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FLOATING DOSAGE FORM IS A MEDICAL BOON IN THE DRUG DELIVERY SYSTEM

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ABSTRACT

Floating drug delivery system is a medical boon in the oral delivery system, because the drugs having narrow absorption window in the gastrointestinal tract or have poor absorption. There are several techniques like mucoadhesive systems, high density systems, floating drug delivery system, low density systems, superporous hydrogels and magnetic systems, have been formulated. Floating drug delivery systems (FDDS) or hydro dynamically 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 on the gastric contents, the drug is released slowly at the desired rate from the system is achive. In this system various dosage forms available like capsules, tablets, granules and microspheres etc by reviewing this article floating dosage forms is the current & recent developments / trends in the drug delivery system.

INTRODUCTION

The purpose of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. There are various routes for introduction the drug like oral, topical, rectal, vaginal and ocular, nasal, etc [1]. But out of these routes oral route of drug delivery is considered as the most favoured and practiced way of delivery, due to certain reasons. It Enhanced bioavailability, dose accuracy [2], Extended time over critical (effective) concentration, Site specific drug delivery ease of administration, Minimized adverse activity at the colon.

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Physiological Consideration

Stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm, its size varies according to the amount of distension up to 1500 ml following a meal, after food [3] has emptied, a collapsed state is obtained with resting volume of 25-50 ml. Anatomically the stomach is divided into 3 part body, fundus, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material [4], whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [5].

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

- Drugs that act locally in the stomach e.g., antacids and misoprostol.
- Drugs that are primarily absorbed in the stomach. e.g. calcium supplements, chlordiazepoxide and cinnarazine [6].
- Drugs those are poorly soluble at an alkaline pH.
- Drugs that have a narrow window of absorption. e.g., riboflavin and levodopa.
- Drugs that is unstable in the intestinal or colonic environment. e.g. ranitidine HCl and metronidazole [7].
- Drugs with variable bioavailability. e.g. sotalol HCl

PHASE OF GASTROINTESTINAL MOTILITY & EMPTYING OF FOOD [8]

Phase I (basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions.

Phase III (burst phase) lasts for 10 to 20 minutes. It is also known as the housekeeper wave. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine [9].

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state [10]. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state.

MECHANISM OF FLOATING SYSTEMS

These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems [11], modified shape systems, gastric-emptying delaying devices and co-administration of gastric.

(Figure A) The drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [12]. 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature [13]. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object [14]. The object floats better if F is on the higher positive side **(Figure B)**.

Capability variations

F = F buoyancy - F gravity

= (Df - Ds) gv---------- (1)

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and g = acceleration due to gravity.

FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM

Density – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density[15].

Size – Dosage form units with a diameter of more than 7.5 mm an increased GRT compared with those with a diameter of 9.9 mm [16].

Shape of dosage form – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI).

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 [17].

Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC [18].

Gender – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age – Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient.

Biological factors – Diabetes and Crohn's disease, etc [19].

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

A. EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates [20] (eg. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus it reducing the density of the system and making it float on the gastric fluid. These effervescent systems further classified into two types [21].

I. Gas generating systems

a. Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These are as shown in figure and formulated intimately mixing the CO2 generating agents and the drug within the matrix tablet [22]. 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 [23].

b. Intra gastric bilayered floating tablets

These are also compressed tablet as shown in figure and contains two layer i.e.,

i) Immediate release layer and ii) Sustained release layer [24].

c. Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers [25]. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer.

II. Volatile Liquid / Vacuum Containing Systems

a. 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 [26], which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.

b. Intragastric floating gastrointestinal drug delivery system

This system can be made to float in the stomach because of floatation chamber [27], which may be a vacuum or filled with air or a harmless gas, as shown in fig. 5.

c. Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floatingsupport in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery.

B. Non effervescent systems [28]

1. 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 maintain bulk density of less than unity.

2. Bilayer floating tablets

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid [29].

3. Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ehanol dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.

4. Alginate beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate [30]. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, which can maintain a floating force for over 12 hours.

Characterization Parameter of FDDS

1. Buoyancy / Floating Test [31,32]

The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaClwith 0.02% Tween 80, pH 1.2) or intestinal fluids (KH2PO4/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 370C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m2).The amount of time the dosage form floats is termed the floating time.

2. Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water up take. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time.

WU = (W1 – W0) x 100/WO

Wt= Weight of dosage form at time t, **W0** = Initial weight of dosage form

3. In Vitro Drug Release Studies [33]

The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37oC. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37oC.

5. Morphological and dimensional analysis

(i) The aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

(ii) % yield of microspheres [34]

This is calculated from Weight of microspheres obtained ×100 Total weight of drug and polymer

(iii) Entrapment efficiency [35,36]

The drug is extracted by a suitable method, analyzed and is calculated from: Practical amount of drug present ×100 Theoretical drug content.

APPLICATIONS [42]

1. 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.

2. Site-Specific Drug Delivery [37]

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.

3. 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 [38].

4. Osmotic Regulated systems [39]

It is comprised of osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric somatically controlled drug delivery device.

5. PVA-PVP Spray Dried Tablets [40]

These tablets shows immediate floating with almost no lag time, floating for 24 hr and do not sink. No swelling and erosion takes place in the GIT, so the release does not depend upon osmolarity of the medium.

6. Ion exchange resins Beads [41]

A coated ion exchange resin bead formulation has been shown to have gastric retention properties which were loaded with bicarbonates. Ion exchange resins were loaded with bicarbonate and a negatively charged drug is bound to the resin.

7. Micro particles

This approach is based on low-density foam powder. This system is advantageous because of its zero to negligible lag time before starting of floatation. These floating microcapsules prepared by emulsion solvent evaporation technique, contain polypropylene foam powder, polymers and model drug.

Table 1. Polymers used in FDDS:

Polymers used in FDDS

Natural	Synthetic
Sodium alginate	HPMC K4M
Pectin	HPMC K 15M
Tragacanth	HPMC K100M
Gelatin	Carbopol 934 p
Carragenan	Carbopol 934 p
Guar gum	Polyvinyl alcohol
Chitosan	Polyamides
Okra gum	Polycarbonates
Gellan gum	Polymethacylic acid

Table 2. Marketed formulations

Marketed Products of FDDS

S.No	Brand Name Drug (Dose)	Company,	Country	Remarks	Price
1	Cifran OD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating Floating tablet	78.00
2	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent Alginate, preparation	80.00
3	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Alginate preparation	90.00
4	Modapar®	Levodopa(100mg), Benserazide(25mg)	Roche, Products, USA	Floating CR capsule	92.5

Table 3. Patent in FDD

Patents for Some FDDS

US patent No.	Patent title
5,443,843	Gastric-retention system for controlled drug release
5,232,704	Sustained-release, bilayer buoyant dosage form
5,169,638	Buoyant controlled-release powder formulation
4,814,179	Floating sustained-release therapeutic compositions
4,767,627	Drug that can be retained in the stomach for a controlled period of time

Figure 1. Phase of gastrointestinal

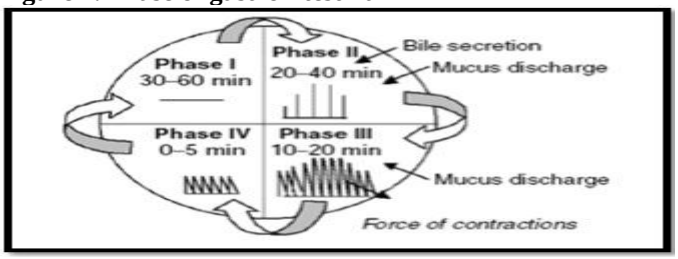


Figure 2. Mechanism of Floating systems

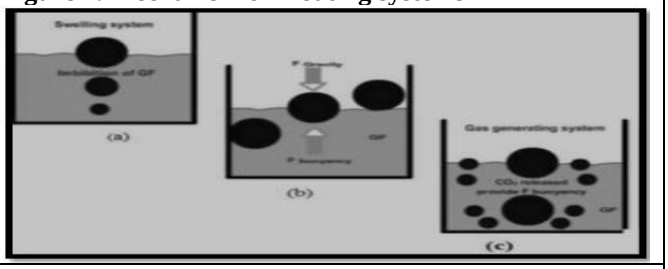


Figure 3. Multiple Unit of Oral FDDS

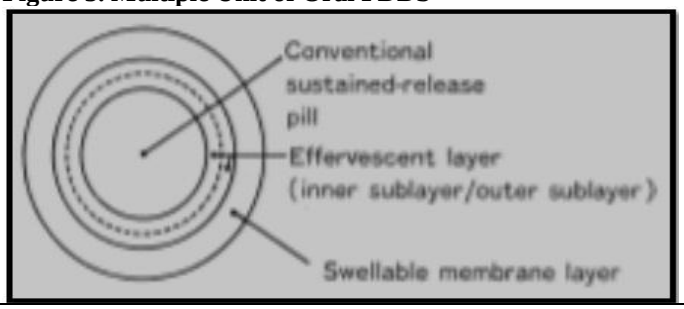


Figure 4. Working Principle of Effervescent FDDS

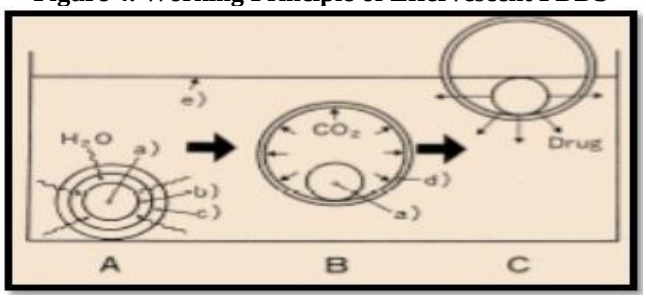


Figure 4. Inflatable gastrointestinal delivery systems

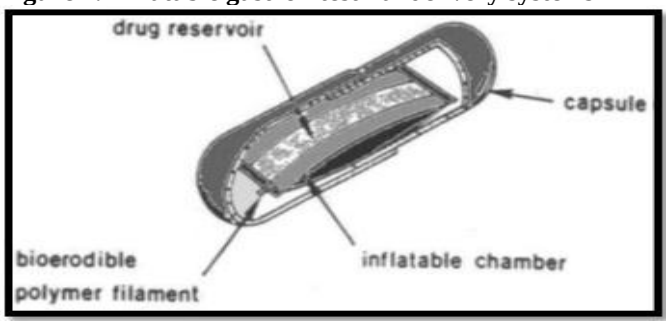


Figure 5. Intra gastric floating gastrointestinal drug delivery device

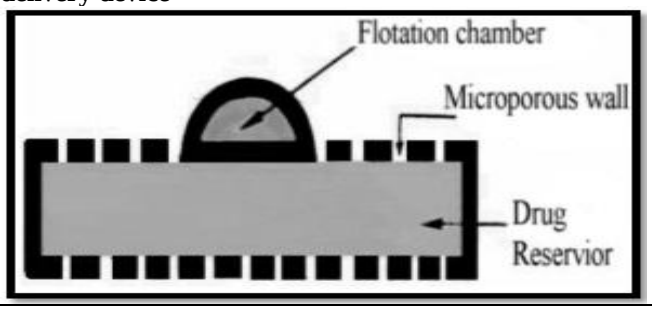


Figure 6. Intragastric osmotically controlled drug delivery system

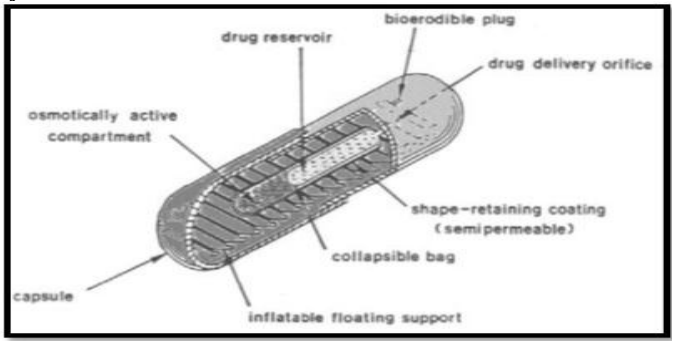


Figure 7. Microsphere

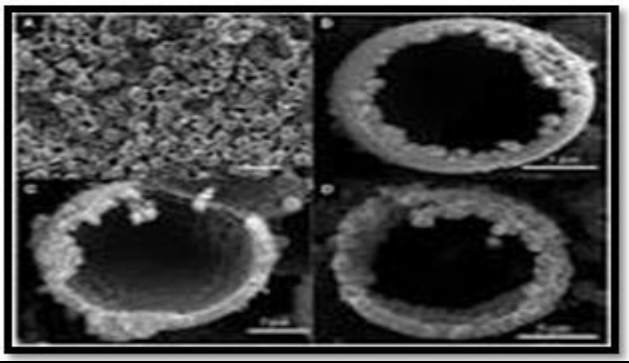
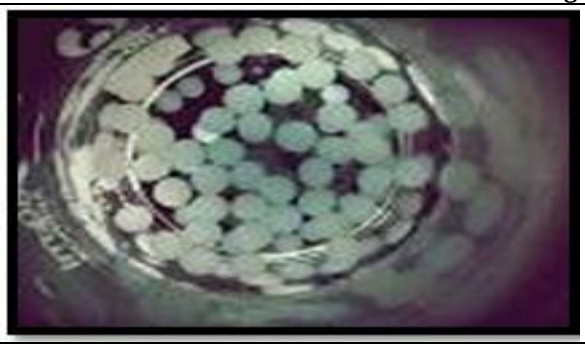


Figure 8. Beeds



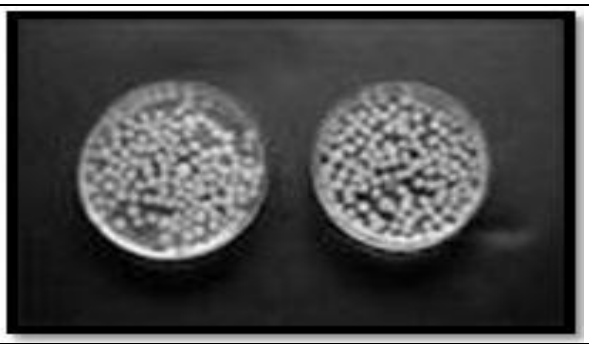


Figure 9. In vitro dissolution method

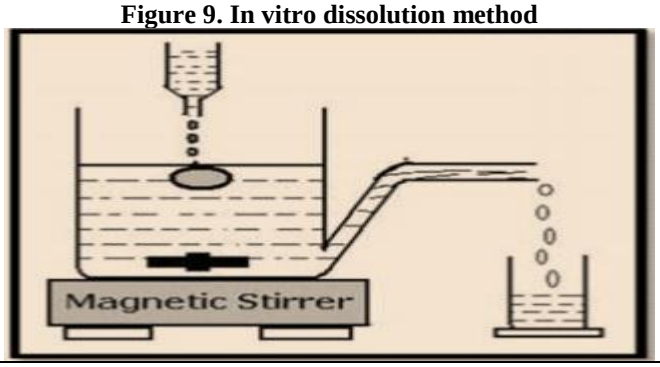
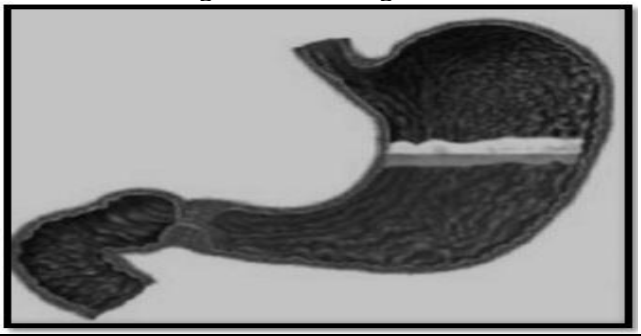


Figure 10. Floating Rafts



8. Lipid based sustained release matrix systems

Floating glycerol monooleate single-unit lipid matrix containing high drug: excipients ratio achieved sustained drug release. Hydrophobic lipid, gelucire 43/01 can be considered as an effective carrier for design of multiple –unit FDDS of highly water-soluble drugs.

9. Chitosan granules/Microcapsules

These are prepared by de-acidification process. When added to acidic and neutral media these granules were immediately buoyant and provide a controlled release of the drug.

10. Floating Rafts

This raft formulation based on an alginate biopolymer. On ingestion, this formulation reacts with gastric acid to form floating raft structure, which impedes the reflux of acid and food by acting as a physical barrier. It is used in the treatment of gastric oesophageal reflux. The raft has a pH value higher than that of the stomach contents so that in the event of gastric reflux, the wall of the oesophagus is not subjected to irritation by HCl. Sodium alginate solution reacting with gastric acid and this gel floats on the surface of the gastric contents due to CO2.

CONCLUSION

Floating drug delivery systems have plenty of advantages over the other drug delivery system. As floating drug delivery system provides a dosage form which is stable and provides a sustained release. In this system it enhances the dose frequency of drug.

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