Floating drug delivery system- a review

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ABSTRACT

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming various physiological problems such as short gastric residence times and unpredictable gastric emptying times. Several approaches are utilized in the prolongation of the gastric residence times, such as floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the *in-vitro* techniques, *in- vivo* studies to evaluate the performance and application of floating systems, and applications of these systems.

Keywords: gastroretentive drug delivery system ; floating system; swelling; expanding system; bio/mucoadhesive system; high density system.

Introduction

Historically, the oral route of administration has been used the most for both conventional and novel drug delivery system. These systems have the obvious advantages of ease of administration and patient acceptance, least sterility constraints and flexibility in the design of dosage form. One would always like to have an ideal drug delivery system that will possess two main properties:

• It will be a single dose for the whole duration of treatment.

• It will deliver the active drug directly at the site of action.

Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible. More than 50% of drugs, available in the market are meant for oral administration. The conventional drug therapy results in fluctuation of drug concentration in systemic circulation, causing either toxic effect or no therapeutic effect.

Now recent scientific and technological advancement have been made in the research and develop of rate controlled oral drug delivery systems by overcoming physiological adversities and short gastric residence time [1].Invariably, conventional drug dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repetitively using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve frequent dosing for drugs with short biologic half-life, and above all the patient non compliance. Now recent scientific and technological advancement have been made in the research and develop of rate controlled oral drug delivery systems by overcoming physiological adversities and short gastric residence time [1].Invariably, conventional drug dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time.

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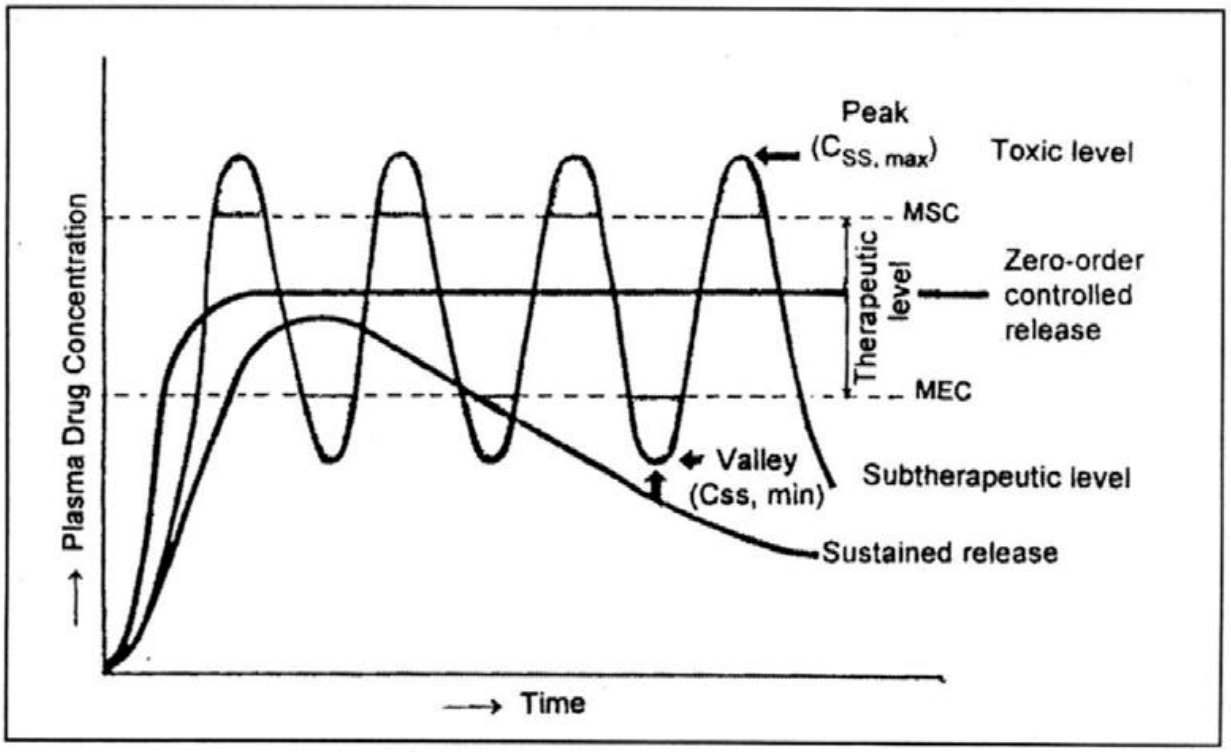

Fig 1:Plasma level profiles following conventional and controlled release dosing

The basic rationale of the controlled drug delivery system (CDDS) is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route **[2].**Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit. Controlled release denotes the system in which release rate of the drug from the system is temporal (related to time) or spatial (related to site) nature or both. In other words system attempts to control the drug concentration in the target tissue or cells.

The broad objectives of controlled release drug delivery system are as follows

- Prolongs the duration of action of the drug at a predetermined rate by maintaining a relatively constant, effective drug level in the body with the minimization of the adverse effect associated with a peak valley kinetic pattern.
- Localization of drug action by spatial placement of controlled release system near to or in the diseased tissue or organ , site or even receptor.
- Target drug action by using carrier or chemical derivatization to deliver drug to a particular target , cell type. Ideally it is desirable to release the drug at the target sites whether it is a tissue , population of cells or receptors , leaving rest of the body drug free **[3].**

Merits of Controlled Drug Delivery

- Reduction in fluctuation in steady state levels and therefore better control of disease and Reduce intensity of local or systemic side effect.
- Improved patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.
- Decreased incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- Controlled rate and site of release.
- Reduce wastage of the drugs.
- More uniform blood concentrations.
- Less therapeutic index.
- A greater selectivity of pharmacological activity**[4]**

Demerits of Controlled Drug Delivery

- Toxicity due to dose dumping.
- Increased cost.
- Increased variability among dosage units.
- Stability problems.
- Retrieval of drugs in difficult in case of toxicity, poisoning or hypersensitivity reactions **[5].**

Classification of oral controlled drug delivery system

Oral controlled drug delivery systems can be broadly classified on the basis of their mechanism of drug release. Primarily, controlled release is achieved by diffusion, degradation and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release systems. Diffusion occurs when bioactive agent passes through the polymer, which forms the building block of controlled release system.

1. Dissolution-controlled release

a) Encapsulation Encapsulation dissolution control

b) Matrix dissolution control

2. Diffusion-controlled release

a) Reservoir devices

b) Matrix devices

3. Osmotic controlled release

4. Ion exchange resins

5. Gastroretentive systems

1.2.1 Dissolution-controlled release

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thicknesses. The rate-limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer.

The rate of dissolution (dm/dt) can be approximated by following Equation

dm/dt=ADS/h….eq (i)

In this equation, S is the aqueous solubility of the drug, A is the surface area of the dissolving particle or tablet, D is the diffusivity of the drug, and h is the thickness of the boundary layer. Some examples of the drugs with limited dissolution rate include digoxin, griseofulvin, salicylamide, and nifedipine. Unfortunately, this approach does not allow for a constant release rate because the surface area (A) changes with time. Also, the solubility (S) of the drug, which is weak acid or base, is affected by the variable pH of the GI tract.Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by encapsulation of a drug-polymer matrix within a relatively insoluble polymeric membrane. The coated beads can be compressed into tablets or capsulated. Since the time required for the membrane coat to dissolve is a function of membrane thickness, granules with varying thicknesses can be employed to achieve sustained release of the drug. Examples of drugs delivered in this manner include antispasmodic sedative combinations, phenothiazines, and anticholinesterase agents **[6].**

Diffusion-controlled release

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of reservoir type diffusion-controlled device, the rate of drug released can be calculated using Equation;

dm/dt=ADK ΔC/ℓ……eq (ii)

Osmotically controlled Release

In the early 1970s, Theeuwes et al. developed an elementary osmotic pump (EOP) to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semi-permeable membrane, which in turn carries the drug outside through a laser-drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semi- permeable membrane govern fluid transport into the system. Therefore, the rate of drug delivered from the system is dependent on the osmotic pressure of the formulation (Πs) as shown in Equation;

dm/dt= AK ΠsS/h…..eq (iv)

where A is the membrane area, k is the membrane permeability, and h is the membrane thickness.

More recently developed several other controlled release technology platforms based on the original concept of osmosis across a semi-permeable membrane. push pull technology has proven to be very useful for delivering compounds of very high or very low solubility such as oxybutynin chloride and nifedipine, respectively. push-pull technology is capable of zero-order drug delivery for 24 h. The system is made of two compartments that are compressed into a bilayer core. The top layer contains the drug and the lower layer contains an osmotic polymeric driving agent. The bilayer tablet is coated with a semi-permeable membrane that is drilled on the drug side to allow delivery of the drug formulation through an orifice. During operation, imbibe water across the membrane. The push layer expands and drives the drug out of the system in the form of a solution or suspension through the orifice.The release rate of the drug from a push-pull system can be estimated by Equation.

dm/dt=K[Ap(Πp- Πd)+A Πd]FCo/h….eq (v)

Where F is the initial drug fraction in the drug compartment, C0 is the solid concentration of the suspension dispensed from the system, Ap is the area of the push layer, A is the total area of the system, Π d is the osmotic pressure of the drug compartment, and Πp is the osmotic pressure of the push layer. Typically, a push-pull system can deliver drug at a constant rate for 80% or more of its theoretical content. systems can maintain zero-order delivery for 24 h **[7].**

Ion Exchange resins

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug resin complex is formed by prolonged exposure of drug to the resin **[8].**

Gastroretentive Systems

Variability in GI transit time is a concern for oral controlled drug delivery systems. A major constraint in oral controlled release drug delivery is that not all the drug candidates are absorbed uniformly throughout the GIT (gastrointestinal tract). Some drugs are absorbed in a particular portion of GI tract only or absorbed to a different extent in various segments of GI tract. Such drugs are said to have an absorption window. Thus only the drugs which are released in the preceding region and in close vicinity to the absorption window are available for absorption. After crossing the absorption window, the release drug goes to waste with negligible or no absorption. Thus the time available for drug absorption drastically decreases.

Gastroretentive dosage form

Gastroretentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment [**9].**Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients **[10].**Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. One of the most feasible approaches for achieving and predictable drug delivery profile in GIT is to control the GRT so that gastric emptying process can be extended from few minutes to 12 hr using GRDF's that offers new and better option for drug therapy **[11].**

Gastric retention can be achieved by mechanism of mucoadhesion or bioadhesion, expansion system, superporous hydrogels, raft forming system, low density system, floatation and simultaneous administration of pharmacological agents that delay the gastric emptying **[12].**

Floating drug delivery system

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methyl celluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy **[13].**Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the

gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time **[14].**

Physiology of gastrointestinal tract

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made up of fundus and 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. Gastric emptying occurs during fasting as well as fed states **[15].** The pattern of motility is however distinct in the two states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by **Wilson and Washington**

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles **[16].**

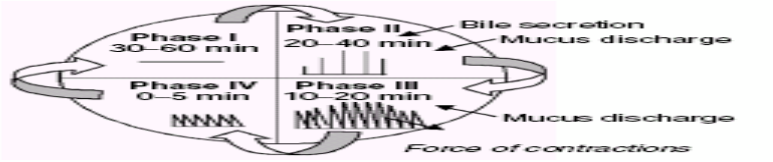

Fig 2: Motility patterns of the GIT in fasted state

Gastric emptying and problems

The process of the gastric emptying occurs both during fasting and fed stages.

- Scintinography study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities,
- The short GRT (Gastric Residence Time)
- Variable (unpredictable) GET (Gastric Emptying Time)

Fig3: Physiology of Gastrointestinal Tract

Table 1.1: salient features of upper gastrointestinal tract

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I, E, CM

P – Passive diffusion ,C – Aqueous channel transport ,A – Active transport, F – Facilitated transport , I – Ion-pair transport ,E – Entero-or pinocytosis ,CM – Carrier mediated transport

Potential candidates for gastro retentive drug delivery system

- Drugs that are primarily absorbed in the stomach eg Amoxicillin.
- Drugs that are poorly soluble in alkaline pH eg Furosemide , Diazepam.
- Drugs that have narrow absorption window eg Levodopa, Methotrexate.
- Drugs that degrade in the colon eg Ranitidine , Metformin HCL.
- Drugs that disturb normal colonic microbes eg Antibiotics against Helicobacter pylori.
- Drugs rapidly absorbed from the gi tract eg Tetracycline.
- Drugs acting locally in the stomach eg Misoprostol **[17].**

Gastroretentive technologies

A number of systems have been pursued to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention.

Expandable systems

These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach.

Bio/Muco-adhesive systems

This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary**[18].**

High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region. Commonly used excipients are Barium sulphate, Zinc oxide, Titanium dioxide and Iron powder, These materials increase density by up to1.5–2.4g/cm^3**[19].**

Floating drug delivery 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 drugconcentration**.[20].**

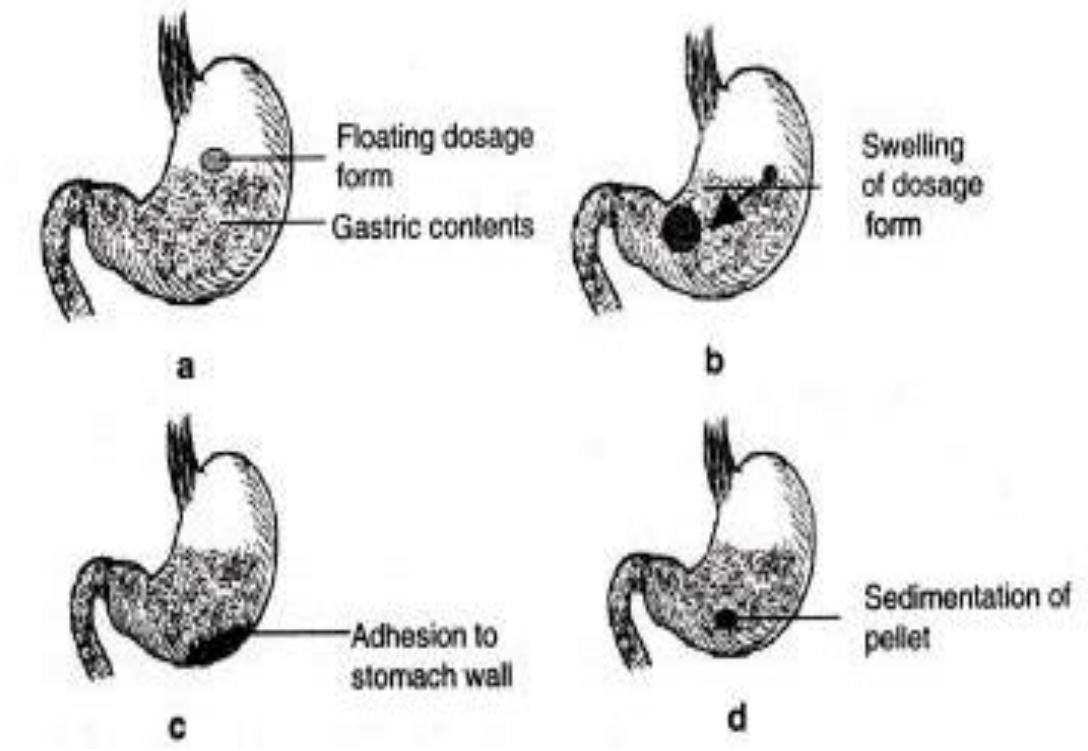

Fig 1.4: Various forms of gastro retentive systems; (a) Floating gastro retentive drug delivery systems; (b) Swelling gastro-retentive drug delivery systems; (c) Bio adhesive gastro-retentive drug delivery systems; (d) High- density gastroretentive drug delivery systems

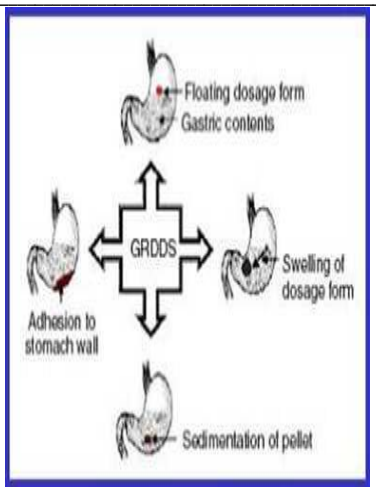

Fig 1.5: Gastro retentive approaches

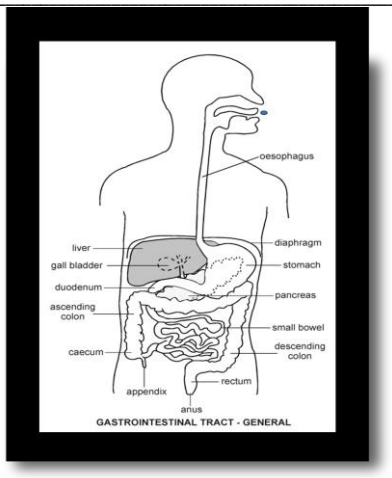

Fig1.6: Gastrointestinal Tract-General

Classification of floating drug delivery system (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are

A. Effervescent System, and
B. Non- Effervescent System.

Effervescent System

These are the matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds,eg,sodium bicarbonate, tartaric acid, and citric acid. They are formulated in a such a way that when in contact with the acidic gastric contents, CO_2 is liberated and entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms **[21]**

I.Gas Generating systems
II.Volatile Liquid/Vacuum Containing Systems

Gas – Generating Systems

Intra Gastric Single Layer Floating Tablets or Hydrodynamically

Balanced System

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach for a prolonged period.

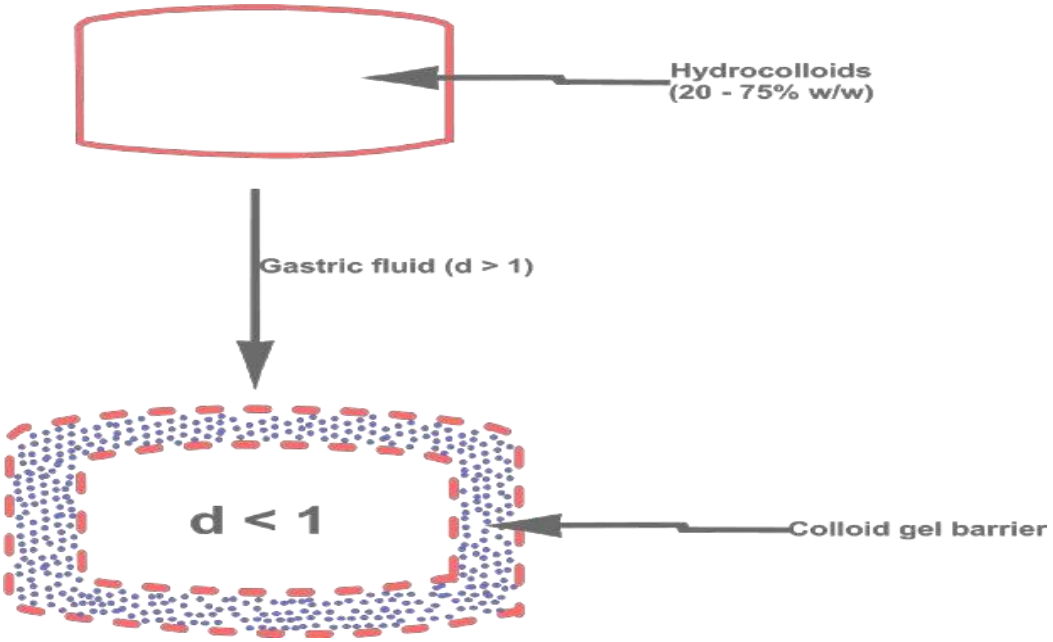

Fig1.7: Intra Gastric Single Layer Floating

Intra Gastric Bi-layer Floating Tablets

These are also compressed tablet containing two layers i.e.,

Immediate release layer

Sustained release layer.

These are as formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet

Multiple Unit type floating pills

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

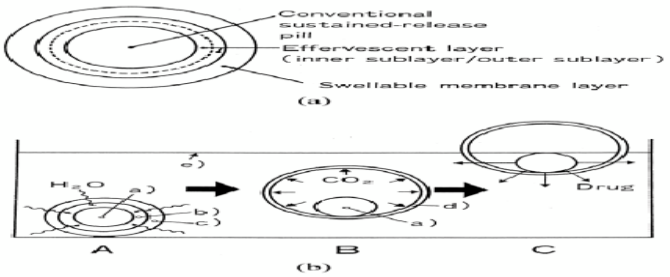

Fig 1.8: A multi-unit oral floating dosage system. Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C)

Volatile Liquid / Vacuum Containing Systems

Intra-gastric Floating Gastrointestinal Drug Delivery System

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment..

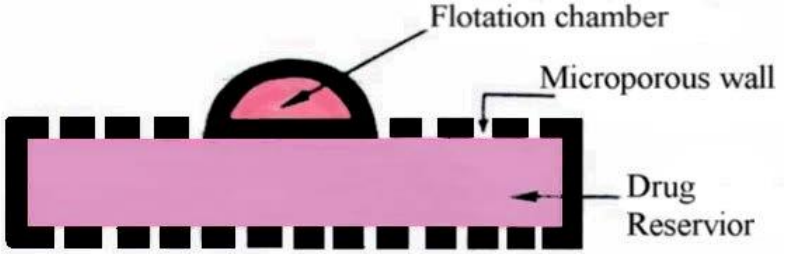

Fig1.9: Intra Gastric Floating Gastrointestinal Drug Delivery Device

Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid **[22].**

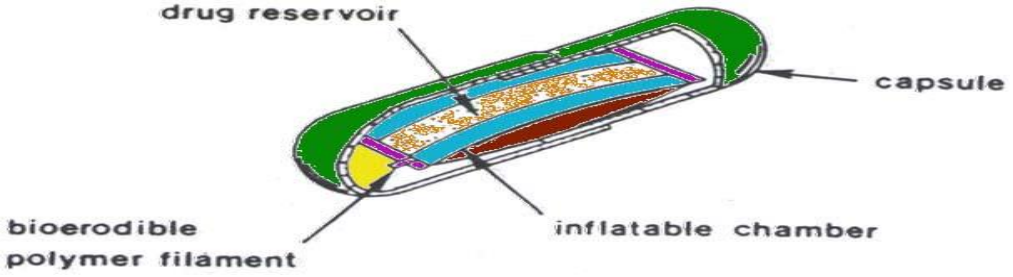

Fig 1.10: Inflatable Gastrointestinal Delivery System

Intra-gastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device[23]. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt[24]. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.The floating support is also made to contain a bioerodible plug that erodes after predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach [25].

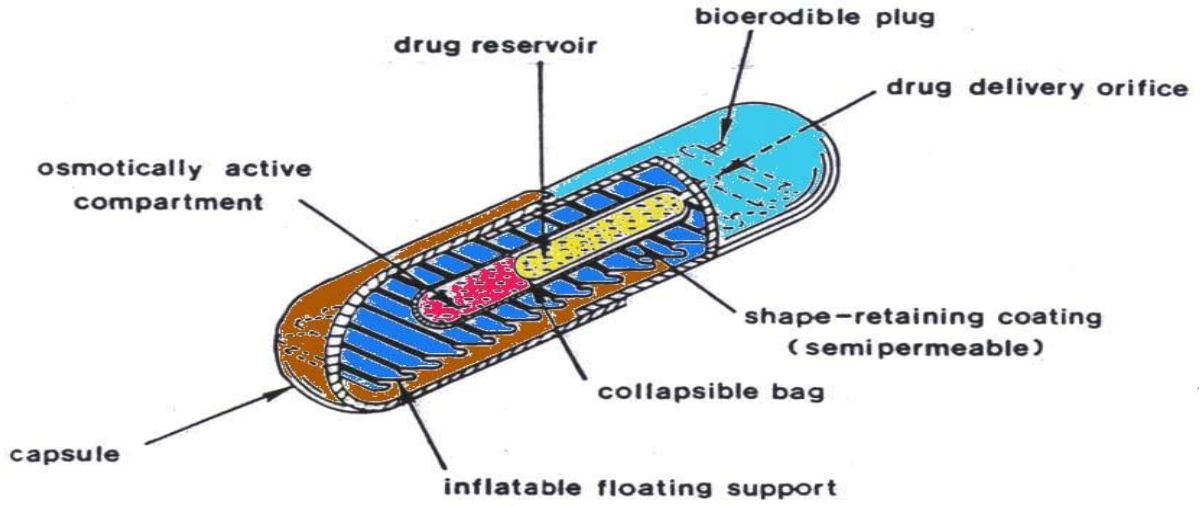

Fig1.11: Intragastric Osmotically Controlled Drug Delivery System

Non Effervescent System

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol [26].

Working principle of this type of FDDS

Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time[27]

Various types of non effervescent floating

Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity [28].

Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from the system while another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[29].

Alginate Beads

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

Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 400C.

Formulation of floating dosage form

Following types of the ingredients can be

incorporated in to HBS dosage form in addition to drugs.

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous [32].

Factors affecting gastric retention

Density of dosage form

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids (≅ 1.004 gm/ml) floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period

Size and shape of dosage form

To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT (≅ 90 to 100 %) retention at 24 hours compared with other shapes [33].

Fasting or fed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state [34].

Nature of the meal (food)

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same.

Effect of liquid, digestible solid and indigestible solid type food

It has been demonstrated using radio labeled technique that there is a difference between gastric emptying times of a liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (>1 mm) indigestible objects from stomach was dependent upon inter digestive migrating myoelectric complex.

Biological factors

Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. GRT can vary between supine and upright ambulatory states of the patients. Stress increases gastric emptying rates while depression slows it down [35].

Frequency of feed

The gastro retentive time can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

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 [35].

Posture

Gastro retentive time can vary between supine and upright ambulatory states of the patients. [36].

Advantages of floating dosage forms

Enhanced bioavailability

The bioavailability of Riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input [37].

Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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 [38].

Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.[39]

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency [40].

Disadvantages of floating dosage forms

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed through out the gastrointestinal tract [41].

Evaluation of floating drug delivery system

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

Floating time

The test for buoyancy is usually performed in simulated gastric and intestinal fluid maintained at 37ºC. The floating time is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the testing medium maintained at 37ºC . The time for which the dosage form floats is termed as the floating or floatation time [42].

Swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling Index} = \frac{Wt - Wo}{Wt} \quad \text{.....eq (vi)}$$

Where, W0 is the initial weight of tablet, and Wt is the weight of the tablet at time t.

***In-vitro* release studies**

The release rate of floating drug delivery system was determined in dissolution apparatus. Different types of dissolution apparatus are used according to formulation. The dissolution fluid was maintained at 37 ± 1°C at a rotation speed. Perfect sink conditions prevailed during the drug release study [43].

***In-vivo* study**

In vivo gastric residence time of a floating dosage form is determined by X-ray diffraction studies, gamma scintigraphy, or roentgenography. In X-ray method the formulation is modified to incorporate Barium Sulphate as X-ray opaque substance. The study is carried out by administering the gastro retentive tablets to human volunteer [44]. The tablet was administered in the fasting state. The X-Ray opaque formulation is administered along with 250 ml of water. The subjects are allowed to remain in sitting or upright position. A light meal is given to volunteer 2 hour after administration of the tablet to evaluate effect of food of gastro retentive property. The position of tablet is monitored by X-Ray screening technique X-Ray photographs taken at desired intervals to monitor tablet position in human gastrointestinal tract [45].

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