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GASTRORETENTIVE DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

Oral delivery of drugs is by far the most preferable route of drug delivery . Oral-rate controlled drug delivery systems have an important area among novel drug delivery system. But these oral sustained release drug delivery systems suffer greatly due to their short gastric residence time/ gastric emptying time. Whereas prolonged gastric residence increases duration of drug release, reduces drug waste, and improves drug solubility in gastric pH. In order to overcome these drawbacks novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time were discovered and they successfully exists today as gastroretentive dosage forms, in academic and industrial research groups. The aim of writing this review on gastroretentive drug delivery system was to present the recent literature in a more concise way with special focus on various techniques to achieve gastric retention. In addition, important factors controlling gastroretention, advantages,analysis techniques and finally, future potentials are also discussed.

KEYWORDS : Gastroretention , Floating , Gastric Residence Time , buoyancy

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INTRODUCTION

An optimum GRDFs (Gastroretentive dosage forms) can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers , releases active moiety in a controlled manner, and finally is easily metabolised in the body. This in turn improves bioavailability, reduces drug wastage, improves solubility of drugs that are less soluble at high pH environment. They also help in achieving local delivery of drugs to the stomach and proximal small intestine and helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances[1]. A major constraint in the oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular segment of GIT only or are absorbed to a different extent in various segments of GIT. Such drug candidates are said to have an 'absorption window'. But, in case of 'narrow absorption window' drugs, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. Again after crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically minimizes the time available for drug absorption after it, which is then accompanied by lesser bioavailability. Thus, the success of oral controlled drug delivery has faced some difficulties related with physiological adversities, like short gastric residence time (GRT) and unpredictable gastric emptying time (GET)[2].One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e., gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options.[3]Many technological attempts have been made to devise various controlled release gastroretentive drug delivery systems namely, high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid[5], mucoadhesive systems that causes bioadhesion to stomach mucosa [6], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[7], superporous hydrogel systems[8], magnetic systems[9] etc.

Drugs that are good candidates for Gastroretentive Drug Delivery System

1. Drugs acting locally in the stomach E.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach E.g. Amoxicillin
3. Drugs that are poorly soluble at alkaline pH E.g. Furosemide, Diazepam, Verapamil, etc.
4. Drugs with a narrow window of absorption E.g. Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs which are absorbed rapidly from the GItract. E.g. etonidazole, tetracycline.
6. Drugs that degrade in the colon.
7. E.g. Ranitidine, Metformin HCl.
8. Drugs that disturb normal colonic microbes E.g. antibiotics against Helicobacter pylori.[10]

Advantages of Gastroretentive Drug Delivery System.

- Improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided,a desirable plasma drug concentration is maintained by continuous drug release.
- Gastric retention time is increased because of buoyancy.
- Enhanced absorption of drugs which solubilise only in stomach.
- Drug releases in a controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.[10]

Limitations of the Techniques of Gastroretention

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

1. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
2. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
3. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.
4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in Unpredictable adherence.
5. In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.[11]

Gastrointestinal Tract

The GIT is a muscular tube like structure which extend from mouth to anus. It takes nutrients in and eliminates waste by secretion, absorption, motility, digestion, and excretion, which are known as physiological processes. The gastrointestinal tract is divided into three main parts according to their structure-

- Stomach
- Small intestine
- Large intestine

Anatomy of stomach-

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and the body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[12] Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[13]

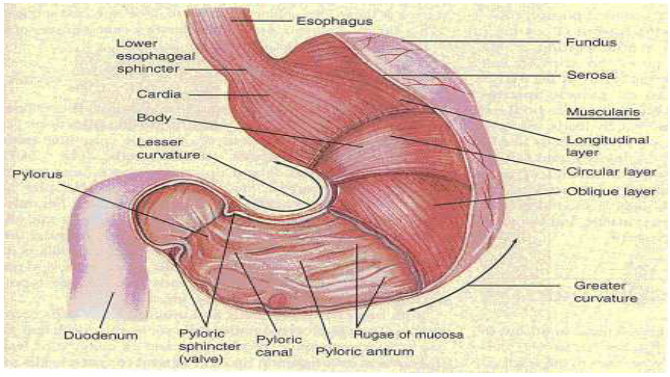

Figure 1
Diagram of human stomach

Table 1
Migrating Myoelectric Cycle [15]

Phase	Time	Comments
Phase I (basal phase)	last for 30-60 minutes	rare contractions
Phase II (pre burst phase)	last for 20-40 minutes	intermediate contractions, as phase progresses intensity and frequency also increase gradually
Phase III (burst phase)	Last for 0-5 minutes	Intense and regular contraction occurs during this phase for short period of time. Due to this undigested food sweeps out from stomach down to small intestine
Phase IV	Last for 10-20 Minutes	occurs between phase 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. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate.[14] The events are summarised in fig 2.

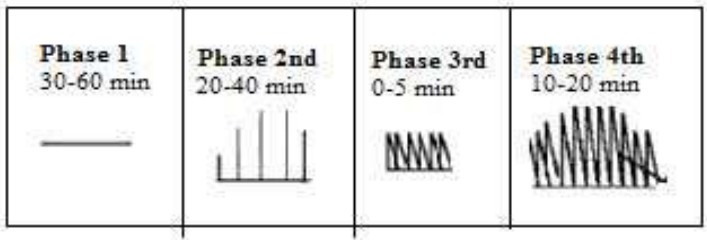

Figure 2
Migrating Myoelectric cycle [13]

Factors affecting gastric retention time of the dosage form[14,16]

1. ***Density of Dosage Form:***GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

2. ***Size & Shape of dosage form:***Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric residence time.

3. ***Gastrointestinal pH:***Gastric emptying is retarded at low stomach pH and promoted at higher pH. HCl > acetic acid > lactic acid >tartric acid > citric acid

4. ***Fed or unfed state:***Under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

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:***GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

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.

8. ***Gender:*** Male- 3.4□}0.6hr to Female- 4.6□}1.2hr.

9. ***Age:*** Elderly people, especially those over 70, have a significantly longer GRT.

10. ***Posture:*** GRT can vary between supine and upright ambulatory states of the patient.

11. ***Concomitantdrug administration:***Anticholinergic like atropine, propentheline- increase GRT. Metoclopramide and cisapride- decrease GRT.

12. ***Disease state:***Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT.

13. ***Electrolytes and osmotic pressure:***Water, isotonic solution and solution of low concentration empty the stomach rapidly where as higher electrolyte concentration decreases gastric emptying rate.

Approaches of gastroretentive formulations

Dosage forms developed for gastric retention should be able to stand up against gastric force caused by

peristaltic movement in the stomach, constant churning and grinding. Gastroretentive dosage forms resist the gastric emptying and once the aim of dosage form is achieved it should be eliminated from the stomach. Gastroretentive dosage forms need wide efforts in both academic and industry towards development. These efforts resulted in gastroretentive drug delivery formulations based on following approaches- Gastroretentive drug delivery system can be broadly classified into two categories-

1*)Non Floating Systems*

a) Bioadhesive Systems
b) Swelling Systems
c) High Density Systems
d) Expandable Systems

2) Floating Systems

The Floating system can be further divided into two types

a) Effervescent System

Volatile liquid containing system

(i) Intra Gastric floating gastrointestinal drug delivery system
(ii) Inflatable gastrointestinal drug delivery system
(iii) Intra Gastric osmotically controlled drug delivery system

Gas generating system-

(i) Floating Capsules
(ii) Floating Pills
(iii) Floating systems with ion exchange resins

b) Non Effervescent Systems

(i) Colloidal Gel Barrier System (Hydrodynamically balanced system)
(ii) Microballons/Hollow microspheres
(iii) Alginate beads
(iv) Layered Tablets a) Single layer tablets b) Bilayer tablet

1*.Non-floating systems*

These are gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are formulated by any of the following approaches.

a) *Bioadhesive systems*

This approach involved the use of muco-adhesive polymer which adhered over mucous layer secreted by the goblet cells of the stomach and hence retains in the stomach for its prolonged release. Mucus is translucent and viscid secretion, which forms gel like continuous thin blanket over mucosal epithelial surface. Some excipients that have been used commonly in these systems include lectins, polycarbophil, chitosan gliadin and carbopol etc. The various theories which involve in adhesion are shown in table 2 and the mechanism of adhesion is represented in fig 3.

Table 2
***muco-adhesive theories*[17]**

Theories	Description
Electronic theory	This theory involve transfer of electron from an adhesive polymer to a glycoprotein network
Absorption theory	Chemical bond formed may be, hydrogen, covalent bond, Vander Wals forces, electrostatic force and hydrophobic bonds
Wetting theory	They have ability to spread over a biological system
Diffusion theory	The polymer chains and the mucus mix to a sufficient depth to form a semipermanent adhesive bond

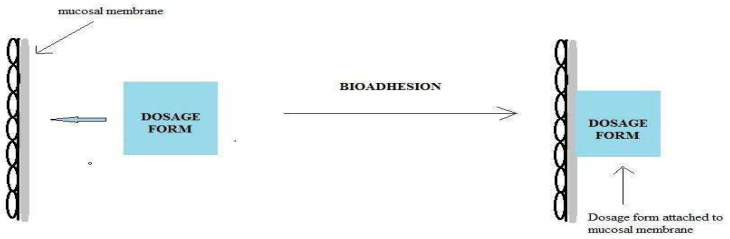

Figure 3
Figure showing mechanism of bioadhesion

b)Swelling Systems

Gastroretentivity of a pharmaceutical dosage form can also be enhanced by increasing its size above the diameter of the pylorus (even in its widest state during a housekeeper wave). If the dosage form can attain the larger size than pylorus, the gastroretentivity of that dosage form will be possible for a long time. This large size should be achieved fairly quickly; otherwise the dosage form will be emptied through the pylorus. Thus, configurations required to develop an expandable system to prolong GRT are[18,19]

(i) A small configuration for oral intake,
(ii) An expanded gastroretentive form, and
(iii) A final small form enabling evacuation following drug release from the device.

In addition they should be able enough to withstand peristalsis and mechanical contractility of the stomach. Swellable systems are also retained in the GIT due to their mechanical properties. The swelling of dosage form is usually resulted from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 4).In general, these size-increasing drug delivery system potentially present the hazard of permanent retention in the stomach and could lead to life threatening effects upon multiple administration. They are also not cost-effective. A major advantage of these size increasing systems is the independence of their performances on the filling state of the stomach.

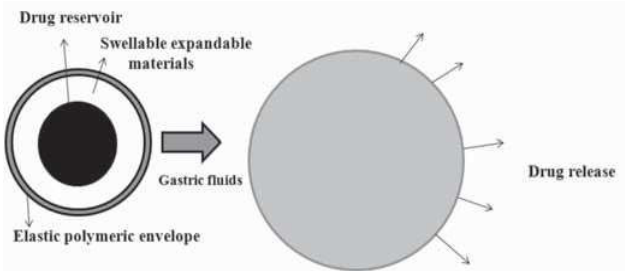

Figure 4
Drug release from swellable systems

c) *High Density Systems*

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3) shown in fig 5. These formulations are prepared by coating drug on a heavy core or mixed with inert materials such asiron powder, barium sulphate, zinc oxide and titanium oxide etc [20]. The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3

seems necessary for significant prolongation of gastric residence time [21]. But, effectiveness of this system in human beings was not observed [22] and no system has been marketed.

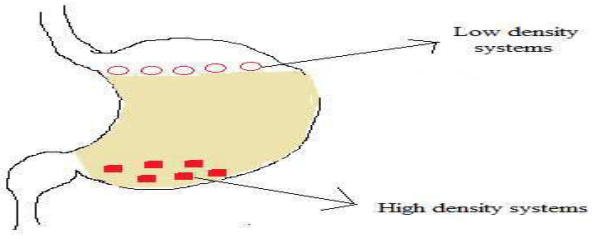

Figure. 5
Figure showing the high density systems which are at the bottom of the stomach and low density systems which are floating.

d)Expandable systems

These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

2.Floating drug delivery systems (FDDS)

These are drug delivery systems that float immediately upon contact with gastric fluids and thus they present promising approaches for increasing drug bioavailability with absorption windows in the upper small intestine. FDDS have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and the drug is released slowly at a 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 fluctuation in plasma drug concentration[23]. 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[24]. The major requirements for floating drug delivery system are[25]:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier Based on the mechanism of buoyancy,there are two distinctly different technologies for FDDS, i.e
- ***Effervescent System***
- ***Non effervescent*** [26.]

a)Effervescent drug delivery system

This system is prepared by swellable polymer like chitosan and effervescent substance like sodium bicarbonate, citric acid or tartaric acid. When the system comes in contact with gastric fluids it releases carbon dioxide, causing the formulation to remain and float in the stomach.[22]

Volatile liquid containing systems

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach.These systems are osmotically controlled floating systems containing a

hollowdeformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid. These are further categorised as

(i) *Intragastric floating gastrointestinal drug delivery system*

This system contains a floatation chamber which contains vacuum or a inert, harmless gas and a microporous compartment enclosing drug reservoir. It is shown in Figure. 6

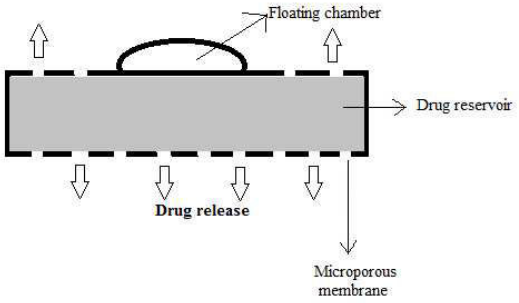

Figure 6
Figure showing intragastric floating Gastrointestinal drug delivery system

ii)Inflatable gastrointestinal delivery system

These systems possess inflatable chamber containing liquid ether which gasifies at body temperature to inflate in the stomach. Inflatable chamber contains bioerodible polymer filament (e.g., copolymer of polyvinyl alcohol and polyethylene) that gradually dissolves in gastric fluid and finally causes inflatable chamber to release gas and collapse. It is shown in Figure7.

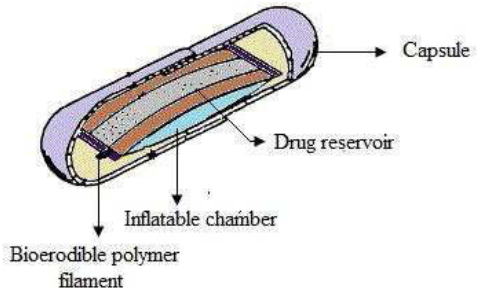

Figure 7
Figure showing inflatable gastrointestinal delivery system

(iii)Intragastric-osmotically controlled drug delivery system

It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule. In the stomach, inflatable capsule disintegrates and releases the osmotically controlled drug delivery system which contains two components; drug reservoir compartment and osmotically active compartment[27,28]. Illustrated in Figure. 8.

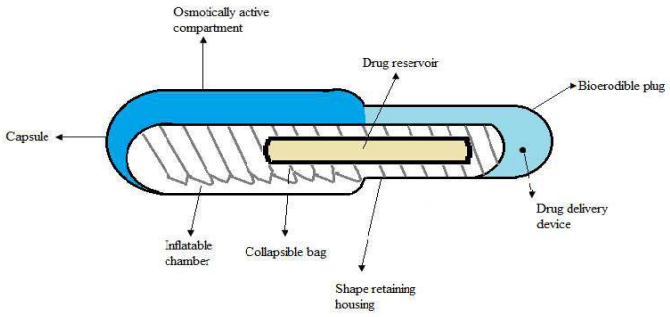

Figure 8
Figure showing Intragastric-osmotically controlled drug delivery system

Gas-generating Systems
The effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2 occurs in this delivery system, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate.

(i)*Floating Capsules*
These are prepared with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC). On exposure to acidic environment, carbon dioxide gas is generated which is trapped in the hydrating gel network and makes the system to float.

(ii) *Floating pills*
These are a type of sustained release formulations which are basically multiple unit type of dosage forms. The sustained release pill is surrounded by two layers. Outer layer consists of swellable membrane and the inner layer consists of effervescent agents. The system swells due to swellable membrane and then sinks. Due to the presence of effervescent agents, CO2 is released and the system floats.

(iii)*Floating systems with ion exchange resins*
The most common approach for formulating these systems involves resin beads loaded with bicarbonate. This is then coated with ethyl cellulose which is usually insoluble but permeable to water. This causes carbon dioxide to release and the system to float.[27,28]

(b) *Noneffervescent system*
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. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.[29]

(i) **Colloidal gel barrier system(*Hydrodynamically Balanced System)***
Sheth and Tossounian first designated this 'hydrodynamically balanced system . These type of systems

contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption site in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly soluble cellulose type hydrocolloid as hydroxypropyl cellulose, hydroxy ethylcellulose,hydroxylpropylmethylcell ulose (HPMC), polysaccharides and matrix forming polymer such as polycarbophil, polyacrylate and polystyrene. This hydrocolloid hydrates and forms a colloidal gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drugs.[30]

(ii) Microballoons / Hollow microspheres

Hallow microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometers. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for prolonged periods. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method. [31]

(iii)Alginate beads

These are generally made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into an aqueous solution of calcium chloride which causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs to 24hrs.[32,33] In a latest research it has been investigated that Sodium Alginate can be oxidized by reaction with sodium periodate NaIO4.This partially oxidized alginate was used to synthesize alginate microbeads.Oxidation altered the microbead properties to control. The degradation time of resultant micro beads increased with degree of oxidation. Current studies are investigating microbead degradation as a function of oxidation. It is hoped solution that implementing predictably degradable alginate can be eventually utilized in islet cell transplantation and drug delivery as a treatment of Type I diabetes.

(iv)Layered tablets

These may be of single layer or double layered.

a. Single layered floating tablets

This type of tablets contain drug mixed with gel forming hydrocolloids and other excipients. Upon contact with gastric fluids, the hydrocolloids swell and maintain bulk density less than one and hence remain buoyant in the stomach.

b. Double layered floating tablets

This type of tablets contain two layers, one of which is immediate releasing layer and the other is sustained release layer [34,35]

Table 3
Marketed preparations of Gastro retentive technologies Available in the International Market [36,37]

Marketed Preprations	Drug	Technology
Glumetza	Metformin	Polymer Based
proQuin XR	Ciprofloxacin	Polymer Based
Cifran OD	Ciprofloxacin (1g)	Gas generating Floating Form
GabapentinGR	Gabapentin (In Phase-III clinical trials) Accordion Pill TM	Polymer Based
Baclofen GRS	Baclofen	Coated multi-layer floating & swelling system
Coreg CR (Carvedilol)	Carvidilol	Gastro retention with osmotic system
Madopar	Levodopa and benserazide	Floating, CR Capsule
Topalkan	Aluminum magnesium antacid	Floating Liquid Alginate
Valrelease	Diazepam	Floating Capsule
Almagate flatcoat	Antacid	Floating Liquid Form
Liquid gavison	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation
Cytotec	Misoprostol (100mcg/200mcg	Bilayer Floating Capsule
Conviron	Ferrous Sulphate	Colloidal gel forming FDDS

INVITRO METHODS OF ANALYSIS

(i) Fourier transform infrared analysis

Fourier transform infrared spectroscopy is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug loaded polymer formulations are obtained on FT-IR. The pellets are prepared on KBr-press under hydraulic pressure of 150kg/cm2; and the spectra are scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.[38.]

(ii) Differential scanning calorimetry (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards are used to calibrate the DSC temperature and enthalpy scale. The sample preparations are hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25° C – 65°C. Inert atmosphere is maintained by purging nitrogen gas at the flow rate of 50ml/min[38].

(iii) Powder x-ray diffraction

X-ray powder diffraction (Philips analytical, modelpw1710) is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples are irradiated with S radiation and analyzed between 2 ºC and 60 ºC .The voltage and current used are 30KV and 30mA respectively[38].

(*iv) Particle size analysis, surface characterization (for floating microspheres and beads*)

The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross sectional morphology (surface characterization) is done by scanning electron microscope (SEM) [39]

(v)Floatation studies

The test for floating time is usually performed in simulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37° C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.[40]

(vi) Swelling studies

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using the Dissolution apparatus (USP dissolution apparatus USP-24) labindia disso 2000) was calculated as per the following formula. [41]

Swelling ratio = Weight of wet formulation / Weight of formulations

(vii)Determination of the drug content

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Microtitrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques.[42]

(viii)In vitro floating and dissolution

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started”. A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms.[43]

INVIVO METHODS

(i) *Xray/gamma scintiagraphy*

X Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio opaque material into a solid dosage form enables it to be visualized by X rays. Similarly, the inclusion of a gamma emitting radionuclide in a formulation allows indirect external observation using a gamma camera or scintiscanner. In case of Gamma scintigraphy, the gamma rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT.[44]

(ii) Pharmacokinetic studies

Pharmacokinetic studies are an integral part of the in vivo studies and several

works have been reported on these. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0- infinity) values (3.75 h and 364.65mg/ml -1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 mg/ml-1h) .[44]

(iii) Gastroscopy

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.[45]

(iv)Ultrasonagraphy

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. The characterization include assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.[46]

FUTURE POTENTIAL

Floating dosage form offers various future potential as evident from several recent publications.

- The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Buoyant delivery system can be considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease.
- To explore the eradication of Helico-bactor pylori by using the narrow spectrum antibiotics.

CONCLUSION

Drug delivery using various gastroretentive technological approaches have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drug candidates. The increasing sophistication of these technologies will ensure the development of numerous gastroretentive drug delivery systems to optimize the delivery of drugs that exhibit absorption window, low bioavailability and extensive first pass metabolism. A number of commercial products and patents issued in this field are the evidence of it.

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