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A review on Emerging Drug Delivery System: "Floating Drug Delivery System"

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ABSTRACT: In recent year, considerable attention has been focused on the formulation and development of new drug for orally targeted drug delivery systems. The oral route is most popular route of drug administration. Conventional dosage forms are unable to control either the rate or site of action. When a drug is delivered as a conventional dosage form they show very short gastric retention time. As such the drug which act locally in the stomach or get degraded by the colonic bacteria or/ and alkaline pH of the small intestine cannot be formulate as conventional dosage form. In conventional dosage forms, fluctuating drug level may lead to some side effect and dosing interval is short, this leads to poor patient compliance. The floating drug delivery systems are useful approach to avoid this variability with increase the retention time of the drug-delivery systems for more than 12 hours. Effervescent and non-effervescent are two class of floating drug delivery system and can formulate either in single unit dosage form or in multiple unit dosage form. Floating drug delivery system provides local delivery to specific region like stomach and proximal small intestine and it's also shows better bioavailability and improved therapeutic activity and substantial benefits to patients. The purpose of this paper is to review the concept of floating drug delivery systems with the recent literature and current technology used in the development of floating drug delivery system as well as summarizes evaluation method and applications of various floating dosage forms.

KEY WORDS: Gastro retention, FDDS, High density system, effervescent system, non-effervescent system, application and evaluation.

1. INTRODUCTION:

Oral delivery continues to be the most popular route of administration due to its versatility, ease of administration and probably most importantly patient compliance. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.[1,2] FDDS are significantly used for drugs that are locally act in stomach and small intestine and have narrow absorption window in small intestine region, unstable in the intestinal or colonic environment and shows low solubility at alkaline environment [3].FDDS have density lower than gastric fluid, due to which they have tendency to float over gastric contents for prolonged period of time without affecting gastric emptying rate. As the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.[4,5].

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Conventional controlled release dosage forms go downwards to the bottom of the stomach once ingested because their density is higher than that of gastric contents.[6] Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs which are less soluble in alkaline pH . [5,7] Floating drug delivery also used in sustained drug delivery, delivery of drug at specific site and in enhancement of absorption.

2. TYPES OF GASTRORETENTIVE DOSAGE FORM:-

1. **FLOATING SYSTEM** - Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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, 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. FDDS can be divided into non-effervescent and effervescent system.

A. NON EFFERVESCENT SYSTEMS

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four subtypes:

a. Colloidal gel barrier system-

Sheth and Tossounian first designated this 'hydrodynamically balanced system's. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorbtion sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the htdrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

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b. Microporous compartment system-

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

c. Hollow Microspheres-

Hollow microspheres are also known as microballoons. Hollow microspheres are prepared by emulsion solvent diffusion method. In this method a solution or dispersion of drug and polymer is prepared in solvent (like dichloromethane, ethanol, isopropanol or a combination of these). This dispersion/solution is introduced into an aqueous solution of PVA (polyvinyl alcohol) forming an O/W type emulsion. This emulsion is agitated using propeller type agitator to remove the organic solvent, which produces the microballoons, size between 500-1000 mm.

d. Alginate beads –

Multi-unit floating dosage forms have been developed from freezedried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40^{o}C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

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B. EFFERVESCENT SYSTEMS-

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

a. Volatile liquid containing systems-

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 PVA, 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 CO2 which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.31-35.

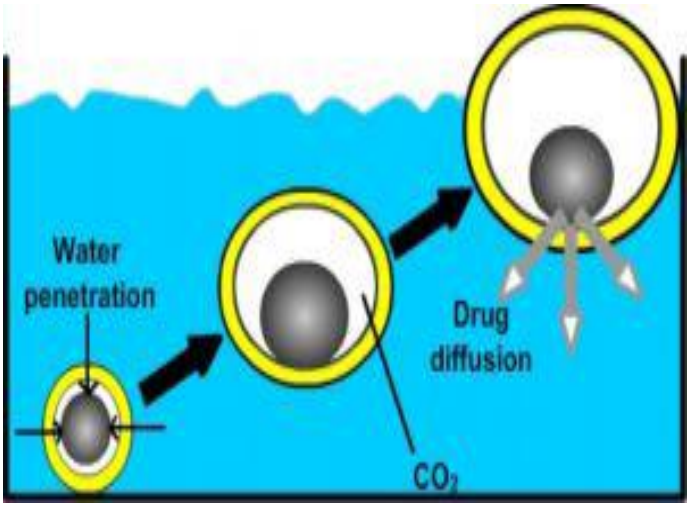

Fig. 1. Mechanism of floatation via CO2 generation.

2.1.1. ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:-[17]

- The bioavailability of drug is increases due to increased absorption with in stomach.
- Gastric retention time increases due to buoyancy principle.
- Drug releases in a controlled manner for prolonged period of time.
- Drugs are directly target to specific site in the organ.
- There is no risk of dose dumping because drug releases uniformly.
- Gastric irritation can be minimized, due to sustained release effect.
- Inter and intra subject variability is less.
- Minimizes the counter activity of the body leading to higher drug efficiency.
- There is no or minimum fluctuations in drug concentration, therefore, concentration
- dependent adverse effects can be reduced.
- Prolonged drug release extends the time period of effective concentration

2.1.2. DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS:[4-6]

- 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.
- Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
- Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

3. APPROPRIATE CANDIDATE DRUGS FOR FLOATING DRUG DELIVERY SYSTEM:[31]

- Drugs acting locally in the stomach: e.g. Antacids and Anti H. Pylori viz. Misoprostol.
- Drugs that are primarily absorbed in the stomach: e.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH: e.g. Furosamide, Diazepam, Verapamil, etc.
- Drugs with a narrow absorption window: e.g. Cyclosporine, Levodopa, Methotrexate
- Drugs which are absorbed rapidly from the GI tract: e.g. Metronidazole, tetracycline.
- Drugs that degrade in the colon: e.g. Ranitidine, Metformin.
- Drugs that disturb normal colonic microbes: e.g. antibiotics against Helicobacter pylori.

4. APPROACHES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM:-[29]

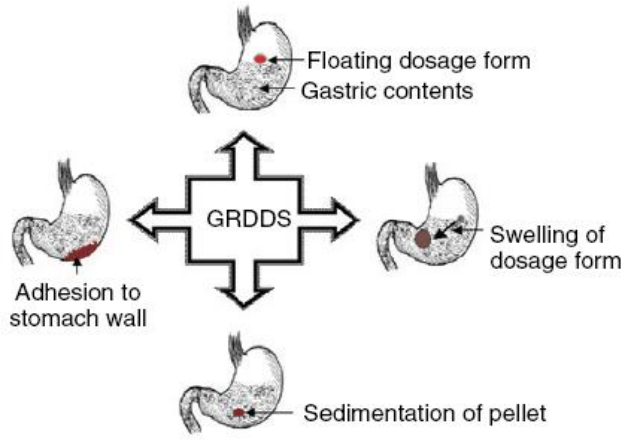

Fig.2. Approaches of gastro-retentive drug delivery system

4.1. Bioadhesive or Mucoadhesive Drug Delivery Systems[3, 27]

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach.

4.2. Expandable, Unfoldable and Swellable Systems [3, 7, 11, 26]

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. An expanded gastroretentive form, and a final small form enabling evacuation following drug release from the device.

4.3 High-density systems[2, 3, 26]

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc.

4.4 Floating Drug Delivery Systems[3, 11]

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period.

5. FORMULATION DESIGN:-

The design of floating drug delivery system formulation depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physicochemical factors include molecular weight, lipophilicity and molecular charge; an anatomical and physiological factor of stomoch, pH of stomach & intestine.

6. APPLICATION OF FLOATING DRUG DELIVERY SYSTEM:-

6.1. Sustained Drug Delivery[2,3,8,]

problems such as gastric residence time in the GIT encountered with oral control release formulations can be overcome with the hydrodynamically balanced system (HBS) systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo.

6.2. Bioavailability Enhancement [3,8]

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. [8, 11] The absorption of bromocriptine is limited to 30% from the gastrointestinal tract. However a hydrodynamically balanced system (HBS) of the bromocriptine can enhance the absorption.

Table 1: List of drugs used in formulation of floating drug delivery system [19,22,23,24]

Floating Microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen (37), Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast (38) and Terfenadine. (39)
Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin trihydrate, Atenolol, Sotalol,Fluorouracil, Isosorbide dinitrate,Isosorbide mononitrate (40), Para – amino benzoic acid, Piretanide (41), Theophylline, Verapamil HCl, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol (1), Pentoxyfilline and Diltiazem HCl, Furosemide,Ciprofloxacin,Captopril,Nimodipine,Cinnarizine,Riboflavin-5phosphate.
Floating Granules	Diclofenac sodium, Indomethacin and Prednisolone
Films	Cinnarizine (42), Albendazole.
Floating Capsules	Nicardipine, Chlordiazepoxide HCl, Diazepam (43), Furosemide, Misoprostol, L-Dopa, Benserazide Ursodeoxycholic acid (44) and Pepstatin, and Propranolol.
Powders	Several basic drugs.

Table 2: Marketed Formulations of Floating Drug Delivery System [1,21,22]

S.No	Brand Name	Drug	Dosage Form
1.	Topalkan	Aluminium - Magnesium antacid	Floating Liquid Alginate Preparation
2.	Liquid Gavison	Aluminium hydroxide, Magnesium Carbonate	Effervescent Floating Liquid Alginate Preparation
3.	Valrelease	Diazepam	Floating Capsule
4.	Madopar	Levodopa, Benserazide	Floating Controlled Release Capsule
5.	Cifran OD	Ciprofloxacin	Gas-generating Floating Tablets
6.	Conviron	Ferrous sulphate	Colloidal Gel Forming FDDS
7.	Cytotec	Misoprostal	Bilayer Floating Capsule
8.	Amalgate Float Coat	Antacid	Floating Dosage Form

Table 3: Polymers Used in Different Approaches to Design Floating Dosage Forms of Drugs [1,19,21,22]

S.No	Drug(s)	Dosage form	Polymers used
1.	Domperidone maleate	Tablet	Methocel K4M, K100M
2.	Loratidine	Floating beads	Pectin, Sodium Alginate, Ethyl cellulose
3.	Glipizide	Tablet	EudragitRS100, HPMCK4M
4.	Nimesulide	Tablets	Guar gum, Carbopol, HPMC low and high Viscosity
5.	Paracetamol	Capsules	Guar gum ,Sodium CMC, Methyl Cellulose, PVP K30, HPMC(K4M, K15M, K100M)
6.	Celiprolol HCl	Capsule	HPMC (K4M, K15M, K100M), EC,Polyethylene oxideWSR- 60K
7.	Piroxicam	Microspheres	Eudragit S 100
8.	Aspirin, Griseofulvin, p-Nitroaniline	Polycarbonate Microspheres	Bisphenol
9.	Ranitidine HCl	Tablet	HPMC K4 M, Guar gum, Xanthan gum
10.	Rosiglitazone maleate	Microspheres	Acrylic polymers

7. EVALUATION AND CHARACTERIZATION OF FLOATING DRUG DELIVERY SYSTEM:- [24,25,26]

7.1. Particle size analysis [24]

The size of 300 particles of each batch was measured by using a calibrated micrometer
attached with a microscope and the average diameter was calculated.

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7.2. :- Test for buoyancy[24]

The microspheres (200 mg) were transferred to a series of six 500 ml beakers containing 400 ml of simulated gastric fluid without enzymes maintained at 37 ◦C. The content of the beakers was stirred at 100rpm by magnetic pellet. At different time intervals (2, 4, 6, 8, 10,12 h) floating and non-floating microspheres were separated, dried at 45 ◦C until a constant weight is obtained. Then the microspheres were weighed and percentage of buoyancy is
calculated by using following equation 1

Buoyancy (%) = Qf / Qf + Qs

Where Qf =weight of floating microspheres, Qs= weight of settled microspheres collected at different time intervals.

7.3. :- Scanning electron microscopy[24]

The sample for the scanning electron microscopy (SEM) analysis was prepared by sprinkling the microspheres one side of double adhesive stub. The stub was then coated with gold using Jeol JFC 1100 sputter coater. The SEM analysis of the microspheres was carried out by using
Jeol JSM 5300, Japan. The microspheres were viewed at an accelerating voltage of 15 kV.

7.4. Determination of drug loading and encapsulation efficiency[27]

The drug content in the microsphere can be determined by pulverising the drug loaded microspheres (10 mg) and then immersing into 100ml simulated gastric fluid (pH 1.2) with agitation at room temperature for 12 h. After filtration through membrane filter drug concentration can be determined by spectrophotometer at appropriate wavelength. The filtered solution from empty microsphere (without drug) taken as blank. Then drug loading
and encapsulation efficiency can be calculated by the following equation 2 and 3

DL (%) =WD x 100/ Wt

DL= drug loading, WD = the weight of the drug loaded in the microsphere, WT = the total weight of the microspheres.

Equation 3

EE (%) =WA x 100/WT

EE=encapsulation efficiency, WA= Actual drug content, WT = theoretical drug content.

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7.5. In vitro drug release studies[28]

In vitro drug release studies performed in USP type II apparatus at 50 rpm maintained at 37 ±5C. A capsule is placed into 900 ml of 0.1 N HCl (pH 1.2). Then 5 ml sample withdrawn from the dissolution vessel at specific time intervals and replaced with equivalent volume of fresh medium. Then samples were filtered by using Whatmann filter (Grade I) paper and then, determine drug concentrations by using spectrophotometer, against a blank.

7.6. Floating lag time and total floating time determination [16].

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 M HCl maintained at 37o C, by using USP dissolution apparatus containing 900 ml of 0.1 M HCl as the dissolution medium.

7.7 Swelling studies[29]

A known weight of microsphere without drug was placed in 500 ml of different solutions : distilled water and enzyme free simulated ggastric fluid (pH 1.2) andand allowed to swell for sufficient time at 37±0.50 using the USP type 1 dissolution apparatus at 50 rpm. The microspheres are removed , blotted with filter paper and their change in weight were measured during swelling untill equilibrium was attained. Finally the weight of swollen microsphere was recorded after 4 h and swelling ratio(SR) was calculated by the following formula 4

SR = WE-Wo/Wo

Where, WE= weight of the swollen microsphere at equilibrium state, Wo = initial weight of dry microsphere.

7.8 Stability studies [30]

Stability studies were performed to check the effect of environmental or storage conditions on formulation. Sample was kept in accelerated stability condition at 40°C temperature 75 ± 5% relative humidity for 3 months as per International Conference on Harmonization (ICH) guidelines. The samples were withdrawn at 1, 2, and 3 months intervals evaluation was carried out for appearance, thickness, hardness, friability, buoyancy lag time, drug content, floating behaviour, and cumulative% drug released.

7.9. Fourier transformer infra red:-[23]

The possibility of drug excipient interaction is investigated by FTIR studies. The FTIR graph of pure drug & combination of drug with excipient are recorded by using KBR pellets.

7.10. Thermal analysis:-[27]

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in drug & excipient Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction.

8. CONCLUSION:-

Among various types of gastro retentive system floating drug delivery system(FDDS) is most promising. Floating drug delivery system can be prepared by two different approaches effervescent and non effervescent system. The drug which act locally in the stomach or get degraded by the colonic bacteria or alkaline pH of the small intestine can be delivered by formulating floating dosage form. The dosage form retains at the site of absorption for prolong period of time and there by increase the bioavailability of drug. It exhibit good stability and better drug release than other conventional dosage forms.

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