

A REVIEW ON MULTIPARTICULATE FLOATING DRUG DELIVERY SYSTEM

Deepak Sharma*, Sanjay Kumar Sharma, Manish Jaimini and Amit Kumar

Department of Pharmaceutics, Jaipur College of Pharmacy, Sitapura,
Jaipur, Rajasthan, India.

ABSTRACT

Recent several technical advancements have led to development of various systems that could revolutionize method of drug delivery and hence could provide definite therapeutic benefits. It is an established fact that the conventional immediate release drug delivery systems when taken frequently in a day can maintain drug concentration levels in therapeutically effective range but this result in significant fluctuations in plasma drug levels. The floating or hydro dynamically controlled drug delivery systems namely, floating microspheres, micro beads, microcapsules etc., are useful in overcoming such uncertainty. Micro beads are small, solid and free flowing particulate carriers containing dispersed drug particles. Placing of these DDS in specific region of the GIT offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon. Recent scientific research has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. The present review deals with the concept, mechanism, recent innovations and applications of multiparticulate drug delivery system.

INTRODUCTION

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends indicate that single and multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral

controlled drug delivery and led to development of Gastro-retentive floating microspheres. Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.¹

Basic physiology of gastrointestinal tract

Anatomically the stomach is divided in to three regions: Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions (Figure 1). Gastric emptying occurs in both the fasting and fed states.

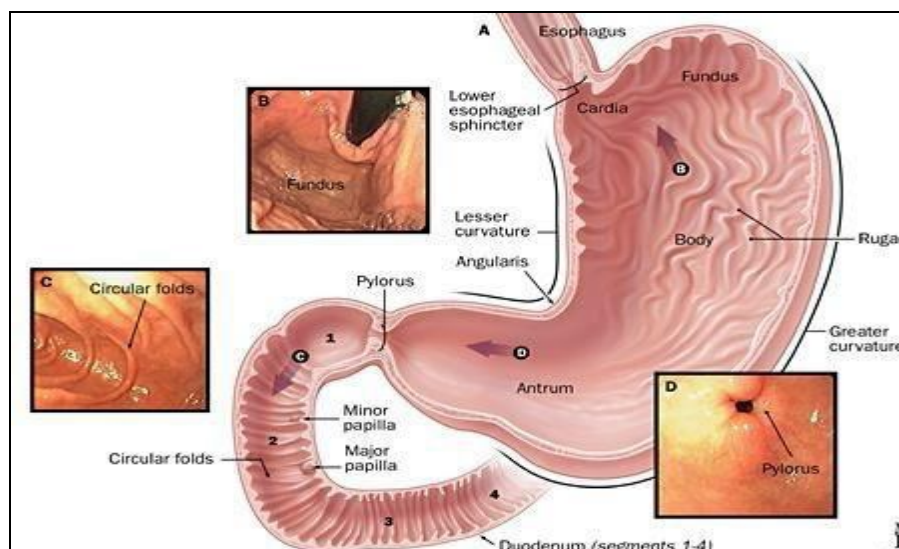


Fig. 1: Physiology of stomach

During the fasting state an inter digestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs which is called as inter digestive myoelectric cycle or migrating myoelectric cycle which is further divided in to four phases After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern.

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase)-last for 10-20 minutes which includes intense and regular contractions for short period also known as housekeeper wave.

4. Phase 4-last for 0-5 minutes and occurs between phase 3 and phase 1of 2 consecutive cycles (Period of transition).¹

Multiparticulate drug delivery system

Floating multiparticulate are gastro-retentive drug delivery systems based on non-effervescent and effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core (Figure 2). These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers. Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm.

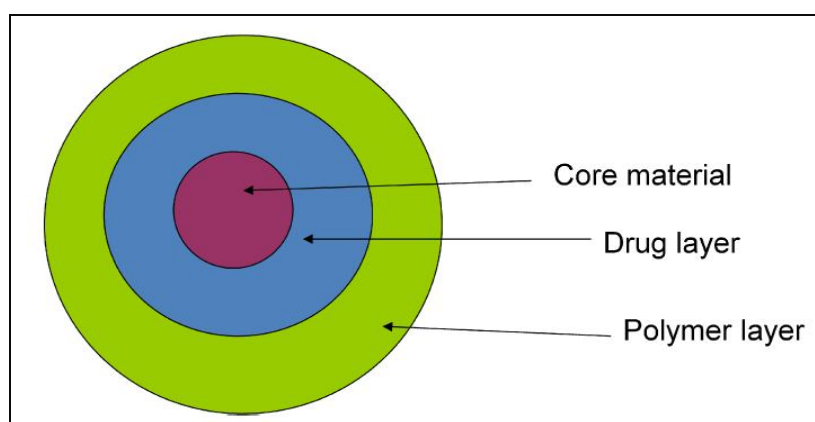


Fig. 2: Multiparticulate drug delivery systems

Advantages of floating multiparticulate drug delivery system

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilise only in stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.²
9. Better therapeutic effect of short half-life drugs can be achieved.

Disadvantages of floating multiparticulate drug delivery systems

1. The residence time in the stomach depends upon the digestive state. Hence, floating multiparticulate drug delivery systems should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep this microsphere floating in-vivo, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. Floating multiparticulate drug delivery systems are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be a desirable candidate for floating multiparticulate drug delivery systems since the slow gastric emptying may lead to the reduced systemic bioavailability.²

Potential drug candidates for gastro retentive drug delivery system

1. Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. LDOPA,

para aminobenzoic acid, furosemide and riboflavin etc.

3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl and metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against *Helicobacter pylori*.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide and verapamil HCl.³

MECHANISM OF ACTION OF MULTIPARTICULATE FLOATING DRUG DELIVERY SYSTEMS

The mechanism of drug release from multiparticulate can be occurring in the following ways:

1. Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

2. Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

3. Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.³

CLASSIFICATION OF MULTIPARTICULATE FLOATING DRUG DELIVERY SYSTEMS^{3, 4, 5}

(A) Non-effervescent systems

i. Colloidal gel barrier systems

Hydro dynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

ii. Micro porous compartment systems

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to

prevent any direct contact of the gastric mucosal surface with the undissolved drug.

iii. Multiparticulate system: Floating beads

Most common method for the preparation of beads is the polymer cross linking method. Beads so formed can be coated with different polymers to tailor the release of the drug from beads. Spherical beads can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system. Ion-exchange resin beads loaded with drug and effervescent agent is coated with a semi permeable membrane. CO_2 is released on contact with the acid gastric juice. Oil entrapped cross linked beads can be prepared by emulsion gelation method.

iv. Micro balloons

This system involves low density materials; entrapping oil or gas. General techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Kawashima and co-workers prepared hollow microspheres ('micro balloons') with a drug loaded in their outer shells by an emulsion-solvent diffusion method. The ethanol /dichloromethane solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol (PVA) that was maintained at 40°C with continuous stirring. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug.

(B) Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

i. Volatile liquid containing systems

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

ii. Gas generating systems

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 , which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chyme. These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

PREPARATION OF GASTRORETENTIVE MULTIPARTICULATE SYSTEM

1. Solvent evaporation method

Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates.⁶

2. Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolyte to cross link in the presence of counter ions to form hydrogels. Since, the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for the encapsulation of drug, ionotropic gelation technique has been widely used for this purpose. The natural polyelectrolyte in spite of property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure.

These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. Dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations produces the hydrogel beads. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crossed linked moiety. Bio molecules can also be loaded into these hydrogel beads under mild conditions to retain their three dimensional structure.⁷

CHARACTERIZATION OF THE FLOATING MICROPARTICULATE SYSTEM

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery.^{6,7}

Particle size and shape

SEM provides higher resolution in contrast to the LM. The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of multiparticulate

Capture efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

Floating behaviour

Appropriate quantity of the floating micro particulate was placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture was stirred with a magnetic stirrer. The layer of buoyant micro particulate was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy (\%)} = \frac{W_f}{W_f + W_s} \text{ Where,}$$

W_f and W_s are the weights of the floating and settled micro particles

Bulk and tapped density

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

Carr's compressibility index

Compressibility index (C.I.) or Carr's index value of micro particles was computed according to the following equation:

$$\text{Carr's index} = \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right] \times 100$$

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Hausner ratio

Hausner's ratio of micro particles was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose (θ)

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h , which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height and r is the radius.

Moisture content

Moisture content is determined by means of Karl Fisher titration.

Content uniformity

Content uniformity (assay) is performed for each batch as per the procedure given in the official pharmacopoeia.

In-Vitro release studies

In vitro drug release from the floating multiparticulate is complicated because the multiparticulate float and adhere to the inner

surfaces of dissolution basket, which leads to the non-participation of multiparticulate or their surface in release study. The release rate of floating multiparticulate was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating multiparticulate equivalent to 50 mg drug was filled into a hard gelatine capsule (No. 0) and placed in the basket of dissolution rate apparatus. The dissolution fluid was maintained at $37 \pm 1^\circ$ at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a $0.25 \mu\text{m}$ membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium.

PROPRIETARY TECHNOLOGIES FOR DEVELOPMENT OF MULTIPLE UNIT DOSAGE FORMS

SODAS[®] Technology (Spheroidal Oral Drug Absorption System)

It is Elan's Multiparticulate drug delivery system. Elan's SODAS[®] Technology is based on the production of uniform spherical beads of 1-2 mm in diameter containing drug plus excipients and coated with product specific controlled release polymers. The most recent regulatory approvals for a SODAS[®] based system occurring with the launch of once-daily oral dosage forms of Avinza[™], Ritalin[®] LA and Focalin[®].⁹

IPDAS[®] Technology (Intestinal Protective Drug Absorption System)

In this, the beads with high density drug are compressed to form controlled release tablets. It is particularly suitable for tablet that cause gastro irritation and disintegrates rapidly. The release is controlled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating. It is extruded and spheronised Multiparticulate based technology. Initially, it was developed for a proprietary formulation of naproxen with fast onset of action to relief pain over a 24-hour period which is marketed in the US and Canada under the trade name Naprelan.⁹

CODAS[®] Technology (Chronotherapeutic Oral Drug Absorption System)

This technology is designed to delay drug release for a predetermined time to tune therapy to the body's circadian rhythms. Again, the technology is based on polymer coated Multiparticulate. The release controlling coating is a blend of water soluble and water insoluble polymers. When water from the gastrointestinal

tract get in touch with the polymer coated beads, the water soluble polymer gradually dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier maintaining the controlled release of drug.¹⁰

Diffucaps[®] Multiparticulate System

Eurand's Diffucaps[®] multiparticulate system customized drug release profiles are created by first layering active drug onto an inert core (such as a sugar/cellulose sphere), then applying one or more rate-controlling, functional polymers, to produce spherical, multi-layered particles. Eurand's Innoproan[®] XL tablet represents commercialized product of Diffucap[®] multiparticulate system.¹⁰

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.^{11, 12}

Sustained drug delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo.

Site-specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum.

Absorption enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the

bioavailability of floating dosage forms (42.9%) could be achieved as compared with

commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%).

Table 1: Market product of pellets^{13, 14, 15}

S. No.	PRODUCT	DRUG	COMPANY
1	Bontril SR	Phendimetrazine Tartrate	Carnick laboratories, Inc
2	Brexin L.A	Chlorpheniramine Pseudoephedrine	Savage Laboratories, Bangalore
3	Compazine	Prochlorperazine	Smith & French, Mumbai
4	Cymbalta	Duloxetine Hydrochloride	Eli Lilly and Company, USA
5	Dilgard XL 180	Diltiazem hydrochloride	Smith kline & French, Mumbai
6	Fastin	Phentermine	Berlex Laboratories, USA
7	Ibugesic S.R 300	Ibuprofen	CIPLA Ltd, Ahamadabad
8	Inderal	Propranolol Hydrochloride	Astrazeneca US Ltd.
9	Nexium	Esomeprazole	Astrazeneca US Ltd.
10	Nicobid T.S	Niacin	U.S Vitamin, USA

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. MDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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