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REVIEW ARTICLE **OPEN ACCESS**

Floating Drug Delivery System : An Updated Systematic Review

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ABSTRACT
The oral drug delivery systems are often associated with variable and short gastric emptying time, which results in incomplete drug release from the delivery system. It certainly leads to diminished efficacy of administered dose. Floating drug delivery systems can retain the dosage form in the gastric region for several hrs. Designing them for prolonging gastric retention helps in improving bioavailability and it also helps in improving the solubility of the drug that are less soluble in a high pH environment. These are applicable for drugs having poor bioavailability because of the narrow absorption window in the GIT. They are known for increasing the bioavailability of the drug by retaining the dosage form at the site of absorption. This review emphasizes on information on the basis of their design, classification, advantages, evaluation, and future scope of floating drug delivery.
Key words: Floating drug delivery system, gastric emptying time, bioavailability.

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INTRODUCTION

The oral drug delivery systems exhibit variable and short gastric emptying time, which result in incomplete drug release from the delivery system. This leads to diminished efficacy of administered dose. To overcome these problems gastro retentive drug delivery systems are used [1]. Oral in situ gel forming system is also known as stomach specific controlled drug delivery system with enhanced gastro retention. This system is a liquid before administration and then converts into gel form that will float on stomach when it comes in contact with it. There are different approaches for the development of in situ gelling system. Examples are ionic cross linking, pH dependent, and temperature dependent. Simply alginic acid undergoes gelation in presence of divalent or polyvalent ions like calcium and magnesium.[2]
Gastro retentive drug delivery systems are the systems which are capable to prolong the retention time of the dosage form in the gastric region and improve the bioavailability of drugs that are mainly absorbed from upper GIT (duodenum and stomach). Gastro retentive systems are remain in the gastric region for longer period and therefore significantly extend the gastric residence time of drugs so that increase bioavailability, reduce drug waste, and improve solubility of drugs that are less soluble in alkaline environment. They prolong dosing interval, so that increase patient compliance. For delivery of sparingly soluble and insoluble drugs gastro retentive dosage forms (GRDF) are chiefly effective. Drugs having narrow absorption window in GI tract and give local action in upper part of small intestine are suitable for GRDDS. They are advantageous for the treatment of peptic ulcer disease. One of the most possible approaches for achieving a prolonged drug delivery in the GI tract is to control the gastric residence time by making gastro retentive floating drug delivery system. Floating drug delivery systems applicable for drugs having poor bioavailability because of narrow absorption window in the GIT. Floating drug delivery systems increase the bioavailability of drug by retains the dosage form at the site of absorption.[3-7]

BASIC PHYSIOLOGY OF STOMACH

Stomach is anatomically divided into three portions: Fundus, body and antrum (pylorus). The proximal stomach have fundus and body, serves as a reservoir for material ingested and the distal stomach is site of mixing. Gastric emptying process occurs during fasting and fed state. The pattern of motility is different in these two states. Fasting state is characterised by an interdigestive series of electrical events which cycle through the stomach and small intestine every 2-3 h. This activity is called the interdigestive myoelectric cycles or migrating myoelecric complex (MMC). MMC have four consecutive phases.[7,8]
Phase I - Quiecent period lasting from 40 to 60 min with rare contraction.

Phase II- Period of similar duration consisting of intermittent action potentials and contractions, that gradually increase in intensity and frequency as the phase progress.
Phase III- Short period of intense, contraction lasting from 4 to 6 min. The cycle in this phase is called "housekeeper" wave, for the reason that it sweep undigested materials out of the stomach.
Phase IV- Brief transitional phase, that occurs between phase III and phase I of two consecutive cycles.[9]
Approaches to gastroretention:
1. High density approach:
These systems have density higher than the stomach fluid (1.004 g/cm3). It would be at least 1.50 g/cm3. These systems are able to withstand peristaltic movement and retained in the stomach for several hours. These system can be manufacture by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder, etc.[9,12,16]

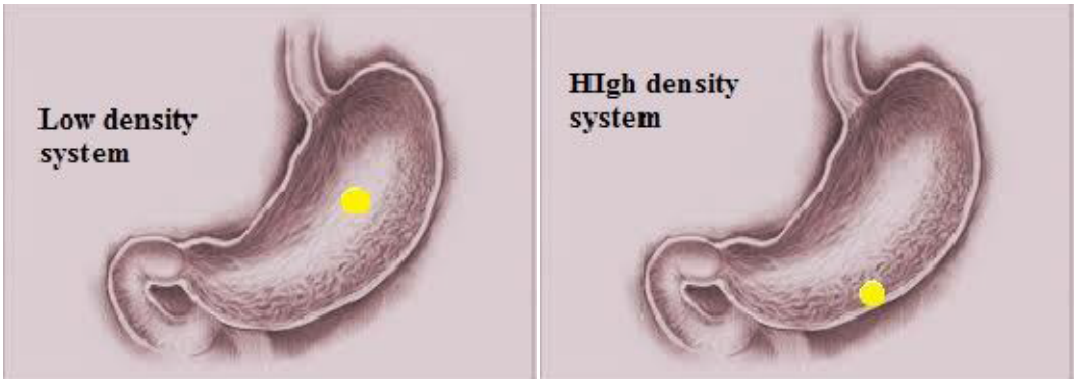

Fig. 1- Low density system and High density systems

Mucoadhesive Drug Delivery System:
Mucoadhesive drug delivery systems are designed to localize a delivery device within the lumen to increase the absorption and retention time of drugs in a specific site. Mucoadhesive drug delivery system offer drug release at controlled manner. They bypass the first pass metabolism and avoid degradation of GI enzymes and have good surface area so that they give rapid absorption and good bioavailability. The concept of mucoadhesive polymer to extend the GI transit time is shown in figure 2. Bio adhesive or mucoadhesive polymers are natural or synthetic polymers capable of producing an adhesive interaction with a biological membrane or with the mucus lining on the GI mucus membrane. Some Bioadhesive or mucoadhesive polymers are- Polycarbophil, Carbopol, Pectins, Chitosan, HPMC, CMC and Gliadin, etc.[17,18]

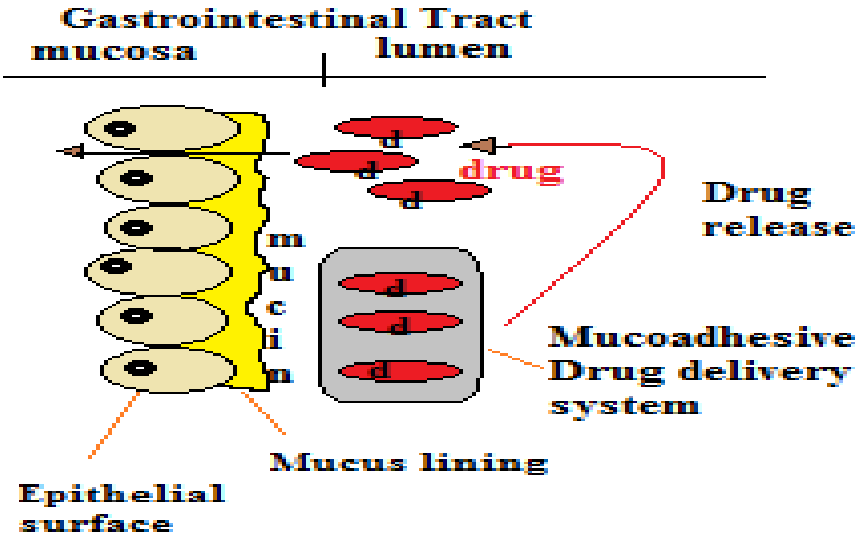

Fig 2: Interaction of a mucoadhesive drug delivery system with the mucus layer on the gastrointestinal surface epithelium.

Swelling and Expandable systems:

If a dosage form is bigger than the pyloric sphincter it will withstand the gastric transit. But the dosage form must be small to be swallowed. There is three configuration are required-A small size for swallowing, An expanded form for gastroretention and finally a small form for evacuation[11] . After swallowing these systems are swells to an extent that prevent their exit from the stomach through the pylorus. These systems are also called as "Plug type systems", since they have tendency to remain logged at the pyloric sphincters[9]. Polymers selected with the proper molecular weight and swelling properties then controlled and sustained drug release can be achieved. When polymers come in contact with gastric fluid, the polymer imbibes water and swells. The swelling of these polymers is due to presence of physical-chemical cross links in the hydrophilic polymer network.[16]

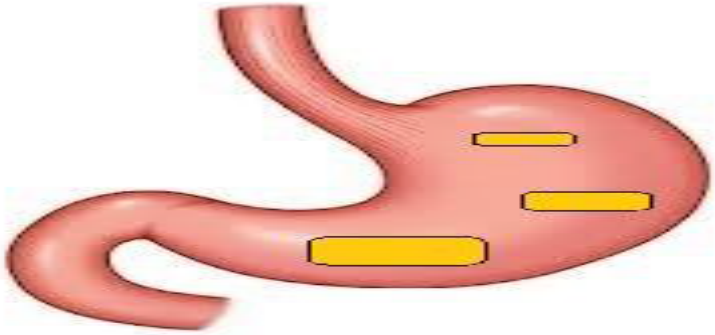

Fig.-3: **Swellable tablet in stomach**

Magnetic Systems:

In Magnetic systems dosage forms hold a small internal magnet and another magnet positioned on the abdomen externally. The problem in this system is that, the external magnet must be placed at the right position with a degree of precision.[7-13]

Superporous Hydrogel:

They are swellable system. They have average pore size >100 micro meter, absorption of water is very fast by capillary wetting, with the help of pores, so that they swell and reach to an equilibrium size within a minute. They have adequate mechanical strength to withstand the pressure by gastric contraction. They are formulated by hydrophilic particulate material Ac-Di-Sol (Crosscarmellose sodium)[12].

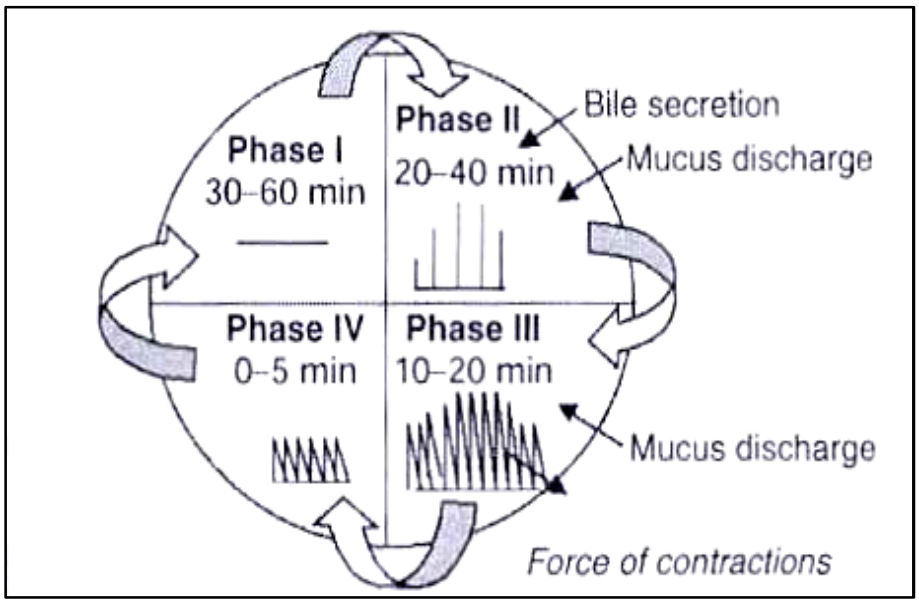

Fig. no. 4 : Motility pattern in GIT

Factors affecting gastric residence time of floating drug delivery systems:

a) Formulation factors:

Size of tablets

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves [14].

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 fluids 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 [16].

Shape of tablets

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr.[13]

Viscosity grade of polymer

Drug release and floating properties of floating drug delivery systems are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.[14]

b) Idiosyncratic factors

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 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[17].

Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT[17].

Posture

i) Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size 14. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements [17].

ii) Supine position

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects [17].

Concomitant intake of drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of floating drug delivery systems. The coadministration of GI-motility decreasing drugs can increase gastric emptying time [17].

Feeding regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins [9].

Conventional drug delivery system	Gastro retentive drug delivery system
More side effect.	Less side effect
Patient compliance is less	Improves patient compliance
Not appropriate for delivery of drugs with narrow absorption window in small intestine region.	Appropriate for delivery of drugs with narrow absorption window in small Intestinal region.
Not much beneficial for drugs Exhibit local action in the stomach. Degrade in the colon. Having rapid absorption through GIT	Beneficial for drugs Exhibit local action in the stomach. Degrade in the colon. Having rapid absorption through GIT
No risk of dose dumping.	High risk of dose dumping
Less gastric retention time.	Improve gastric retention time

Table No.1 Comparison between Conventional and Gastro retentive drug delivery system[12,13]

Suitable drugs for gastro retention:

Sustained release in the stomach is useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Drugs that have narrow absorption window in gastrointestinal tract (GIT), e.g., riboflavin, para amino benzoic acid, furosemide and levodopa.
2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and misoprostol.
5. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl and metronidazole.
6. Drugs that exhibit low solubility at high pHvalues e.g. diazepam, chlordiazepoxide and verapamil HCl [18].

Classification of floating drug delivery systems based on mechanism of buoyancy:

A) Single unit

- Non effervescent systems
- Effervescent systems or gas generating systems

B) Multiple unit

- Non effervescent systems
- Effervescent systems
- Floating microspheres

C) Raft forming systems

D) Low density system

Approaches to floating drug delivery system:

Various types of floating system have been developed which may involve generation of effervescent or non effervescent.

Hydrodynamically Balanced System:

Single unit system (e.g. Hydrodynamically balanced system) may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract. The hydrodynamically balanced system in either capsule or tablet form, is designed to prolong GI residence time. Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Ethyl Cellulose (HEC), Hydroxy Propyl Cellulose (HPC), Sodium Carboxy Methyl Cellulose (NaCMC), Agar, Carrageenans or Alginic acid are the excipients used in the formulation of HBS. The drug and polymer mixed together and administered in gelatin capsule. The capsule is rapidly dissolve when comes in contact with gastric fluid and the hydrocolloids in the floating device start to become hydrate and form a colloidal gel barrier around its surface with thickness growing with time. These gel barrier controls the rate of fluid penetration into the device and consequent drug releases from the barrier. The gel barrier act as a reservoir for sustained release of drug. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density less than 1 and remain buoyant in the stomach for up to six hours. The working principle of HBS is shown in figure 5.[9,19]

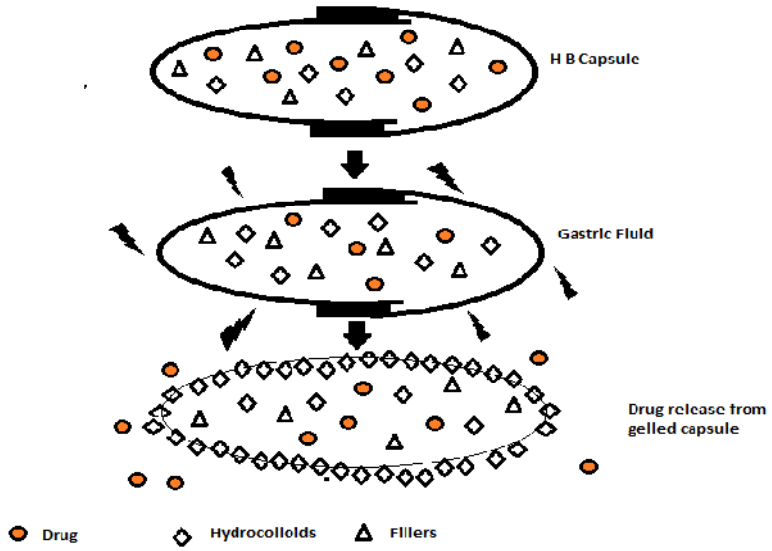

Fig. 5-Working Principles of Hydrodynamically Balanced System

Gas generating system (Effervescent System):

These systems are prepared with swellable polymer such as methylcellulose, chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. When they are come in contact with gastric fluid CO_2 is librated and get entrapped in swollen polymer which provide buoyancy to the system. The system consisted of sustained release pills and the pill surrounded by two layers. The inner layer was an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Furthermore, the effervescent layer was separated into two sub layers to avoid direct contact between tartaric acid and sodium bicarbonate. Tartaric acid was contained in the outer sub layer and sodium bicarbonate was contained in the inner sub layer. When the system was immersed in a buffer solution at 37^0C, a swollen pill was formed, having a density less than 1g/ml. The neutralization reaction occurs between effervescent layers, and CO2 gas evolved. The system was found to float completely within 10 min.[9,11,21]

(A) A multiple-unit oral floating dosage system,

(B) Stages of floating mechanism

Raft forming system:

In Raft forming system, a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonate) when comes in contact with gastric fluid, swell and form a viscous cohesive gel and forming a continuous layer called a raft. Because of low bulk density created by the formation of CO2, this raft floats on gastric fluids. Floating raft act as a barrier to prevent the reflux of gastric contents into oesophagus so that they are used for gastroesophageal reflux treatment e.g. Liquid Gaviscon (GlaxoSmithKline)[11,16]

Low density system: The limitation of the gas generating system is that, they have a lag time before floating on the gastric fluid, so that dosage form may undergo premature evacuation from the stomach. Therefore, low density system (<1 g/cm3) have been developed, which exhibit immediate floating. They are composed of low density material entrapping oil or air [11]. In this approach, the density of the device should be less than the density of gastric fluid i.e. 1 g/ml, so as to float in the gastric fluid of stomach for a prolong period of time without affecting the gastric emptying rate. As the system is floating on the gastric contents, the drug is released slowly for longer period of time. After release of drug, the left over system is emptied from the system.[12]

TYPES OF FLOATING DRUG DELIVERY SYSTEM

A. Single unit system

Single unit system (e.g. Hydrodynamically balanced system) may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract. These systems are unreliable in prolonging the GRT owing to their 'all-or-nothing' emptying process.[20]

B. Multiple unit system

Multiple-unit systems (e.g. microspheres) are passing through the GIT uniformly. They avoid the 'all-or-none' gastric emptying nature of single unit system. They reduce inter subject variability in

absorption and risk of local irritation. A variety of multiple-unit floating systems are based on various principles, such as air compartment multiple-unit system, micro particles based on porous carriers, hollow microspheres (microballoons), oil-entrapped gel beads prepared by gelation method. [28,29]

Advantages of floating dosage form:

(1) 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.

(2) The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

(3) The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.

(4) Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.

(5) Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

(6) 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.

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

(1) A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

(2) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

(3) Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.

(4) Drugs which are irritant to Gastric mucosa are also not desirable.

(5) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems[31].

***In vitro* and *in vivo* evaluation parameters of stomach specific floating drug delivery systems:**

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence *in vitro* floating behavior show prolonged gastric residence *in vivo*. Although, in vitro floating behavior alone is not sufficient proof for efficient gastric retention so *in vivo* studies can provide definite proof that prolonged gastric residence is obtained.

1) Hardness, friability, assay, content uniformity (Tablets)

These tests are performed as per described in specified monographs.

2) Floating lag time and total floating time determination

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.[31]

3) Drug release

The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^0C. Dissolution tests are performed using the USP dissolution apparatus.[31]

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry.[31]

5) Resultant weight determination.

Bulk density and floating duration have been the main parameters to describe the adequacy of a dosage form's buoyancy Although single density determination does not predict the floating force evolution of the dosage form because the dry material of it is made progressively reacts or interacts with in the gastric fluid to releaseits drug contents.

6) Weight gain and water uptake (WU)

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form.

7) XRay/ Gamma scintigraphy

For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form.[32]

8) 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.[33]

9) Specific Gravity

Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium.[35]

Brand Name	Drug	Dosage form	Polymers used	Manufacturers
Glumetza	Metformin Hcl	Tablet	HPMC	Depomed
Cifran O.D	Ciprofloxacin	Tablet	Xanthan gum and sodiumalginate	Ranbaxy
Liquid Gavison	Mixture of Alginates	Liquid	Alginates	Glaxo Smith Kline
Madopar HBS	Levodopa and Benserazide	Capsule	HPMC	Roche

Table no.2:Commercially available floating products.

FUTURE SCOPE

Floating drug delivery systems 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),and antidepresant 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, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of floating drug delivery systems include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, 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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