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A REVIEW OF FLOATING DRUG DELIVERY SYSTEM

Jawale S. K.[1], Bairagi A. S. [1] ,Jaybhai S. [1], Deshmukh V.K. [1]

[1]M.E.S College of Pharmacy, Sonai, Tal-Newasa, Dist-Ahmednagar, Maharashtra-414105, India

E-mail- sunilkj390@gmail.com

ABSTRACT

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, drug is released slowly at a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric Residence Time (GRT) and a better control of fluctuations in plasma drug concentration. The system must have sufficient structure to form a cohesive gel barrier to maintain an overall specific gravity lower than that of gastric contents and to dissolve slowly enough to serve as a drug reservoir. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. noneffervescent and effervescent systems, have been utilized in the development of FDDS.

INTRODUCTION

Oral administration of a drug is perhaps the least predictable route of drug administration, yet it is the route that is used most frequently. Oral medications such as tablets, capsules are relatively cheap to manufacture, offer convenient form of drug administration and reduce the possibility of errors in total dose if the patient is self administering the dosage form. Classically, oral medications are administered as immediate release dosage forms. The major disadvantage of such immediate release preparations is the repeated frequency of drug administration and fluctuations in plasma drug levels. So, controlled release preparations were introduced. Oral controlled drug delivery systems (CDDS) have been developed for the past three decades due to their advantages. The design of oral CDDS is primarily aimed at achieving more predictable and increased bioavailability of drugs, hence, improving the efficiency of treatment. They help in reducing the frequency of administration, and single doses at periodic intervals of time are sufficient, resulting in improved patient compliance. However, the developmental process is precluded by

several physiological difficulties, such as inability to restrain and locate the CDDS within desired regions of gastrointestinal (GI) tract due to variable gastric emptying and motility.

Floating drug delivery systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, drug is released slowly at a desired rate from the system.

Advantages

1. This type of drug delivery system is especially very useful in the treatment of the disorders related to the stomach, as the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach.
2. All those molecules with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
3. This is a primary manner in which the bioavailability of a therapeutic agent can be enhanced. Especially all those drugs which get metabolized in the upper GIT.
4. They also have an advantage over the conventional system as it can be used to over come the adversities of gastric retention time as well as the gastric emptying time. As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric fluids.
5. The duration of treatment through a single dose, which releases the active ingredient over an extended period of time.

Practical approaches in the development of FDDS

The concept of FDDS was described in the literature as early as 1968, when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging and choking while swallowing medicinal pills. The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems:

Single Unit Dosage Forms

It was suggested that most of the floating systems suggested in literature are single unit systems.

In low density approach, globular shells having lower density than that of gastric fluid can be used as a drug carrier for its controlled release.

In fluid filled systems, gas filled floatation chamber is incorporated into a microporous component that also has drug reservoir incorporated within it.

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 multiple-unit floatable dosage forms have been designed.

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 in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

The major advantage of multiple unit dosage forms over single unit dosage forms is that they distribute uniformly within the gastric content and are gradually emptied from the stomach, possibly resulting in long lasting effects and reduced variability in absorption with lower probability of dose dumping.

Classification of FDDS

Based on the mechanism of buoyancy, two distinctly different technologies, i.e. effervescent and non-effervescent have been used in the development of FDDS.

FDDS are classified as follows:

1) Non-effervescent floating dosage forms:
a) Colloidal gel barrier system
b) Microporous compartment system
c) Alginate beads
d) Hollow microspheres
2) Effervescent floating dosage forms:
a) Volatile liquid containing systems
b) Gas generating system

Dosage forms available

The various buoyant preparations include single-unit as well as multiple-unit dosage forms including tablets (pills), capsules, powders, microspheres (including microballoons).

The most used FDDS are the single unit systems i.e. tablets and capsules, though they have several disadvantages as discussed previously. The major dosage forms have been discussed as follows:

Tablets

Among all the orally administered forms of drug the tablets are most convenient both from the point of view of the patient as well as the manufacturer. The tablets are the unit dosage forms which are mainly spherical in shape but the shape can be round, oval, oblong, etc.

Excipients

The floating tablet formulation uses excipients that are different from the one used in conventional tablet formulation.

The excipients used in conventional formulations are:

(i) Diluents: Lactose, Dextrose, Microcrystalline cellulose, hydrolyzed starches, Sucrose, sorbitol, Mannitol.
(ii) Binders and Adhesives: Acacia, tragacanth, Gelatin, starch, polyvinyl pyrrolidone
(iii) Disintegrants: Starch, clays, cellulose, Alginates.
(iv) Lubricants: Stearic acid, talc, stearic acid salts, waxes, surfactants.

(v) Glidants: Silica derivatives, talc, etc.
(vi) Color and Flavor: FD and C and D and C dyes and lakes as color.

Excipients used in floating tablets are

(i) Hydrophilic Polymers: Hydroxy propylmethylcellulose (HPMC)
(ii) Carrier matrix: Gelucire
(iii) Gel forming hydrocolloids / Matrix Formers: Polycarbonate, Polyacrylate, Polymethacrylate and polystyrene
(iv) Swellable polymers used in Effervescent Systems: Chitosan and sodium bicarbonate and citric acid or tartaric acid
(v) Matrix forming polymers: HPMC, Polyarcylates, cargeenan gum guar, gum arabic
(vi) Fillers: Lactose, microcrystaline cellulose.
(vii) Lubricant: Magnesium stearate, purified talc
(viii) Buoyancy Agents: Cellulose, gums, polysaccharides, starch, gelatin.
(ix) Diluents: Lactose, mannitol, glucose, microcrystalline cellulose, starch, di-calcium phosphate.
(x) Porosity Agents: Lactose.

Excipients used in FDDS

The major excipients other than the conventional ones used are the bioadhesive polymers and their properties are explained as follows:

1. Hydroxypropyl methylcellulose (HPMC)

HPMC is a hydrocolloid used in the HBS. The HBS would contain or be covered by a capsule of HPMC, which upon dissolution on contact with gastric fluid would form a soft gelatinous mass on the surface by hydration as discussed previously. The hydrated layer slowly dissolves releasing the medicament.

Synonyms: Cellulose, 2-Hydroxypropylmethyl Ether; Hypromellose

Definition:

Hydroxypropylmethylcellulose is a cellulose having some of the hydroxyl groups in the form of the methyl ether and some in the form of the 2-hydroxypropyl ether. The various grades commercially available are distinguished by a number indicative of the apparent viscosity in millipascal seconds of a 2% w/v solution measured at 20^{o}.

Category: Treatment of tear deficiency; pharmaceutical aid (tablet excipient; suspending agent).

Description: White or yellowish white, fibrous or granular powder; almost odourless; hygroscopic after drying.

Solubility: Practically insoluble in hot *water*, in *acetone*, in *ethanol*, in *ether* and in *toluene*. It swells in *water* forming an opalescent, viscous colloidal solution.

2. Gelucire

Gelucires are a family of vehicles derived from mixtures of mono-,di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-18) and melting point (33°C-65°C)

range. The various types available in the market manufactured by **Gattefossé** (St Priest, Cedex, France) are:

a) Gelucire 33/01 Glycerol esters of sat. C8-C18 fatty acids; used as excipient, carrier, vehicle, antioxidant
b) Gelucire 37/02 Saturated polyglycolized glycerides; used as excipient
c) Gelucire 39/01 Glycerol esters of sat. C12-C18 fatty acids; used as excipient, vehicle, consistency agent, fatting agent, antioxidant

3. Chitosan

They are biodegradable high weight cationic polysaccharides used widely in pharmaceutical industry.

4. Poly(ethylene oxide)

Poylethyleneglycol (PEG) and PEO are terms for materials containing repeated connected units of structure [-CH_2CH_2-O-]. PEG is the subspecies of PEO that contains hydroxyl group on each end of chain i.e. HO[-CH_2CH_2-O-]$_n$H. depending upon the molecular weight, PEO is a liquid, a waxy solid or a solid. Solid PEO has a very regular backbone structure, free of side chains.

5. Polymethacrylates

Polymethacrylates are metacrylic acid-ethyl ethacrylate copolymers (1:1) as copolymer of methacrylic acid and ethyl ethacrylate.

Synonyms: Eudragit, polymeric methacrylates.

Evaluation of FDDS

The various parameters that need to be evaluated for their effects on GRT of FDDS which are common to all dosage forms are described as follows:

A. In vitro evaluation

1. **Floating time:** The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1N HCl as a testing medium maintained at 37°C. The time required to float the dosage form is noted as **floating or floatation time.**

2. **Dissolution tests: Dissolution tests** are performed using the USP dissolution apparatus to see the in vitro drug release. It is performed using USP Apparatus 1 (Paddle) or Apparatus 2 (basket) or Apparatus 3 (modified disintegration testing apparatus) or Apparatus 4 (flow through cell) using 900 mL of 0.1N HCl at rotation of 50 or 100 rpm at 37°C ± 0.5°C. The samples are withdrawn at predetermined time intervals for a period of time and replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution.

3. **Specific gravity test:** The **specific gravity** of FDDS can be determined by the displacement method using

analytical grade benzene as a displacing medium.

4. **Resultant weight test:** An *in vitro* measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid.

   This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy ($\mathbf{F}_{bouy}$) and gravity ($\mathbf{F}_{grav}$) forces acting on the object as shown in the equation

   $$\mathbf{F = F_{buoy} - F_{grav}}$$
   $$\mathbf{F = d_f gV - d_s gV = (d_f - d_s) gV}$$
   $$\mathbf{F = (df - M / V) gV}$$

   in which **F** or **RW** is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d_f is the fluid density, d_s is the object density, M is the object mass, and V is the volume of the object .By convention, a positive resultant weight signifies that the force **F** is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force **F** or **RW** acts downward and that the object sinks.

B. In vivo evaluation

The *in vivo* **gastric retentivity** of a floating dosage form is usually determined by gamma scintigraphy or roentgenography. The dosage forms are labeled by a radiopharmaceutical and are monitored. In case the dosage form contains different layers, then each layer is labeled using a different radiopharmaceutical each time. Studies are done both under fasted and fed conditions using F and NF (control) dosage forms. It is also important that both dosage forms are non disintegrating units, and human subjects are young and healthy.

Applications and scope

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.

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 less than 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.

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. 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.

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%).

FDDS of bromocriptine, might lead to better treatment of Parkinson's disease. Furthermore, the codelivery of bromicriptine and metoclopramide based on dual delivery concept similar to that of Madopar HBS might further improve the therapeutic efficacy of HBS dosage form. The use of metoclopramide, a standard antiemetic agent is justifiable because it can prevent the side-effects caused especially by high doses of bromocriptine.

Seeing the various advantages of FDDS over the conventional systems and the vast amount of research work being performed in this area, there is an immense amount of scope for it to be more popular and useful. The day-by-day increasing popularity of FDDS shows more promise for a bright future.

CONCLUSION

Dosage forms with a prolonged GRT will bring about new and important therapeutic options. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing CRDFs. Many of the "Once-a-day" formulations will be replaced by products with release and absorption phases of approximately 24 hrs. Also, FDDS will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which are sustained over a large period. Finally, FDDS will be used as carriers of drugs with the "absorption window".

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