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RESEARCH ARTICLE

FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Recent technological and scientific research has been devoted to the development of rate-controlled drug delivery system to overcome physiological adversities such as unpredictable gastric emptying times and gastric residence time. FDDS are of particular interest of drugs that are locally active and have narrow absorption window in stomach. FDDS offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are least soluble in a high pH environment. This review summarizes the design of the FDDS systems, factors that affect floating system, advantages, limitations, evaluation parameters and applications.

Introduction:-

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes[1]. Among the many oral route of administrations, floating drug delivery attains much attention to the researcher to develop and deliver the drugs which are highly soluble at acidic environment and drugs which are unstable at alkaline environment. The concept of floating drug delivery systems (FDDS) was first described in the literature in 1968 when Davis developed a method for overcoming the difficulty experienced by persons of gagging and choking while swallowing medicinal pills. He suggested that such difficulty could be overcome by providing pills with a density of less than 1g/cm such that the pill will float on the surface of water. FDDS are low-density systems that have sufficient buoyancy float over the gastric contents and remain in the stomach for a prolonged period. FDDS are preferred as they are economic and has improved patient compliance and they are advantageous for drugs absorbed from the stomach[2]. Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract[3]. A modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs- acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values[4]. To formulate a successful gastroprotective drug delivery system, several techniques are currently used such as floating drug delivery system, low density systems, raft systems incorporating alginate gel, bio adhesive or mucoadhesive systems, high density systems, superporous hydrogel and magnetic system. Among these, the floating dosage forms have been most commonly used[5]. Floating dosage forms may be made as tablets or capsules by using appropriate excipients and including gas-generating agents, which give the dosage form buoyancy in gastrointestinal fluids[6].

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Approaches to Gastroretention:
Several techniques are reported in the literature to increase the Gastroretention of drugs[7-10]. Among many few major approaches are listed below.

High Density systems:
These systems which have density of ≥3g/cm^3, are retained in the stomach rugae of stomach and capable withstanding its peristaltic movements[11]. The only major drawback with these systems is that it is technically difficult to manufacture them with large amount of drug (>50%) and to achieve required density of 2.4-2.8g/cm^3. Diluents such as barium sulphate, zinc oxide, titanium oxide and iron powder must be used to manufacture such high-density formulations[11].

Swelling and Expanding systems:
These systems are also as "Plug type systems", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in the fed state[12].

Mucoadhesive and bioadhesive systems:
Mucoadhesive and bioadhesive systems are used to localize the deliver with device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to epithelial surface in the stomach. Some of most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin etc,[13-14].

Low density systems:
Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation[22].

Classification of FDDS based on mechanism of bouncy:
Non effervescent systems:
These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC) is the most commonly used excipient; although ethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl agar, carrageen or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces floating mass[15-16]. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy[17]. Incorporation of fatty excipients gives low-density formulations and reduced penetration of water, reducing the erosion. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile[18]. Non effervescent system further classified into

1. Colloidal gel barrier system / Hydrodynamically balanced systems (HBS)
2. Microballoons / Hollow microspheres.
3. Alginate beads.
4. Microporous compartment system.
5. Layered tablets.

Effervescent systems:
These are matrix type systems prepared with the help of swellable polymers such as Hydroxypropyl methyl-cellulose or polysaccharides and chitosan and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, Carbon dioxide is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the do-sage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet[19]. effervescent system further classified into:

1. Gas generating system
2. Volatile/Vacuum containing systems[20].

Raft Forming system:
Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrappedCO2 bubbles oncontact with gastric fluid. Formulations also

typicallycontain antiacids suchas aluminiumhydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatmentas with Liquid Gaviscon (GlaxoSmithkline)[21].

Advantages of floating drug delivery system[23-25].

1. Increases the oral bioavailability of drug.
2. Enhanced first pass biotransformation.
3. Sustained drug delivery/ reduced frequency of dosing.
4. Reduced fluctuations of plasma drug concentration.
5. Improved receptor activation selectivity.
6. Provide higher efficiency due to reduced counter-activity of body.
7. Extended time over critical (Effective) concentration.
8. Minimized adverse activity at the colon.
9. Targeted therapy for local ailments within the upper GIT.
10. Site specific Drug Delivery.

Limitations of floating drug delivery system[26-30].

1. Drugs having solubility or stability problem in GIT aren't suitable for FDDS.
2. Drugs like Nifedipine, Propranolol etc. which are well absorbed throughout GIT and which undergoes first pass metabolism aren't be desirable candidate.
3. Drugs which are irritant to Gastric mucosa also are not desirable.
4. Drugs that are unstable in the acidic environment of the stomach aren't suitable in this type of systems.
5. High level of fluid in the stomach is required for maintaining buoyancy; float and work efficiently.

Factors affecting on floating drug delivery system:

1. **Density of tablets:** Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluid's floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities[31].
2. **Shape and shape of dosage form:**Size and Shape: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes[32].
3. **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[33].
4. **Nature of the meal and caloric content:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release[34] GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.
5. **Age:**Elderly people, especially those over 70, have a significantly longer; floating. Disease condition such as diabetes and crohn's disease etc also affect drug delivery[35].
6. **Posture:** Floating can vary between supine and upright ambulatory states of the patient[36].
7. **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[37].

Manufacturing methods of floating drug delivery system:

The floating tablets are manufacture based on drug and excipients properties, duration intended for(immediate or sustained), stability of drug (against, temperature, oxidation, etc.,) and feasibility using below methods

1. Direct compression
2. Wet granulation
3. Dry granulation

Evaluation Of Floating Dosage Forms:

Drug-excipient (DE) interactions:

This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the DE interaction. Apart from the above mentioned evaluation parameters, for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy[38-39].

Precompression and post compression parameters:

The precompression parameters like angle of repose, bulk density, hausner ration, compressibility index and post compression parameters like hardness, friability, uniformity of weight should be monitored as per pharmacopeial standards.

Morphology and surface topography:

The surface topography and structures were determined using scanning electron microscope (SEM) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer[40].

Floating Lag Time / Total Floating Time:

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 / flotation time/ Total floating time. These tests are usually performed in Simulated Gastric Fluid (SGF) or 0.1 N HCl (900ml) maintained at 37°C, by using USP dissolution apparatus as the dissolution medium[41].

Tablet swelling indices:

Tablet are weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5° C. At regular time intervals, the tablet are removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet are then reweighed (W2). The swelling index (SI) is calculated using the formula:

$$\text{Swellingindex} = \frac{W2 - W1}{W1}$$

Where, W2 = Final Weight, W1 = Initial Weight

Specific gravity:

Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium[42-43].

Weight gain and water uptake:

Weight gain or water uptake can be studied by considering the swelling behaviour of Floating dosage form[44].

Entrapment efficiency:

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the pre-pared formulations. The drug is extracted by a suitable method, analysed and is calculated from[45]:

$$\text{Entrapment efficiency} = \frac{\text{Practicaldrugloading}}{\text{Theoreticaldrugloading}} \text{X } 100$$

Drug release:

The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. Dissolution tests are performed using the USP dissolution apparatus[46].

Pharmacokinetic studies:

Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration(Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance[47].

Table I:- List of marketed formulation available in market[50].

Brand name	Drug (dose)	Company, country	Dosage form
Madopar®	Levodopa(l00mg), benserazide(25mg)	Roche Products, US	Floating controlled release capsule
Valrelease®	Diazepam (15mg)	Hoffmann-La Roche, US	Floating capsule
Liquid Gaviscon®	Al. hydroxide (95mg), Mg. carbonate (358mg)	GlaxoSmithKline, India	Raft-forming liquid alginate preparation
Topalkan®	Aluminium-magnesium antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
Conviron®	Ferrous sulphate	Ranbaxy, India	gel-forming floating system
Cifran OD®	Ciprofioxacin (500mg & 1g)	Ranbaxy, India	Gas-generating floating tablet
Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas-generating floating tablet
Cytotec®	Misoprostol (100ng/200|.ig)	Pharmacia, US	Bilayer floating capsule

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[48-49].

Conclusion:-

Developing an efficient FDDS is a real challenge and the drug delivery system must remain for a sufficient time in the stomach. Various techniques and approaches have been employed to develop FDDS has emerged as one of the most promising gastro-retentive drug delivery system. we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

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