel Approach For Gastroretentive Drug Delivery

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ABSTRACT:
Oral controlled drug delivery system have an important area in novel drug delivery system to achieving efficient drug delivery that have poor bioavailability and short gastric residence time (GRT). Several approaches are currently utilized in prolongation of gastric residence time, including floating drug delivery system, swelling system, Bio/muco-adhesive system, high density system, HBS, delaying gastric emptying excipients etc. In this review compile the recent available literature on gastroretentive drug delivery and marketed products have been discussed. In addition, the pharmaceutical basis of their design, their advantages and future potential for oral controlled drug delivery are discussed.

KEYWORDS: floating drug delivery systems, low density, controlled release, Buoyancy , Gastric retention.

INTRODUCTION:
Oral drug administration is the most widely used for drug delivery system. Approximately 50% of the drug delivery system available in the market are oral drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.

Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Drugs that are easily absorbed from GIT and have short half lives are eliminated quickly from the systemic circulation.

Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained release formulation is used to release the drug slowly into GIT and maintain the effective concentration of drug in the systemic circulation for log time. After oral drug delivery retained in the stomach, drug release in controlled manner and supplied continuously in the GIT. GRDDS is approach to prolong retention time in the stomach and there by improve the bioavailability, reduces wastage of drug and enhance the drug solubility that are less soluble in the intestine.

Drug that are poorly soluble in high pH are formulated as GRDF by this dosage form the drug is soluble in the stomach before the emptying the stomach. Certain types of drugs can benefit from using gastric retentive system. These include:

- Drugs acting locally in the stomach
- Drugs that are primarily absorbed in the stomach
- Drugs that is poorly soluble at an alkaline pH
- Drugs with a narrow window of absorption
- Drugs absorbed rapidly from the GI tract
- Drugs that degrade in the colon

STOMACH PHYSIOLOGY:
The stomach is J-shaped organ located in the left upper part of the abdomen immediately below the diaphragm. The stomach can also be divided into three anatomical regions (Fig.1) (Fundus, Body and Antrum). The main function of the stomach is to store the food and mixed or grind and then it release for the intestine.
GASTRO RETENTETIVE APPROACHES:
Bioadhesive or Mucoadhesive:
These systems are used to deliver drug within the lumen and cavity of the body to a site-specific manner. These approaches involve the use of bioadhesive polymers that can be adhere to the epithelial surface of GIT. The adherence of the delivery system to the gastric wall increases the residence time at a particular site thereby bioavailability increased. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.1,2

Swelling System:
These type of dosage form swell to an extent that prevent their exist in the stomach through the pylorus. This type of dosage form retained longer period of time in stomach. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter.3,4

Incorporation of delaying gastric emptying excipients:
The presence of food in the stomach, drug absorption was more rapid then under fast condition. In the addition of excipients like Monoglycerides, Diglycerides and Fatty acids of chain lengths of C10 – C14 decreased gastric emptying rate.5

High density System:
These system have the density greater than that of the stomach content (1.004 gm/cm3) retained the dosage form in the lower part of the stomach. Sedimentation has been employed as a retention mechanism for high density system. For sufficient prolongation of GRT ~3 g/cm3 density required. The high density of formulation like pellets should be used. These pellets can be coated or mixed with heavy, nontoxic materials such as barium sulfate, titanium dioxide, etc.6

Ion-exchange resins:
An ion exchange resin loaded with bicarbonate shown gastric retentive property. Then a semi-permeable membrane were coated on the ion exchange resin to achieved no rapid loss of CO2. When arrived in the acidic pH of stomach, chloride and bicarbonate ion exchange take place resultant CO2 was released and trapped in the membrane thereby carrying beads toward the top of the stomach content and a floating layer of resin beads formed.7

Hydrodynamically balanced system (HBS):
These are single-unit dosage form having gel-forming hydrophilic polymers. The polymer is mixed with drugs and usually administered in HBS capsule. When system contact with water the capsule shell dissolves and mixture swells to form a gel barrier, which imparts buoyancy to dosage form in gastric juice for a long period.8

Magnetic System:
This approach based on incorporation of magnetically active compounds in the dosage form for site specific delivery. The system contains a small internal magnet and a magnet placed on 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.9

Floating system:
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.10,11,12

TYPES OF FLOATING DRUG DELIVERY SYSTEM (FDDS):
According to the mechanism of buoyancy, there are two distinctly different technologies used to development of FDDS which are:
A. Effervescent System, and
B. Non- Effervescent System.

(A) Effervescent Systems:
These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan while sodium bicarbonate, tartaric acid, and citric acid used as effervescent compounds. When the formulation of these compound contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.13

Asnaashari et al developed metronidazole floating dosage forms for better eradication of Helicobacter Pylori in peptic ulcer diseases that are retain in the stomach for a long time by using multi-factorial design. HPMC, psyllium and carbopol in different concentrations were used as floating agents, and sodium bicarbonate was added as a gas-generating agent. Formulations containing HPMC as filler showed prolonged lag times for buoyancy. Adding psyllium to these formulations had reduced relative lag times. Overall, selected formulations were able to float and showed buoyancy for at least 8 h.14,15

Chen et al develop an optimal GRDDS for administering Losartan by swellable and floatable tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate were prepared at different compression pressures for evaluating swelling characteristics and floating capacity. At lower compression force and appropriate ratio of HEC to NaCMC, addition of sodium bicarbonate resulted in the tablets floating over SGF for more than 16 h and swelling to 2 cm in diameter within 3h.16

Nagarwal et al developed floating matrix tablets cinnarizine HCl (CNZ). floating matrix formulations containing four viscosity grades of hydroxypropyl methylcellulose, sodium
alginate or polyethylene oxide, and sodium bicarbonate as gas-forming agent used. CNZ releasing data were analyzed by using Higuchi, Peppas, Weibull, and Vergnau models. On the basis of in-vitro release data, tablet was subjected to bioavailability studies in rabbits and was compared with CNZ suspension. Greater bioavailability achieved due to longer retention in the gastric environment.20

Bandari et al introduced a multiple biphasic tablet of fenoterol for gastroretentive drug delivery system. By this system drug released 0.1 mol L(-1) HCl and SGF (enzyme free) in sustained manner with buoyant properties. No significant change occur in dissolution profiles. HPMC containing floating multiple matrix tablet with a zero-order release profile was suitable GRDDS (Fig.3).23

Bomma et al developed floating matrix tablets of norfloxacin to increase drug bioavailability. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum used as polymer. Physical properties and In-vitro release of drug from tablet formulation was studies. Non-Fickian diffusion was confirmed as the drug release mechanism from these tablets, indicating that water diffusion and polymer rearrangement played an essential role in drug release. And Bomma found maximum retention of tablet in stomach about 180 min.21

Lingam et al developed a biphasic with multiple unit minitable by gas formation method. In this system loading dose have uncoated core units and prolong core units which is coated with three coating layers one is seal coat, second is effervescent and third outer layer is polymeric of polymethacrylates. With the Eutragit RL30D system was floated immediately on gastric contents and was released linear on controlled manner.24

Kulkarni et al developed bilayer floating tablets of diltiazem HCl and lovastatin. For lovastatin, sodium starch glycolate used as superdisintegrant in the immediate release layer and hydroxypropyl methylcellulose (HPMC) K4M and Xanthan gum used for diltiazem HCl in the controlled release layer. Sodium bicarbonate and Dicalcium phosphate was used as the gas generating agent and channeling agent respectively. Formulations have good matrix integrity and lovastatin released within 30 min. The concentration of polymer controle the diffusion of diltiazem HCl. HPMC and Xanthan gum decrease the release of diltiazem HCl for 12 h. The release of one drug remained unaffected in presence of the other drug.25

Meka et al developed a multiple-unit minitablets based on Effervescent technique for furosemide. The system consists of core units (solid dispersion of furosemide:povidone and other excipients), and coated with an effervescent (sodium bicarbonate) layer and other one an outer polymeric layer of polyethacrylates. With the Eutragit RL30D system was floated immediately on gastric contents and was released linear on controlled manner.26

Rahman et al developed a bilayer tablet of captopril using HPMC, K-grade and mixture of citric acid and sodium bicarbonate as effervescent compound which formed the floating layer. In release layer captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, in combination with the drug. The floating behavior the system was studies in vitro dissolution in gastric fluid having 1.2 pH. Approximately 95% drug was released in vitro, and have floating lag time 10 min.27

Jang et al developed a GRDDS of DA-6034 (synthetic flavonoid derivative), for the treatment of gastritis by using effervescent floating matrix system (EFMS) because its low solubility in acidic medium, which was float in gastric contents and continuously release the drug. By this system the release of DA-6034 from tablets increased in acidic media.28

Jainini et al prepared an effervescent floating tablet of famotidine by using two different grades of methocel
(K100 and K15M) which is responsible for gel forming properties. Sodium bicarbonate as a gas-generating agent was essential to found in vitro buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.\textsuperscript{39}

**B) Non-Effervescent:**
Non-effervescent floating dosage forms based on the mechanism of swelling of excipients or bio-adhesion to GIT mucosa. Gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polycrylate, polyethylene glycol, and polystyrene are used as non-effervescent polymers. After swallowing this dosage form swells in contact with gastric fluids. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.\textsuperscript{30}

Garse et al, prepared a non-effervescent floating tablets of labetrolol hydrochloride has been developed using various grades of HPMC and Poloxamer M127 as wetting agent. The tablets formulated with HPMC K4M CR and HPMC K15M CR along with Poloxamer showed negligible floating lag time with a total floating time over 12 hrs with complete release. The formulation have good floating and swelling behaviour and drug release in a controlled manner.\textsuperscript{31}

Abdelbar et al, developed Trimeprazine extended-release floating tablets by using polymers including HPMC 4000 cps, carbopol 971P, polycarbophil, and guar gum. The tablets were fabricated by dry coating technique. Stability study of the dosage form was carried out for 3 months at three different temperatures. All tablet formulas achieved <0.5 min of floating lag time, more than 12 h of floating duration, and extended t (1/2). The drug release followed zero-order kinetics.\textsuperscript{32}

Elmowafy et al, developed single-unit floating matrix tablets of famotidine by the use of the low density polypropylene foam powder. The matrix integrity of prepared floating tablets is good. The differential scanning calorimetry and Fourier transform infrared spectroscopy studies revealed that changing the polymer matrix system by formulation of polymers blends resulted in formation of molecular interactions which may have implications on drug release characteristics. This was obvious from the retardation in drug release and change in its mechanistic.\textsuperscript{33}

Hu et al was developed rosiglitazone maleate floating microspheres by an emulsion-solvent diffusion method with ethyl cellulose and octadecyl alcohol as the carrier materials. After 12 h microspheres floating was (91.45 +/- 1.62)\% , and the dose loading were (9.31 +/- 0.31)\% . The AUC of plasma concentration-time of the floating microspheres was equivalent to that of reference tablets. Therefore floating microspheres are a feasible approach for the sustained-release preparation of drugs which have limited absorption sites in the upper small intestine (figure-4).\textsuperscript{34}

Streubel et al, developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethylmethacrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system.\textsuperscript{35}

Regmi et al, developed hydrodynamic balance system of ethmozine (E-HBS). In vitro release of E-HBS were shown the first order of kinetics. The gamma-scientific study showed that E-HBS remained in the human stomach for more than 6h after ingestion, much longer than the conventional tablet (1-1.5 h). The plasma concentration-time curve of E-HBS exhibited typical sustained-release characteristics. The percentage of drug released in linear (figure-5).\textsuperscript{36}

Prajapati et al, developed floating matrix tablets of domperidone for increasing drug bioavailability. Hydroxypropylmethylcellulose K4M, carbopol 934P, and sodium alginate used in the tablet. Tablets were evaluated for in vitro release for 24h according to linear regression analysis. Tablets exhibited desired floating and prolonged drug release time. Carbopol decreased floating properties of tablet but were helpful to control the release rate of drug.\textsuperscript{37}

**FACTORS AFFECTING THE FLOATING DRUG DELIVERY SYSTEM:**
The gastric retention time (GRT) of oral dosages form is affected by the several factors which is depend on the efficiency of the GR system.\textsuperscript{38}

1. Age – Age of the people also affects the gastric emptying time. Especially elderly people those over 70, have a significantly longer GRT.
2. Gender – Mean ambulatory gastric retention time in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

3. Size of dosages form - 7.5mm diameter of dosages form having better gastric residence time compare to the 9.5mm.

4. Shape of dosages form - Shape of the dosage form also affected the gastric emptying . Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better gastric retention time 90 to 100 per cent at 24 h compared with other shape.

5. Density – Gastric retention time also dependent on the density of the dosage form. A buoyant dosage form having lower density than gastric fluids and therefore remain floating in the stomach for a long period of time.

6. Nature of meal – Fatty acid, monoglycerides, diglycerides or indigestible polymers can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

7. Size of meal - Large meals tend to empty more slowly in first few hour and then more quickly compared to a small meal.

### POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEMS:

In FDDS inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols. Hydrocolloids such as Acaicia, pectin, Chitosan,agar, casein, bentonite, veegum, HPMC(K4M, K100M and K15M),Gellan gum(Gelrite®), Sodium CMC, MC, HPC, 20%-75% are used in formulation. Effervescent agents Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine), 5%-60% lactose, mannitol are use as release rate accelerants. Upto 80% ethyl cellulose used as buoyancy increasing agents and Low density material such as Polypropylene foam powder (Accurel MP 1000®). Many other polymers also use in FDDS that are given as following. [39]

#### Hydroxypropyl methylcellulose (HPMC) :

Rabaj et al developed a metformin HCl effervescent tablet. In this formulation HPMC was used as the hydrophilic polymer, other ingredients also incorporated such as sodium bicarbonate and stearic acid. [40]

Jagdale et al developed the propranolol HCl floating tablet for achieving good drug bioavailability. All floating tablets were formulated with HPMC K4 and hydroxypropyl cellulose. Xanthan gum also use it show good retaining ability. [41]

Bomma et al, developed norfloxacin floating matrix tablet by using HPMC and xanthan gum. All formulation have non fickian diffusion release characteristics (In vitro). Tablets retained in stomach approximately three hours. [42]

Patel et al formulated floating tablet of verapamil HCl for controlled drug delivery in the Stomach. Formulation was formulated with hydroxypropyl methylcellulose (HPMC), carbopol ,xanthan gum and effervescent agent such as citric acid and sodium bicarbonate for achieving buoyancy. Drug released form formulation in zero order kinetic and non fickian diffusion. [43]

Arza et al develope swellable, floating and sustained release tablets with the combination of HPMC as hydrophilic polymer , crosopodone, sodium bicarbonate. All formulation show good swelling , drug release, floating characters than CIFRAN OD (marketed product) when comprises with it. [44]

Garg et al used hydroxypropyl methylcellulose K4M K15M for preparation of Acyclovir floating effervescent tablet to prolong the gastric retention time. [45]

#### Microcrystalline cellulose :

Sawicki et al compare the utility of microcrystalline cellulose and powdered cellulose in the floating pellet cores of verapamil HCl. In this study sawicki was found that verapamil HCl release rate from coated pellets with higher amount of powdered cellulose was considerably slower than the pellets containing higher microcrystalline cellulose. [46]

Garg et al developed a floating tablet of Acyclovir for enhancing the gastric residence time. In the formulation microcrystalline cellulose used for increasing the swelling property of the Acyclovir floating tablet and other material such as HPMC, psyllium husk, sodium bicarbonate as gas generating agent was also used. [45]

#### Hydroxyethyl cellulose :

Chen et al developed a GR drug delivery system for administration of losarton. In this system chen used hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose and sodium bicarbonate and compressed at low pressure resulting tablet float over SGF for <16h and swelling 2 cm in diameter within 3 hours. Releasing of drug from the tablet was depend upon pH. [19]

#### Eudragit :

Lingam et al used Eudragit RL30D in the formation of biphasic floating drug delivery system with multiple unit mini tablet. This system based on gas formation technique to maintain the drug concentration in the plasma. [24]

Goole et al developed a new coated multiple unit sustained release floating system for Levodopa which is based on gas formation method. Eudragit RL30D used as film former and coating level fixed at 20% w/w. [47]
Meka et al developed FDDS with multiple unit mini tablet. System consist of three successive. Eudragit RL30D was used in this system as outer gas entrapped polymeric membrane layer.

Zhai et al prepared a phenols gastric tablet by using Eudragit IV, HPMC and octadecanol.

MARKETED PRODUCTS OF FDDS:
Some of the marketed floating drug delivery system based formulations are listed in above table:

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Brand name</th>
<th>Delivery system</th>
<th>Drug and Dose</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Madopar® HBS (Prolopa® HBS)</td>
<td>Floating CR capsule</td>
<td>Benserazide(25mg) And L-Dopa (100mg)</td>
<td>Roche Products, USA</td>
</tr>
<tr>
<td>2</td>
<td>Cifran OD®</td>
<td>Gas-generating floating form</td>
<td>Ciprofloxacin (1gm)</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>3</td>
<td>Liquid Gaviscon®</td>
<td>Effervescent Floating liquid alginate preparations</td>
<td>Al hydroxide (95 mg), Mg Carbonate (358 mg)</td>
<td>GlaxoSmithkline, India</td>
</tr>
<tr>
<td>4</td>
<td>Conviron®</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>5</td>
<td>Topalkan®</td>
<td>Floating liquid alginate preparation</td>
<td>Al – Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>6</td>
<td>Cytotech®</td>
<td>Bilayer floating capsule</td>
<td>Misoprostol (100µg/200µg)</td>
<td>Pharmacia, USA</td>
</tr>
<tr>
<td>7</td>
<td>Valrelease®</td>
<td>Floating capsule</td>
<td>Diazepam (15mg)</td>
<td>Hoffmann-LaRoche, USA</td>
</tr>
</tbody>
</table>

ADVANTAGE OF FLOATING DRUG DELIVERY SYSTEM:
1. Improved the absorption of drug because FDDS increased the gastric retention time and dosage form spend long time in the stomach.
2. It is important for drug which is absorbed through the stomach.
3. Minimizing the mucosal irritation due to acidic drug. For these type of drug formulated by Hydrodynamically Balanced System which release the drug at controlled rate.
4. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:
1. Drug which have solubility or stability problem in GIT are not suitable for this system.
2. In gastric emptying time high variability occur due to its all or non emptying process.
3. It is require high level of fluid in the stomach.
4. Drug that causes irritation to the gastric mucosa are also not suitable for FDDS.

CONCLUSION:
GRDDS offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper GIT and they can be delivered efficiently thereby maximizing their absorption and enhancing bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, swelling and expanding systems, bioadhesive systems, ion exchange systems, high density systems and other delayed gastric emptying excipient. Floating tablets provide a dosage form which is stable and provides a sustained release drug delivery. Now –a-days lot of work is running to develop different types of gastroretentive delivery systems of various drugs. Day by day the FDDS shows more promise for a bright future.

REFERENCES:


