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A Review on Gastro Retentive Drug Delivery System

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ABSTRACT

The purpose of writing this review article on gastro- retentive drug delivery systems (GRDDS) have been developed; the principle mechanism of floatation to achieve gastric retention. The recent developments of (FDSS) including the physiological and formulation variables affecting the gastric retention. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, super- porous hydro- gels and magnetic systems, have been employed. Floating drug delivery systems have a bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releasing the drug slowly at the desired rate from the system. Dosage forms available as gastric floating systems include tablets, capsules, granules and microspheres.

Keywords: Floating tablet, Gastro- retentive drug delivery system, Gastric resistance time, Rosuvastatin calcium.

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INTRODUCTION

Orally administered dosage forms have several physiological limitations, such as GI transit time, impaired drug absorption due to incomplete release of drug from the dosage forms and too short residence time of the dosage forms in the absorption region of GI tract. Gastro-retentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs. Prolonged gastro retention of the therapeutic moiety may offer numerous advantages: better bioavailability, reduced drug waste and improved solubility of drugs that are less soluble in a high pH environment of small intestine. To formulate a successful[9, 23]

Stomach specific or gastro-retentive drug delivery system; several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system1. It has been frequently observed that the drugs that are easily absorbed from GI tract have short half lives and are eliminated quickly from the systemic circulation which leads to incomplete absorption of drugs from the upper part of the small intestine. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastro- retentive drug delivery systems offer the advantages in prolonging the gastric emptying time. To formulate a successful stomach specific or gastro- retentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system, low density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, super-porous hydro-gels and magnetic systems. Swellable, floating and sustained release tablets are developed by using a combination of hydrophilic polymer (Hydroxypropyl methylcellulose), swelling agents (Crospovidone and Crosscarmellose) and effervescent substances (sodium bicarbonate and citric acid). Controlled release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period, enhancement of activity of duration for short half, life drugs, elimination of side effects, reducing frequency of dosing and wastage of drugs, optimized therapy and better patient compliances.

Approaches of Gastric Retention [18]

- Low density system
- High density system
- Mucoadhesive and bioadhesive System
- Expandable system

- Magnetic System

High Density System [10]

This approach involves formulation of dosage forms with density that must exceed density of normal stomach content (1.004g/ml). These systems have some drawbacks like they are technically difficult to manufacture with a large amount of drug because the dry material of which it is made interacts within the gastric fluid to release its drug contents. One other problem is that no such system is available in the market.

Low Density System

FDDS remain afloat above the gastric contents for prolonged periods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GRRDS is also evident from the large number of floating dosage forms being commercialized and marketed world-wide.

Mucoadhesive & Bioadhesive Systems

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and glident, etc.

Magnetic system

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using an extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time.

Factors Affecting on Gastric Retention Time [23, 11, 22]

PHYSICOCHEMICAL FACTORS

Size of dosage form

Dosage forms having diameter greater than the diameter of pyloric sphincter escape from gastric emptying and remain within gastric region.

Shape of dosage form

Round or Ring shaped dosage form are considered better in shape.

Density

Location of the particular gastro retentive dosage form in gastric region depends on density of the system. Those with low density tend to float on the gastric fluid surface while high density systems sink to the bottom of the stomach.

BIOLOGICAL FACTORS

Age

Geriatric patients show a longer gastric retention time, while the neonates and children have low gastric retention time, in comparison to a normal adult.

Gender

Gastric retention time in male (3-4 hrs) is less than the female (4-6 hrs).

Fed or Unfed state

Gastric motility is higher in fasting condition which depicts lesser GRT.

Feed frequency

Higher the frequency of taking food, longer will be the GRT.

Nature of meal

High amount of fatty acids and other indigestible polymers generally decreases the gastric retention time by altering gastric motility.

Disease state

Gastro retentive time is altered during the various gastric diseases like 'Crohns disease'.

Mechanism of Floating System [5, 26]

Floating drug delivery systems (FDDS) have 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 (Figure 3 (a)), 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. A minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing (FDDS) with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy Capability variations.

$$F = F_{buoyancy} - F_{gravity}$$

$$= (Df - Ds)\, gv$$

Where,

F= total vertical force, Df = fluid density, Ds = object density, v = volume and

g = acceleration due to gravity.

Classification of Floating System

1. Single Unit Floating Dosage Systems

a) Effervescent system

b) Non-effervescent Systems

2. Multiple Unit Floating Dosage Systems

a) Effervescent Systems

b) Non-effervescent Systems

c) Hollow microspheres

3). Raft forming system

Single Unit Floating Dosage Systems [7, 9]

a) Effervescent systems

Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid.

b) Non effervescent system [16]

Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration, this dosage forms wells in contact with gastric fluids and attains a bulk density of less than 1 g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form.

Multiple Unit Floating Dosage Systems [6, 9]

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variability in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in different forms, and using

principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS.

a) Effervescent system [16, 18]

Ichikawa et, al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub-layers to avoid direct contact between the 2 agents. This is surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, produce swollen pills (like balloons) with a density less than 1.0 g/ml due to incorporation of co_2. The Non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GIT. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bio adhesive polymer such as chitosan and carbopol. In one approach, gel forming hydrocolloid swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and the bulk density of less than unity within gastric environment. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio. Thanoo et; al. developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated bio-fluids, as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug. Sheth et; al. developed hydro-dynamically balanced capsules containing mixture of drug and hydrocolloids containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1, thereby being buoyant on the gastric contents of stomach, until all the drug was released.

c) Hollow micro-spheres [18, 19]

Hollow microspheres are considered as one of the most promising buoyant systems; as they possess the unique advantages of multiple unit systems as well as better floating properties,

because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers in preparation of hollow microsphere. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

Raft forming system [16]

On contact with Gastric fluid a gel-forming solution (eg. Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles. Which forms Raft layer on top of gastric fluid which releases drug slowly in stomach such formulation typically contains antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. They are often used for gastro oesophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithkline)

Advantages of gastro-retentive drug delivery system

1. It increases patient compliance by reducing dosing frequency.
2. Buoyancy increases gastric residence time.
3. Better therapeutic effect of short half life drugs.
4. Site specific drug delivery to stomach can be achieved.
5. In this drug is released in a controlled manner.
6. Gastric irritation can be avoided by designing sustained release.
7. Improved selectivity in receptor activation.

DISADVANTAGES OF FDDS [19, 14]

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or none emptying process.
4. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

Evaluation of Floating Drug Delivery System [15, 18, 26]

1. Evaluation of powder

a) Angle of Repose

b) Bulk Density

c) Compressibility index (Carr's index)

d) Hausner's ratio

2) Evaluation of tablets

a) Buoyancy Test

b) Swelling Index

c) In vitro drug release study

d) Weight variation

e) Hardness & friability

f) Particle size analysis, surface characterization (for floating microspheres and beads)

g) X-Ray/Gamma Scintigraphy

h) Pharmacokinetic studies

1) Evaluation of powder blend [24, 26]

a) Angle of repose

Angle of repose is defined as "the maximum angle possible between the surface of the pile of powder and the horizontal plane." Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where,

h=height of the pile, r=radius of the pile, θ=angle of repose

b) Bulk Density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles.

$$\text{Bulk density} = M/Vo$$

Where,

M = mass of the powder, Vo = bulk volume of the powder

c) Compressibility index (Carr's index)

Compressibility index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is Simple, fast and popular method for predicting flow characteristics. Carr's index can be represented.

$$\text{Carr's index (\%)} = \text{Tapped density} - \text{Bulk density} * 100/\text{Tapped density}$$

d) Hausner's ratio

It is the ratio of tapped density to bulk density. It is given by

Hausner ratio = Tapped density / Bulk density

2) Evaluation of tablets [24, 26, 28]

a) Buoyancy test

The *in vitro* buoyancy was determined by floating lag time and total floating time in a 100 ml beaker containing 0.1N HCl solution (pH 1.2) maintained at 37 °C. The time required for the tablet to rise to the surface was determined as floating lag time and total duration of time by which dosage form remain buoyant was determined as total floating time.

b) swelling index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at 37 ºC. The swollen weight of the tablet was determined at predefined time intervals over a period of 5 hr. The swelling index (SI) expressed as a percentage was calculated from the following equation.

$$\textbf{Swelling index (SI)} = (W_t - W_O)/W_O \times 100$$

Where,

W_t =weight of the tablet at time t

W_O =initial weight of the table

c) *In vitro* drug release studies

The *in vitro* dissolution studies was carried out in 01.N HCL using USP type 2 Dissolution test apparatus employing paddle stirrer was placed inside the dissolution medium and paddle was rotated as 75 rpm. 5ml samples were withdrawn at specific time intervals and the same volume was replaced to maintained sink conditions. The sample was analyzed for drug content spectrophotometrically. Dissolution mechanism of the formulation was analyzed by plotting drug release versus time plot.

Kinetics Analysis of In vitro Release Rates [5, 10]

1. Zero-order kinetic model-Cumulative %drug release versus time.
2. First –order kinetics model-Log cumulative %drug drug remaining versus time.
3. Higuchi's model-Cumulative % drug release versus square root of time.
4. Korsmayer equation/Peppa's model-Log cumulative % drug released versus log time.

d) Weight variation

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the %limit and none of the tablet differs by more than double %limit.

$$PD = W_{avg} - W_{ind}/W_{avg} * 100$$

e) Particle size analysis, surface characterization

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

Application of Floating Drug Delivery System [27, 21]

Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin furosemide and misoprostal. The controlled slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drugs. This reduces the side effects that are caused by the drug in blood circulation.

Absorption Enhancement

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

Sustained drug delivery

HBS system can remain in the stomach for long periods and hence can release the drug over a Prolonged period of time. These systems have bulk density of <1, as a result of which they can float on the gastric contents. This feature is associated with improved patient compliance and thereby improves therapy.

Minimized Adverse Activity at the Colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamics aspect provides the rationale for GRDF formulation for beta lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads development of microorganism's resistance

Reduced Fluctuations of Drug Concentration:

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Improved selectivity in receptor

Minimization of fluctuation in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptor at different concentration.

Table 1: Polymers used for increasing gastric resistance time [24, 26]

Polymers and other ingredients	Examples
Hydrocolloids (20%-75%)	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate,Carbopol, β Cyclodextrin, CMC, Polyethylene glycol, polycarbonate, PVA etc.
Inert fatty materials (5%-75%)	Beeswax, fatty acids, long chain fatty alcohols, Gelucires etc.
Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, Di- SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine) etc.
Release rate accelerants (5%-60%)	Lactose, Mannitol etc.
Release rate retardants (5%-60%)	Dicalcium phosphate, Talc, Magnesium stearate etc.
Buoyancy increasing agents (upto80%)	Ethyl cellulose etc.
Low density material	Polypropylene foam powder (Accurel MP 1000®) etc.

Table 2: Powder flow characteristics in relation to Angle of repose

Sr. no.	Angle of repose	Powder flow characteristics
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	>40	Very poor

Table 3: Powder flow Characteristics in relation to Carr's index & Hausner's ratio

Compressibility index (%)	Flow characteristics	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Extremely poor	>1.60

Table 4: Drugs used in the formulations of stomach specific floating dosage forms [24]

Sr. No.	Dosage form	Drugs
1	Microspheres, Tablets, Pills	Chlorpheniramine maleate, Aspirin, Griseofulvin, Acetaminophen**,** P-nitroaniline, Acetylsalicylic acid, Ibuprofene etc.
2	Films	P-Aminobenzoic acid, Cinnarizine, Piretanide 61, Prednisolone, Quinidine gluconate etc.
3	Granules	Cinnarizine [53], Diclofenac sodium, Diltiazem etc.
4	Powders	Riboflavin-60-phosphate**,** Sotalol, Theophylline etc.
5	Capsules	Verapamil HCl, Chlordiazepoxide HCl, Diazepam , Furosemide **,** L-Dopa and Benserazide , Misoprostol etc.

Future Scope

The floating drug delivery concept can be used in development of anti reflux formulations. Buoyant delivery system is beneficial in the treatment of gastric and duodenal ulcers. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease. The explore eradication of Helicobacter pylori using the narrow spectrum antibodies.

CONCLUSION

Gastro retentive drug delivery systems are the most preferable systems in order to deliver the drugs which have a narrow absorption window near the gastric region. Now days a number of drug delivery devices are being developed which aim at releasing the drug at gastric region. Even though these drug delivery systems have several advantages they also have disadvantages like their *invitro and invivo* correlation is very less.

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