(Review Article)

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Floating drug delivery systems to increase gastric retention of drugs: a Review

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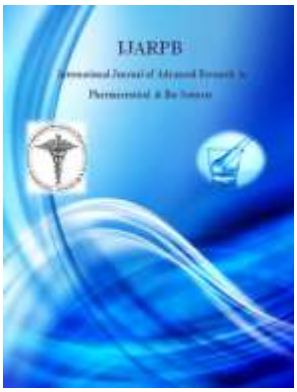

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ABSTRACT

Floating tablet of Furosemide (F) was prepared by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG-6000 is used as complexing agent for increasing solubility of Furosemide in water. Hydroxypropylmethylcellulose, sodium bicarbonate and carbapole were used as Matrixing agent gas generating agent and floating enhancers' respectively. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug delivery systems for more than 12 hours. The floating or hydro dynamically controlled drug delivery systems are useful in such application.

KEY WORDS: Chlorpheniraminemaleate,Theophlline,Furosemide,Ciprofolxacin,Pentoxyfillin.

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INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[1].

Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretensive systems 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 for 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. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, 2 flotation, 3 sedimentation, 4 expansion modified shape systems5 or by the simultaneous administration of pharmacological agent6, 7 that delay gastric emptying. This review focuses on the principal mechanism of floatation to achieve gastric retention.

Furosemide (FUR) is poorly water-soluble drug and its bioavailability is very low from its crystalline form. For poorly water- soluble, low permeable the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The FUR exhibits highly erratic and very low dissolution profile in gastric and intestinal fluids. This is possibly due to its very high hydrophobic character. The rate of absorption and/or the extent of bioavailability for such insoluble hydrophobic drug are controlled by the rate of dissolution in the gastrointestinal fluids. Hence, number of attempts were made to increase the rate of dissolution of such poorly water soluble hydrophobic drugs, to increase their effectiveness and simultaneously reduce their doses and hence the toxic effects[2].

FLOATING DRUG DELIVERY SYSTEM

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating onthe 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. However, besides 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 (Fig 1). Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow[3].

Single-Unit Dosage Forms

In low density approaches,3 the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells9 popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer ofchoice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of released desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Aperture or opening are present along the top and bottom walls through which the gastrointestinal fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior.

The device is of swallowable size, remains afloat within the stomach for a prolong time, and after microspheres. Table 1 enlists examples of various drugs formulated as different forms of FDDS.

The complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolong period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. Single unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential
Danger of producing irritation.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multipleunit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and poly alkyl cyanoacrylate. Spherical polymeric microsponges also referred to as “microballoons” have been prepared.

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Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability.In Carbon dioxide- generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to18 mm in their expanded state is exceeded.

Classification of Floating Drug Delivery
Effervescent Floating Dosage Forms
Gas Generating Systems

These are matrix type of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms.

In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer, and CO2bubbles are trapped in the swollen matrix (Fig. 1a)**.** In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10h. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h.
Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (Fig. 1b). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO2 (Fig.1c). The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer[4,5].

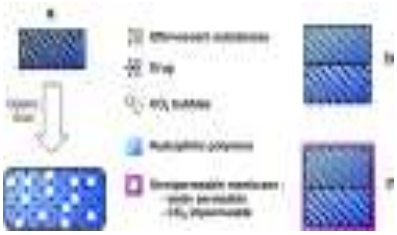

Fig No 1: Gas-generating systems. Schematic monolayer drug delivery system (a). Bilayer gas-generatingsystems, with (c) or without (b) semipermeable membrane

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles (Fig. 2) on contact with gastric fluid. Formulations also typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems producea layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gaviscon\ (GlaxoSmithkline).

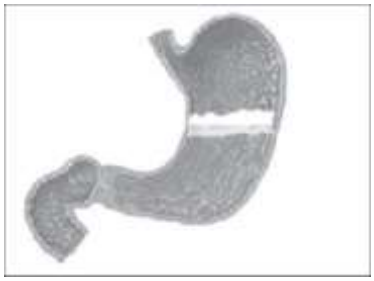

Fig No 2: Schematic illustration of the barrier formed By a raft-forming system

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Low-density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have therefore beendeveloped. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core (Fig. 3a). Streubel et al. developed foam-based floating microparticles consisting of polypropylene foam powder, drug (chlorpheniramine maleate, diltiazem HCl, theophylline or verapamil HCl) and polymer (Eudragit RS\ or polymethyl methacrylate). They were prepared by soaking the micropo-rous foam carrier with an organic solution of drug and polymer, and subsequent drying. The mixture was poured into an organic liquid (ethanol or methylene chloride) forming a suspension. The polypropylene foam particles acted like microsponges, absorbing the organic liquid, and becoming free-flowing, low-density microparticles following solvent evaporation(Fig. 3b). Good in vitro buoyancy was observed in most cases and a broad variety of drug release patterns could be achieved by varying drug loading and type of polymer: more than 77% or 98% of particles floated for at least 8 h depending on the polymer type (Eudragit RS\ or polymethyl methacrylate, respectively) and initial drug loading of the system (10% or 23%).

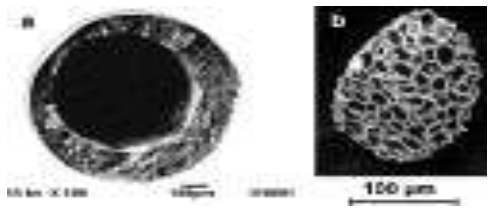

Fig No 3: Microballoons (a) from Sato et al. and foamparticles (b) from Streubel et al. Used with permissions

Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrixforming polymers like 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 form swells in contact with gastric fluids and attains a bulk density of < 1. 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[6].

Hydrodynamically Balanced systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcell ulose (HPC),sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatincapsule. The capsule rapidly dissolves in the gas gastric fluid,

and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuouserosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy.

Table 1. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

Tablets	Chlorpheniramine maleate Theophylline Acetylsalicylic acid Nimodipine Amoxycillin trihydrate Verapamil HCl Isosorbide dinitrate Atenolol Acetaminophen Ampicillin Diltiazem Riboflavin- 5' Phosphate
Capsules	Nicardipine L-Dopaandbenserazide Furosemide Diazepam Propranlol Urodeoxycholic acid
Microspheres	Microspheres Verapamil Aspirin, griseofulvin, and p-nitroaniline Ketoprofen Terfenadine
Granules	Indomathacin Diclofenac sodium
Films	Cinnarizine
Powders	Several basic drugs

Table2. Marketed Preparations of Gastro retentive technologies available in the international market

Product		**Active Ingredient**	**Remarks/Type**
1.	Glumetza	Metformin	Polymer Based
2.	proQuin XR	Ciprofloxacin	Polymer Based
3.	Cifran OD	Cifrofloaxacin (1 g)	Gas generating Floating Form
4.	GabapentinGR	Gabapentin (In Phase-III clinical trials)	Polymer Based
5.	-	Accordion Pill TM	Expandable film filled in capsule
6.	Baclofen GRS	Baclofen	Coated multi-layer floating
7.	Coreg CR (Carvedilol)	Carvedilol	Gastro retention with osmotic system
8.	Madopar	Levodopa and benserzide	Floating, CR Capsule
9.	Valrelease	Diazepam	
10.	Topalkan	Aluminum magnesium antacid	
	Almagate flatcoat		
	Liquid gavison		

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Advantages of Floating drug delivery system

1. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.

Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

Application 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.

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. Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

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. Eg.

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets[7].

Absorption Enhancement:

Drugs that have poor bioavailability because of sitespecific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

Eg. A significantly 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%).

CONCLUSION

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism.

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