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Review Article

A Review on Floating Drug Delivery System and Its Possible Future Scope

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ABSTRACT
The purpose of writing this review on floating drug delivery systems attempts to compile the recent literature with special focus on various floating drug delivery systems approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. So generally floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. In this review current and recent development of floating drug delivery system is discussed.

Keywords: Floating drug delivery, Types of Floating drug delivery systems, Gastric Retention, Gastric Residence Time.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. The objective of any drug delivery system is to afford a therapeutic amount of drug to the proper site of action in the body to attain promptly, and then maintain the desired drug concentration. Recently a pharmaceutical formulation scientist is well versed with the fact that the overall action of a drug molecule is not merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. An ideal drug delivery system (DDS) should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of the body over the period of treatment. DDS may be employed for spatial placement (i.e., targeting a drug to a specific organ or tissue) or temporal delivery (i.e., controlling the rate of drug delivery to the target tissue)**.**

An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the gastrointestinal tract (GIT). Therefore there is a need of developing drug delivery system that releases the drug at the right time, at the specific site and with the desired rate.

Controlled release (CR) DDS is an attempt to sustained drug blood concentration at relatively constant and effective level in the body by spatial placement or temporal delivery. Thus controlled release drug delivery system (CRDDS) offer various advantages *viz.* reduce blood level fluctuations, minimize drug accumulation, employed less total drug, improve patient compliance, and minimize local and systemic side effects.[1]

Floating drug delivery system (FDDS)[2]

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolonged period. Floating systems can be of effervescent or non effervescent in nature. In effervescent gas generating excipients, e.g., bicarbonate salts and acidic ingredients are used that can form CO_2 in the presence of gastric acid. Also, volatile organic solvents have been introduced into the floating chamber to generate gas at physiological temperature. In non effervescent systems, usually high level (about 75%) of highly swellable and gel forming excipients are used. Systems based on super porous hydrogels and porous carriers are new type of non effervescent floating drug delivery systems. Floating granules containing Florite® RE with single (primary coated granules) or double coat (secondary coated granules) of ethyl cellulose. The floating properties of secondary coated granules were better than primary coated granules. Formulated multiparticulate and tablet gastroretentive drug delivery system using polypropylene foam powder**.**[3]

Approaches to design floating dosage form:

The following approaches have been used for the design of floating dosage forms of single and multiple-unit systems.[4]

Single-Unit Dosage Forms

In Low-density approach 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 shells popcorn, pop rice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as meth acrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl Cellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose.

The 3-layer principle has been improved by development of an asymmetric configuration drug delivery

system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process. The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability.

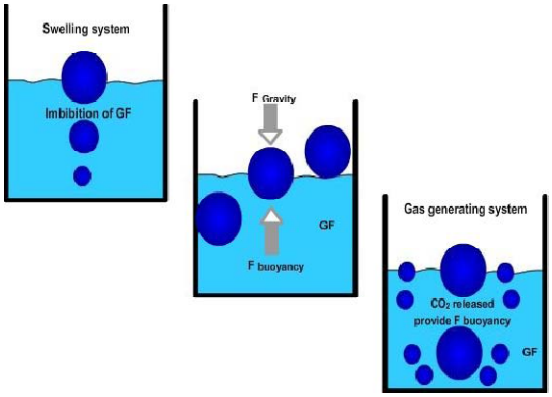

Fig. 1 Mechanism of floating systems, GF= Gastric fluid

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. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability**.**Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS.

Clasification of floating system:

The floating drug delivery systems are classified into two categories on the basis of formulation variables:

(1) Effervescent system
(2) Noneffervescent system.

Effervescent floating dosage form

These are matrix types 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, carbondioxide is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

A. Volatile liquid containing system*:*

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

B. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate carbondioxide,which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme**.**[5,6]

Ozdemir et al., developed floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio.[7]

Choi et al., prepared floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO2 generation on the physical properties, morphology, and release rates.[8]

Non-effervescent floating dosage form:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid**.**[9]

The various types of this system are as:

a) Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

b) Bi-layer Floating Tablets:

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

c) Alginate 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 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, and these floating beads gave a prolonged residence time of more than 5.5 hours.

d) Hollow Microspheres:

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

polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

Thanoo et al., developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM).[10]

Nur and Zhang et al., developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P.[11]

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

Dosage Form	Drugs
Tablets	Furosemide, Ciprofloxacin, Captopril, Theophylline, Nimodipine, Amoxycillin, Acetylsalicylic acid, Verapamil, Isosorbide di nitrate
Capsules	Furosemide, Misoprostal, Diazepam, Chlordiazepoxide HCI, Propranlol, Urodeoxycholic acid
Microspheres	Aspirin, Griseofulvin, p-nitroanilline, Ketoprofen,Iboprufen, Terfenadine, Piroxicam
Granules	Indomethacin, Diclofenacsodium, Prednisolone
Filme	Cinnarizine, Albendazole

Factors affecting floating and floating time:[12]

1. **Density**: Density of a dosage form plays a vital role in determining its buoyancy and henceforth, its floating efficiency.
2. **Shape of dosage form**: Compared to other shapes, devices with tetrahedron and ring shape have better floating potential. They have 90-98% better retention for 24 hrs.
3. **Single or multiple unit formulation**: Multiple unit formulations permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
4. **Fed or unfed state**: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.
5. **Nature of meal**: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
6. **Caloric content**: A meal rich in protein and fat content can increase floating by 4-10 hrs.
7. **Frequency of feed**: - The floating can increase by over 400 minutes when successive meals are given compared with single dose.
8. **Age**: Elderly people, above the age of 60, have a significantly longer floating.
9. **Posture**: Floating varies considerably between supine and upright ambulatory states of the patient.
10. **Concomitant drug administration**: Anticholinergics like atropine, opiates like codeine and prokinetic agents like metoclopramide and cisapride affect floating time.
11. **Biological factors**: floating may vary as per health conditions or physiological status of a person.eg. Diabetes and Crohn's disease alters floating time.

Drugs that would benefit from GRDDS

CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine), Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics, Anti-hypertension drugs, Anti-diabetic agents for Type 2diabetes, Drugs for local treatment of GI infections and gastric enzyme replacement

Evaluation of floating dosage forms

A. For Single Unit Dosage Forms[13]

1) Floating lag time:

It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.

2) In vitro drug release and duration of floating:

This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analysed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.

3) In vivo evaluation for gastro-retention:

This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc.

B. For Multiple Unit Dosage Forms [13]

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for:

(i) Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

(ii) Entrapment efficiency: The drug is extracted by a suitable method, analysed and is calculated from Practical amount of drug present.

(iii) In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours.

Advantages:[14]

1. The principle of HBS of FDDS can be used for any particular medicament or class of medicament.
2. The FDDS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed fromthe intestine e.g. Chlorpheniramine maleate.
3. The FDDS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

4. The efficacy of the medicaments administered utilizing the sustained release principle of FDDS has been found to be independent of the site of absorption of the particular medicaments.
5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the drug infloating condition in stomach to get a relatively better response.
6. FDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
7. Certain types of drugs can benefit from using FDDS.

These include:

a) Drugs acting locally in the stomach.
b) Drugs those are primarily absorbed in the stomach.
c) Drugs those are poorly soluble at an alkaline pH.
d) Drugs with a narrow window of absorption.
e) Drugs absorbed rapidly from the GI tract.
f) Drugs those degrade in the colon.

Disadvantages

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3. Furthermore, other drugs, such as isosorbidedinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

LIMITATIONS

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4. The drugs, which are absorbed throughout gastrointestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.
5. Some drugs present in the floating system causes irritation to gastric mucosa.[14]

Future Prospectives

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics.

Some of the unresolved critical issues related to the rational development of FDDS include,

i. The quantitative efficiency of floating delivery systems in the fasted and fed states;
ii. The role of buoyancy in enhancing GRT of FDDS; and the correlation between prolonged GRT and SR/PK characteristics.

FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibility arrives.

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