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An overview on floating microsphere: Gastro Retention Floating drug delivery system (FDDS)

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Abstract

Drug absorption in the gastrointestinal tract is a highly variable process. Floating microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

Keywords: Gastro Retention, Hollow microspheres, Floating microspheres, Short half-life, Solvent Diffusion, Floating drug delivery system (FDDS).

Introduction

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range only when taken several times a day depending upon the dosage regimen. This result shows significant fluctuation in drug level. An approach overcome such fluctuations conventional led to the development of several novel drug delivery systems (NDDS) that could revolutionize methods of formulation and provide a number of therapeutic benefits.

The main objectives of these new drug delivery systems are:

1) It would be single dose which releases the active ingredient over an extended period of time.
2) It should deliver the active entity directly to the site of action thus minimizing or eliminating the side effects.[1]

Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal / spatial nature or both. By this the system attempts to control drug concentrations in target tissues for a controlled period of time.

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects.

In general, the goal of sustained release dosage forms is to maintain therapeutic concentration of drug for prolonged period of time. This is usually accomplished by attempting to obtain zero order release of drug from the dosage form which is independent of the concentration of drug in the delivery system (Fig. 1).

Sustained release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e. concentration dependent).[2]

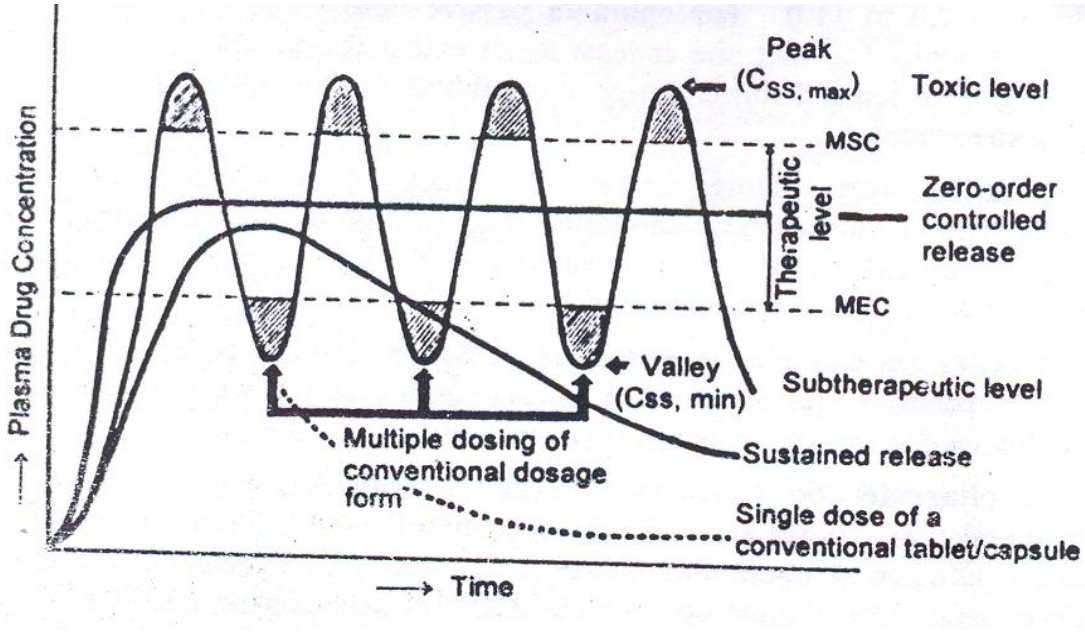

Figure 1: Drug blood level versus time profiles

Gastroretentive Drug Delivery System:

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation.

However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of gastrointestinal tract (GIT) due to variable gastric emptying and motility.

Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine, can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.

Therefore, control on placement of a variety of important drugs through appropriately designed drug delivery system (DDS) in a specific region of the GI tract offers advantages particularly for those having a narrow absorption window in the GIT or those with stability problems.

These considerations have led to the development of a unique oral controlled release dosage form with gastroretentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.

Gastroretentive dosage form 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 is also suitable for local drug delivery to the stomach and proximal small intestine.[3]

Table 1: Conventional v/s Gastroretentive drug delivery system[1]

Conventional drug delivery system	Gastroretentive drug delivery system
-High risk of toxicity	-Very low risk of toxicity
-Less patient compliance	-Improves patient compliance
-Not suitable for delivery of drugs with narrow absorption window in small intestinal region.	-Suitable for delivery of drugs with narrow absorption window in small intestinal region.
-Not much advantageous for	-Very much advantageous for
Drugs having rapid absorption through GIT	Drugs acting locally in the stomach.
Drugs which degrade in the colon.	Drugs which degrade in the colon.
Drugs acting locally in the stomach.	Drugs having rapid absorption through GIT
Drugs which are poorly soluble at an alkaline pH	-Possibility of dose dumping.
-No risk of dose dumping	

Potential Drug Candidates for Gastroretentive Drug Delivery Systems:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
- Low density form of the DF that causes buoyancy in gastric fluid.
- High density DF that is retained in the bottom of the stomach.
- Bioadhesion to stomach mucosa.
- Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients.
- Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.[3]

Drug candidates not suitable for Gastroretentive drug delivery systems:

- Drugs that have very limited acid solubility e.g. phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

A number of systems have been applied to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention (Fig. 2).

1) Floating drug delivery system (FDDS) with low density providing sufficient buoyancy to float over the gastric contents.

2) Bioadhesive systems enabling the localized retention of the drug in the stomach.

3) Swelling and expanding systems preventing transit from the gastric sphinctor.

4) High density systems remaining in the stomach for longer period of time by sedimenting to the folds of stomach. Fig no.3: Illustrates the mechanism of these systems in stomach.

A number of other methods like use of passage-delaying agents and modified shape systems have also been used for gastro retention purposes.[4, 5]

Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on noneffervescent

approach. The word Floating systems, first described by **Davis in 1968,** have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. While the system is floating on the gastric contents, the drug is released slowly at the desired rate and the system is eliminated from the stomach.

The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' (HBS) because they are able to maintain their low apparent density, while the polymer hydrates and builds a gel like barrier which remain buoyant (3-4 h) in the gastric contents without affecting the intrinsic rate of emptying.

Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect.

Among the different hydrocolloids recommended for floating formulations, cellulose ether polymers are the most popular, especially hydroxypropylmethylcellulose (HPMC). Fatty material with a bulk density lower than 1 may be added to the formulation to decrease the water intake rate and increase buoyancy.

In parallel with formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performance of floating forms. These assessments were carried out either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the transit through the GI tract.

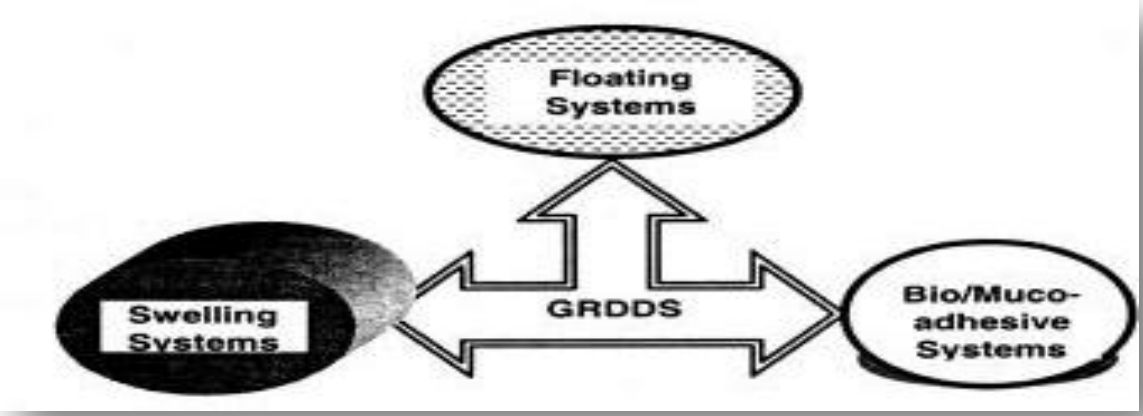

Figure 2: Classification of gastrorentive drug delivery system

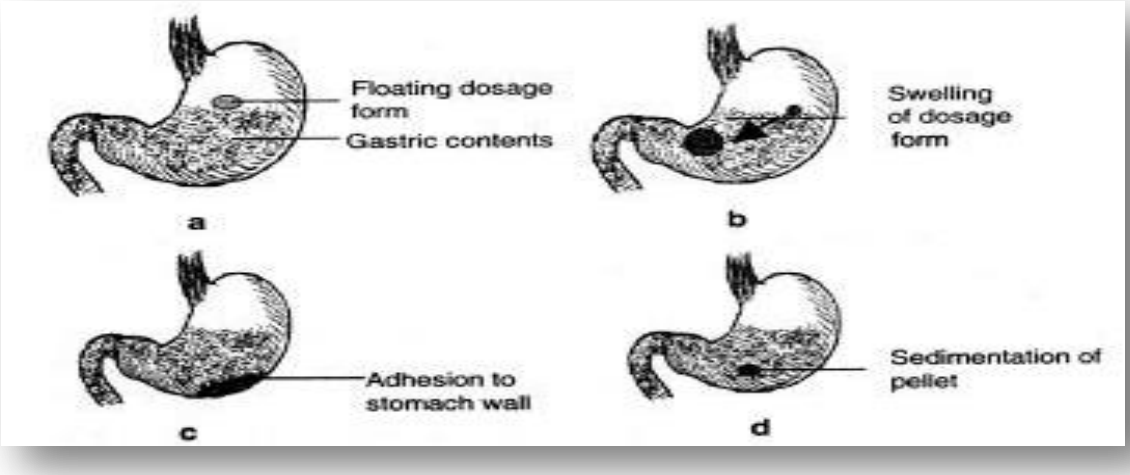

Figure 3: Mechanism of various gastroretentive drug delivery systems in stomach

When a floating capsule is administered to subjects who have consumed a fat and protein meal, it remains buoyant at the surface of the gastric contents in the upper part of the stomach and moves to the lower region progressively as the meal empties from the stomach. The reported gastric retention times range from 4 to 10 h. Pharmacokinetic and bioavailability evaluation studies confirmed the favourable effect of this prolonged gastric residence time.[5]

Advantages:

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastro retentive drug delivery approach in comparison to the administration of non gastro retentive drug delivery. There are several factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.

2) For drugs with relatively short half lives, the sustained release formulations may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

3) They also have an advantage over conventional systems as these can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).

4) Gastro retentive drug delivery can produce sustained release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

5) The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects or side effects.

6) Gastro retentive dosage forms minimize the fluctuation of drug concentrations and its effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

7) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

8) The sustained mode of drug release from Gastro retentive dosage form enables extension of the time over a critical concentration and thus enhances the pharmacological effects.[6]

Types of FDDS:

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS:

A. Effervescent System and

B. Non- Effervescent System.

Effervescent System:

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it floatable on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas on evaporation at the body temperature.

These effervescent systems further are classified into two types.

1) Gas generating systems

2) Volatile Liquid/Vacuum system

Gas generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO2 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 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.[7, 8]

Intra Gastric Bilayer Floating Tablets

These are also compressed tablets (as shown in Fig: 4) containing two layers i.e.

i) Immediate release layer

ii) Sustained release layer

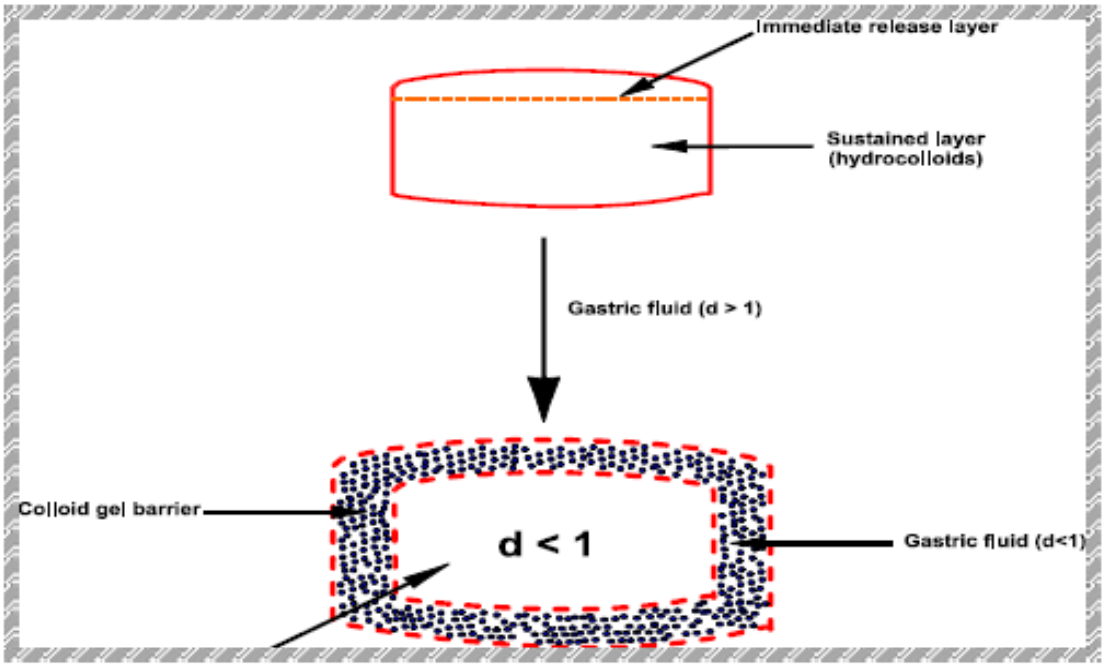

Figure 4: Intra gastric bilayer floating tablet

Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system (Fig. 5).[7, 8]

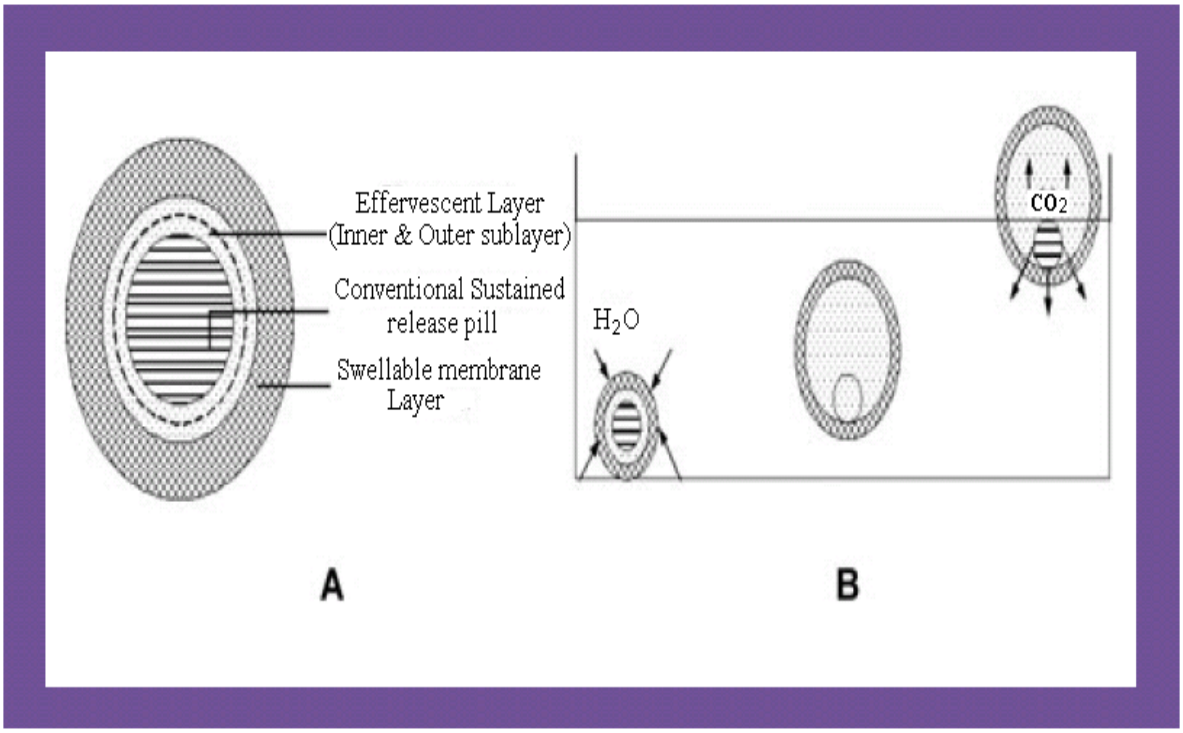

Figure 5: (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system

Volatile Liquid / Vacuum Containing Systems:

Intragastric Floating Gastrointestinal Drug Delivery System

These system can be made to float in the stomach because of floatation chamber which may be a vacum or filled with air or a harmless gas. while drug reservoir is encapsulated inside a microprous compartment, as shown in Fig.6.

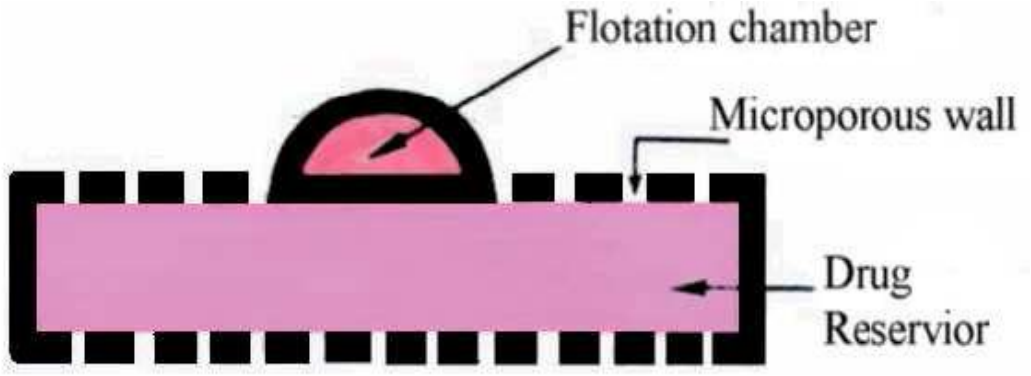

Figure 6: Intra Gastric Floating Gastrointestinal Drug Delivery Device

Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach.These systems are fabricated by loading the inflatable chamber with a drug reservoir which can be a drug impregnated polymeric matrix and then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug gets continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 7.

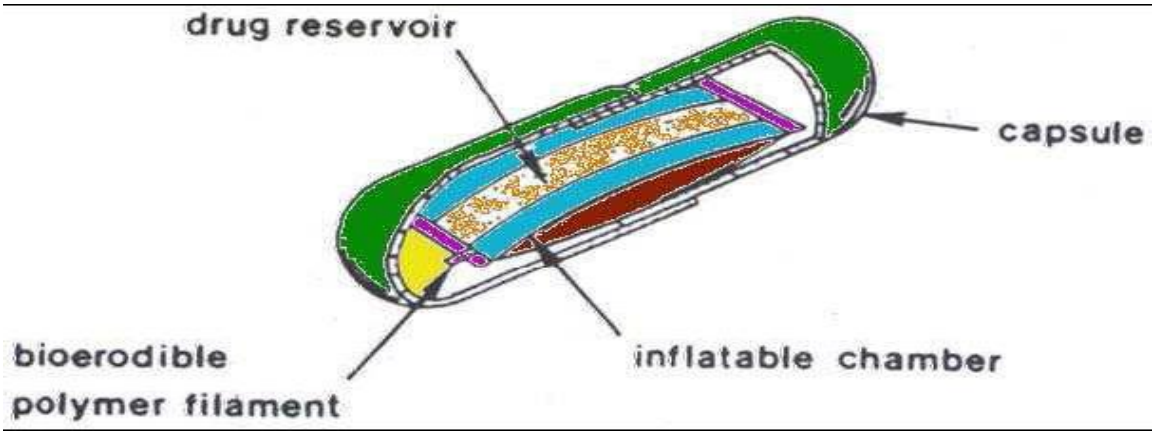

Figure 7: Inflatable Gastrointestinal Delivery System

Intragastric Osmotically Controlled Drug Delivery System

It comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support located inside forms a deformable hollow polymeric bag that contains a liquid which gasifies at body temperature to inflate the bag.

The osmotic pressure controlled drug delivery device consists of two components; drug reservoir and an osmotically active compartment.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the

support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig.8.[9]

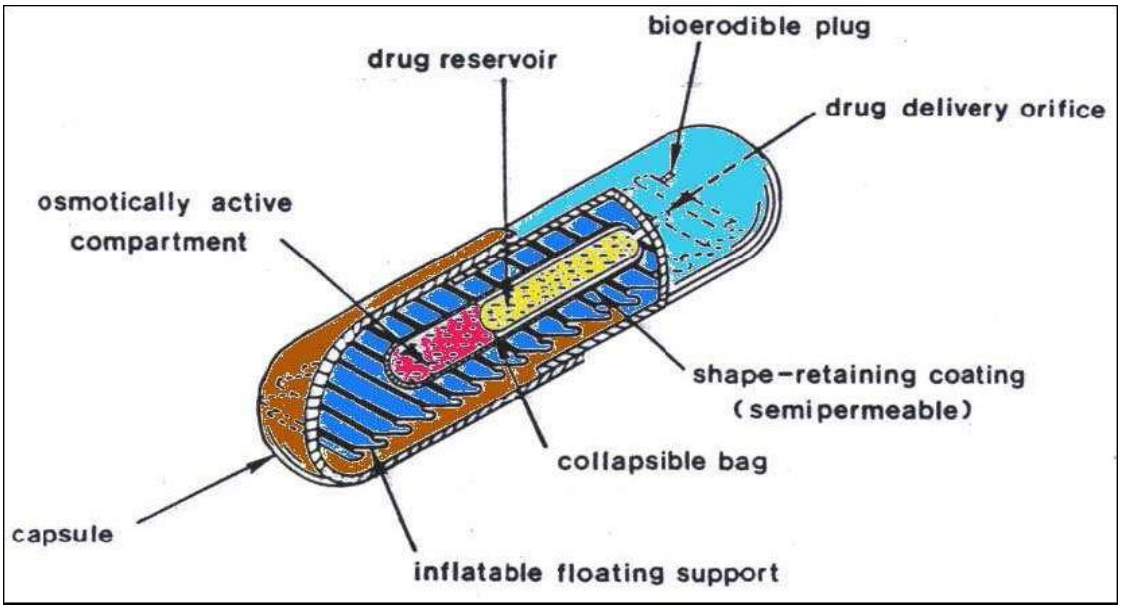

Figure 8: Intragastric Osmotically Controlled Drug Delivery System

Non effervescent systems:

The Non-effervescent FDDS are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials i.e. polycarbonate, polyacrylate, polymath.

acrylate, polystyrene as well as bioadhesive polymers e.g. chitosan and carbopol. Various types of such systems are as:

Colloidal Gel Barrier system:

Sheth and Tossounian first designated this hydro dynamically balanced system. Such a system contained drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolonged GRT and maximized the amount of drug that reached its absorption sites in the solution form for ready absorption. This system incorporated a high level of one or more gel-forming highly soluble cellulose type hydrocolloids e.g. hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymers i.e. polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrated and formed a colloidal gel barrier around its surface.[10]

Micro porous compartment system:

This technology was based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment get completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air caused the delivery system to float over the gastric content. Gastric fluid entered through the aperture, dissolved the drug and carried the dissolved drug for continuous transport across the intestine for absorption.[11]

Alignate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride causing precipitation of calcium alginate leading to formation of porous system which can maintain a floating force for over 12 hours.

When compared with solid beads which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour.

Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells, were prepared by a novel emulsion solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated

aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in microspherical particles containing drug.[11]

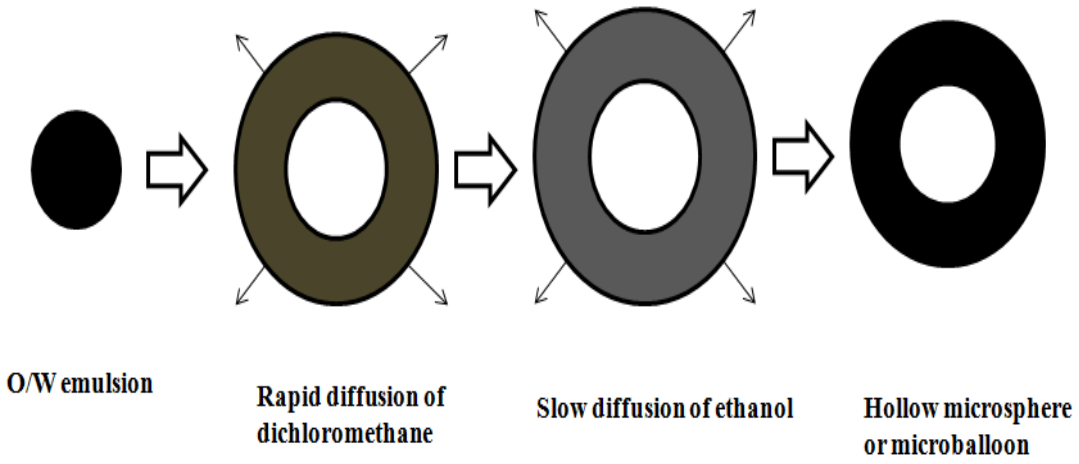

Figure 9: Formulation of floating hollow microsphere or microballoon

Advantages of Hollow Microspheres [12-16]

* Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.

* Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

* Improved receptor activation selectivity

* Extended time over critical (effective) concentration

* Less inter- and intra-subject variability.

* Flexibility in dosage form design.

* Improves patient compliance by decreasing dosing frequency.

* Better therapeutic effect of short half-life drugs can be achieved.

* Gastric retention time is increased because of buoyancy.

* Drug releases in controlled manner for prolonged period.

* Enhanced first-pass biotransformation

* Sustained drug delivery/reduced frequency of dosing

* Targeted therapy for local ailments in the upper GIT

* Extend patent protection, globalize product, and provide new business opportunities.

* Site-specific drug delivery to stomach can be achieved.

* Enhanced absorption of drugs which solubilize only in stomach.

* 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.

Disadvantages [17-18]

* Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin,theophylline, corticoster oids, iron (ferrous sulfate), oral contraceptives, and tricyclic

* Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.

* They are not suitable candidates for drugs with stability or solubility problem in stomach.eg.ranolazine.

* Single unit floating capsules or tablets are associated with an “all or none concept,” but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.

* FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of

water (200- 250 ml) of water to be taken together with FDDS.antidepressants.

Development of Floating Microspheres

Floating microspheres are gastroretentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs27. Gastroretentive floating microspheres are lowdensity systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Mechanism of Floating Microspheres

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, Eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.[19, 20]

Raft forming systems:

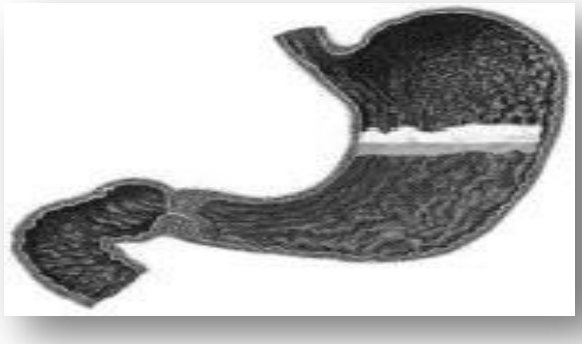

Figure 10: Schematic representation of the barrier created by a raft forming System

Raft forming systems have received much attention for the delivery of antacids and drugs for gastrointestinal infections and other disorders. The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluid because of the low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and able to float on the gastric fluids.[21]

Applications of Floating Microspheres[22]

* Floating microspheres are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. e.g Furosemide, Riboflavin etc.

* The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.

* Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of nonsteroidal anti inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients.

* Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

* Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug

release, leading to high drug concentrations at the gastric mucosa, thus eradicating Helicobacter pylori from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. The development of such systems allow administration of nonsystemic, controlled release antacid formulations containing calcium carbonate and also locally acting antiulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

* These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin frusemide and misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

* These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system.

* The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin, aspirin, griseofulvin, ibuprofen, terfenadine.

There are several others significant applications of FDDS as summarized below:

Sustained Drug Delivery

HBS systems can remain in the stomach for longer 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. Such 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 thus the passage from the pyloric opening is prohibited.

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 e. g riboflavin and furosemide.

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.

Conclusion

Floating microspheres has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. Optimized multi-unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Increased sophistication of this system will ensure the successful advancements in the avenue of gastro retentive microspheres therapy so as to optimize the delivery of molecules in a more efficient manner.

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