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AN OVERVIEW ON FLOATING TABLETS AND MICROBALLOONS: GASTRO RETENTION FLOATING DRUG DELIVERY SYSTEM (FDDS)

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ABSTRACT

Floating drug delivery systems (FDDS) have a lower bulk density than gastric fluids, consequently they float in the stomach for longer decades of time without altering the gastric emptying rate. The medicine is released gradually and at a controlled pace from the system while it is floating on the stomach contents. The residual approach in the stomach is emptied once the medicine is released. As a consequence, the Gastric Residence Time (GRT) is enhanced, and differences in plasma drug concentration are better controlled. The system must have enough structure to formulate a cohesive gel barrier and disintegrate gradually enough to act as a drug reservoir while maintaining an overall specific gravity lower than that of stomach contents. The methodologies exploited in the growth of FDDS by formulating effervescent and non-effervescent floating tablets based on buoyancy mechanism. By utilizing above viable approaches it is feasible to deliver drugs which have narrow therapeutic window. Our review article is in pursuit of giving comprehensive data on the pharmaceutical underpinnings of their design, classification, preparation determinants affecting on FDDS, advantages, applications, drawbacks and the future capability of FDDS.

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INTRODUCTION

Current pharmaceutical scenario focuses on the formulation of controlled drug delivery systems to achieve the required therapeutic concentration of drug substance with less amount of dose. Despite of enormous advancement in drug delivery, oral route of administration is the most useful for drug delivery due to its versatility, ease of administration and most important having the highest degree of patient compliance.Oral drug delivery route has received extra attention and success because the gastrointestinal physiology offers high flexibility in dosage form design than other routes. It has been observed that drugs having short half-lives and drugs that are easily absorbed from gastrointestinal tract (GIT) are eliminated quickly from the systemic circulation which leads to incomplete absorption of such drugs from upper part of small intestine. Hence, research continuously keeps on searching ways for the development of oral sustained-controlled release formulations with an attempt to release the drug slowly from dosage form into the gastrointestinal tract (GIT) and maintain an effective drug concentration over an extended period of time in the systemic circulation.[1]

In an attempt to get around this restriction, oral sustained-release formulations were developed. These formulations slowly release the drug into the gastrointestinal tract (GIT) and sustain an effective drug concentration in the systemic circulation for a prolonged period of time. [2] After oral administration, the drug would remain in the stomach and release in a controlled manner, allowing the drug to be continuously given to its absorption sites in the GIT. [3] The main disadvantages of these drug delivery systems are short gastric retention time (GRT) and unpredictable short gastric emptying time (GET).[4,5]

Types of Floating Drug Delivery System:

Fig 1: Describes the classification of FDDS with consideration of its Physicochemical behaviour and appearance.

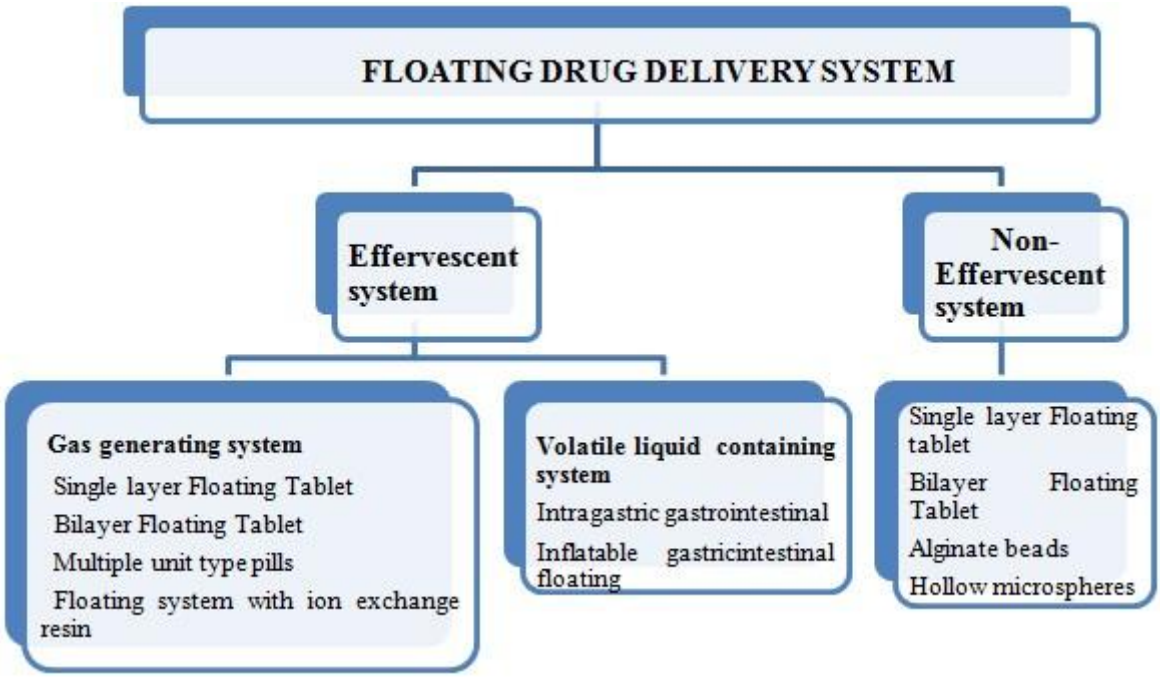

Fig 1: Classification of FDDS.

Anatomy and Physiology:[6]

The stomach is divided into three anatomical districts lobe funds, body and pylorus. The former two act as reservoir for ingested material whereas the latter is the major site for motions (gastric emptying). The gastric emptying process is variable from limited minutes to little hours, depending on physiological state of the subject and the design of the formulation. This variability in turn could lead to altered bioavailability. The relatively brief gastric emptying time (GET) in humans, which normally averages 2-3 hours through the major absorption zones (stomach or upper part of the intestine) can result in inadequate drug release from the drug delivery system leading to reduced efficacy of the administered dose. Thus, orally administered controlled release forms suffer from mainly two adversities the short gastric retention time and unpredictable GET.

Stomach:

Basic Anatomy, Physiology and Problems:

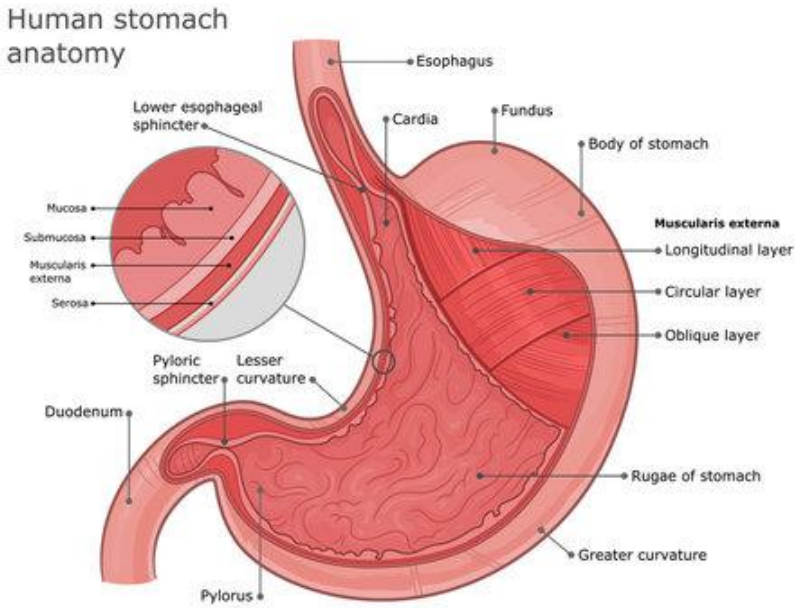

Fig 2: Human Stomach Anatomy.

Anatomy The stomach situated between the oesophagus (proximally) and the duodenum (distally). It contrasts broadly in size and shape depending on the person, the food content, and the posture of the body. Anatomically stomach is J-shaped normally and the pyloric part lies horizontally or ascends to meet the proximal part of the duodenum Anatomically, the stomach is divided into 3 parts.

Fundus: The superior part of the stomach, this lies above the imaginary horizontal plane passing through the cardiac orifice.

Body: This lies between the fundus and the antrum, and it is the largest part of the stomach.

Antrum: This lies in the imaginary transpyloric plane and to the right of the angular notch (incisuraangularis). Antrum and pyloric canal joints with each other and it are on right side of the pyloric canal.

Physiology: The physiology and disease state of stomach has a direct on design of controlled drug delivery system because drug is absorbed from and enters into site of action. Different factors as like pH, nature of the stomach, volume of gastric secretions, and gastric mucosa play an important role in drug release and absorption.

pH Environmental pH affects the performance of orally administered drugs in to GIT. When patient administrated large volume of water with any oral dosage form initially changes the pH of stomach. This change occurs because stomach does not have enough time produce sufficient quantity of acid before emptying of liquid the stomach.

Volume The resting volume of stomach is about 25-52ml and gastric volume have significant role for dissolution of oral dosage forms in vivo study.

Gastric Secretion Acid's pepsin, gastric, mucus and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60ml with approximately 4mmol of hydrogen ions every hour. Other potent stimulators of gastric acid are the hormone gastric, peptides amino acids and gastric distention.

MECHANISM OF FLOATING DRUG DELIVERY SYSTEM: [7,8]

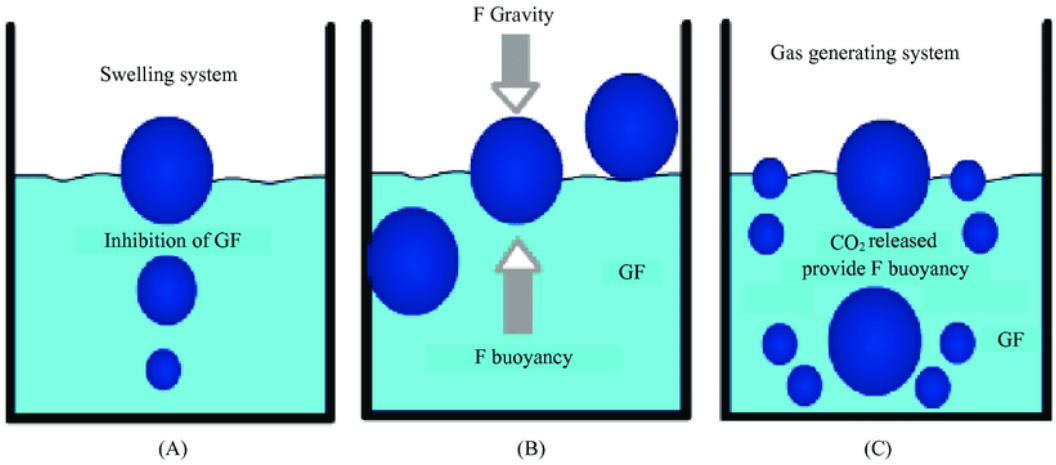

Fig 3: Mechanism of floating systems, GF= Gast

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F that is required to maintain the submerged object. The object floats better if F is on the higher positive side.

Commonly used Drugs for GRDDS: [9,10]

Tablets	Cephalexin, Ziduvudine, Losartan, Pentoxyfillin, Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Cinnarazine, Dilitiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5`Phosphate, Metformin Hydrochloride, Atenolol, Diltiazem, p- Aminobenzoic acid(PABA), Verapamil HCI, Isosorbide di nitrate, Sotalol, Isosorbide mononitrate, Aceraminophen, Ampicillin.
Capsules	Nicardipine, L-Dopa and benserazide, chlordizepoxide HCI, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid, Pepstatin, Celiprolol HCl.
Microspheres	Verapamil, Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine, Piroxicam, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Rosiglitazone maleate, Flurbiprofen, Orlistat.
Granules	Indomethacin, Diclofenac sodium, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil , Isosorbide mononitrate ,Isosorbide dinitrate, Ranitidine HCl.
Films	Drug delivery device, Albendazole, P-aminobenzoic Acid, Piretanide, Prednisolone, Quinidine gluconate, Cinnarizine.
Powders	Several basic drugs-Riboflavin, Sotalol, Theophylline.
Bilayer tablet	Misoprostal, Trimetazidine hydrochloride and Metoprolol succinate, Diltiazem HCI and Lovastatin, Atenolol.
Beads	Ranitidine HCl, Loratadine, Curcumin β-cyclodextrin complex, Diltiazem HCl.

ADVANTAGES:[11,12,13,14]

1. This method can be used to administer drugs with a short half-life that nonetheless have a major therapeutic impact.
2. Higher bioavailability for drugs that the upper gastrointestinal system can metabolize.
3. They may also be utilized to address the problems of stomach retention and emptying time, which is an advantage over the traditional method.
4. The duration of a long century required for the release of an active module from a single dose.
5. Adverse effects are minimized or eliminated when the active component is delivered
6. Directly to the site of action.

7. FDDS is advantageous for medications that cause stomach vexation in the first place. Such as Antacids.
8. FDDS is beneficial in treating gastrointestinal disorders such gastroesophageal reflux illness.
9. Simplicity in case compliance and administration.
10. Lowers the dosage frequency.
11. It improves the medications' bioavailability.
12. Enhanced bioavailability for certain substances that the upper gastrointestinal tract can metabolize
13. Due to the medication's floatability, invariant release, and sustained release effect
14. There is no gastrointestinal discomfort when using the multi-particulate method1.
15. Thirteen) It helps relieve GERD (gastric influx problem).
16. Advantageous when experiencing diarrhoea.

Disadvantages of FDDS: [15.16]

1. The major disadvantage of floating system is requiring a high level of fluids in the stomach for drug delivery to float and work efficiently.
2. These systems are not feasible for those drugs that have solubility or stability problem in GI tract. 3. Drugs such as Nifedipine, Propranolol etc. Which are well absorbed throughout GIT and which undergoes first pass metabolism are not be desirable candidate.
3. Drugs (like NSAIDS) that can cause irritation and lesions to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
4. The drug candidates that are unstable in the stomach acidic environment are not suitable to be incorporated in the FDDS systems.
5. Ability to float relies in the hydration state of dosage form.
6. The mucus present on the walls of the stomach is in a state of constant renewal which results in unpredictable adherence.
7. Dosage form requires faster swelling properties as well as complete swelling of the system must be achieved before the gastric emptying time.

Rationale Behind Floating Tablet:

Administration of Prolonged release floating dosage forms, tablets or capsules, causes dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid before getting absorbed in the small intestine with emptying stomach content.

Rationale Behind Microballons: [17]

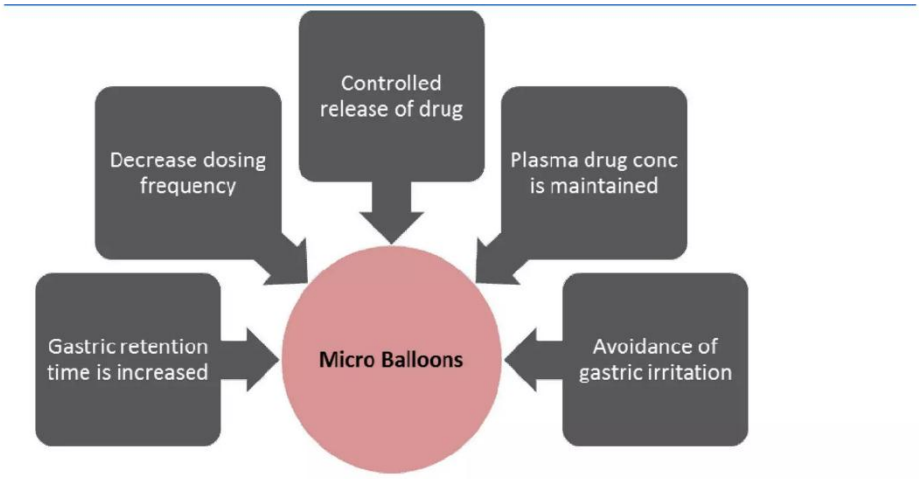

Fig 4: Rationale Behind Microballons.

Mechanism of Floating Microballoons: [18]

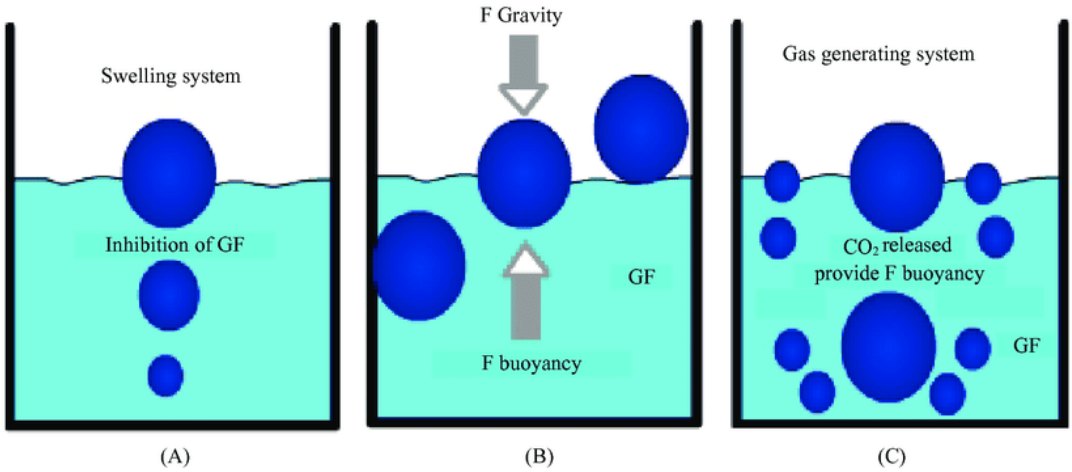

Fig 5:Mechanism of Floating Microballoons.

When microballoons come incontact withgastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. 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 and confers buoyancy to the microballoons. However, a minimal gastric content needed to allow proper achievement of buoyancy. Microballoons of acrylicresins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and Gelucire floating granules are the recent development.

Formulation aspectsof floating tablets:[33]

The design of novel controlled release dosage forms should take into account three important criteria, viz., drug, delivery, and destination. Preformulation studies help in studying the physiochemical properties of drugs. These properties include pKa, pH, solubility, and incompatibility. The solubility of a compoundaffects the choice of a controlled drug delivery system. If the compound has very low solubility (i.e. less than0.01mg/ml), it is inherently sustained. A drug has to cross a variety of biological membranes in order to produce a therapeutic effect when it is administered to the gastrointestinal tract. Thus, a partition coefficient of a drug is important in determining penetration of these membrane barriers by the drug. Compounds with very low partition coefficients will not easily penetrate these membranes, resulting in poor bioavailability. Acid-base hydrolysis and enzymatic degradation attack orally administered drugs. Compounds such as propantheline are unstable in small intestine. This results in decrease bioavailability when administered in controlled release delivery form. In case of oral drug delivery systems, the first destination is the gastrointestinal tract. From here the drug is absorbed and is taken to the site of action. Thus, physiology of the gastrointestinal tract has a direct effect on the design of controlled release delivery systems. In addition, effects of disease conditions and co-administered drugs also affect the design.

Techniques used in the preparation of microballoons: [19,20,21]

The different methods used for various microballoons preparation depends on route of administration, duration of drug release and particle size. The various methods of preparations are:

Emulsion solvent evaporation technique:

The drug is dissolved in chloroform and then dissolved in polymer and the resulting solution is added to aqueous phase containing 0.2% sodium of PVP as emulsifier. This mixture was stirred at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microballoons by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. For these techniques, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

Oil in water solvent evaporation technique:

In this technique, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. The polymer is dissolved in an organic solvent such as dichloromethane, methanol and chloroform. The drug is either dissolved or dispersed into polymer solution and this solution is emulsified into an aqueous phase to make an oil-in water emulsion by emulsifying agent. After that the organic solvent is decanted and the micro particles are separated by filtration.

Water-in-oil emulsification solvent evaporation technique:

This water-in-oil emulsification process is also known as non-aqueous emulsification solvent evaporation. Drug and polymers are co dissolved at room temperature with vigorous agitation to form uniform drug–polymer dispersion. This mixture is poured into the dispersion medium consisting of light / heavy liquid paraffin in the presence of oil soluble surfactant such as Span. Then this mixture is stirred using propeller agitator at 500 rpm over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid layer is decanted and micro particles are separated by filtration through a Whitman filter paper, washed with n-hexane and dried for 24 h and subsequently stored in desiccators.

Emulsion-solvent diffusion technique:

The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hour and formed floating microballoons were washed and dried in a desiccator at room temperature.

Ionic gelation technique:

The drug was added to 1.2% (w/v) aqueous solution of sodium alginate and continue stirring is preferred for complete solubility. After that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid Microballoons were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The maximum release of the drug was obtained at pH 6.4-7.2. Alginate/ chitosan particulate system for diclofenac sodium release was prepared using this technique.

Single emulsion technique:

Micro particulate carriers of natural polymers (proteins and carbohydrates) are prepared by single emulsion technique. The natural polymers (proteins and carbohydrates) are dispersed in aqueous media followed by dispersion in non-aqueous medium like oil with the help of cross-linking agent.

Double emulsion technique:

Double emulsion technique is the formation of the multiple emulsions or the double emulsion such as w/o/w.

Coacervation phase separation technique:

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug was dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

Factors Affecting Gastric Retention:[22,23,24,25]

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form.These factors are as follows.

Density:

GRT is a function of dosage form buoyancy that is dependent on the density. A buoyant dosage form having a density of less than that of the gastric fluid's floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Size:

Dosage form units with a diameter of less than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form:

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT ≈ 90–100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation:

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single-unit dosage forms.

Fed or unfed state:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5–2 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.

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.

Caloric content:

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

Frequency of feed: GRT 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 males (3.4 ± 0.6 hours) is lesser compared with their age- and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

Age:

Elderly people, especially those over 70, have a significantly longer GRT.

Posture:

Gastric emptying is favored while standing and lying on the right side since the normal curvature of the stomach provides a downhill path, whereas lying on the left side or in supine position retards it.

Disease states:

Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying, while partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote it.

Concomitant drug administration:

Drugs that retard gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and drugs such as tricyclic antidepressants (imipramine, amitriptyline), metoclopramide, domperidone, cisapride stimulate gastric emptying.

Evaluation of floating drug delivery system:[26,27,28,29,30,31,3234,35]

Shape of tablets Compressed tablets designed for FDDS are examined under the magnifying lens for the determination of its shape consistency.

Tablet dimensions As per official compendia, the thickness and diameter of tablets in FDDS form are measured using a calibrated Vernier callipers same with that of conventional tablets. Three tablets of each formulation are picked randomly, and thickness is measured individually.

Determination of hardness of the tablet Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester

Determination of weight variation Twenty tablets selected at random are weighed accurately, and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

Determination of thicknessof the tablet The individual crown to crown thickness of ten tablets is determined using slide calipers for each batch

Density of the tablet: Density of the tablet is a critical parameter for floating tablets. The tablet would float only when its density is less than that of gastric fluid (1.004). The density is determined utilizing following relationship.

$$V = r2\ h\ d$$

Were,

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

d = mass/volume 5)

Floating test:

The time between presentation of dose structure and its buoyancy on the reproduced gastric fluid and the time during which the dose structure remain were estimated. The time taken for dose structure to rise on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and all out term of time by which dose structure remain is called Total Floating Time (TFT) 6)

Swelling study:

The swelling conduct of a dose structure is evaluated by considering its weight gain or water uptake the dimensional modifications could be estimated as far as the expansion in tablet diameter across as well as thickness after some time. Water take-up is estimated regarding percent weight gain, as given by the equation:

$$\mathbf{WU = (Wt\ W0)\ x\ 100}$$

Where,
Wt = Weight of dosage form at time t
W0 = Initial weight of dosage form

Surface Topography: [28]

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

Determination of Moisture Content:

For the determination of moisture content of the prepared formulations Karl fisher titration was used. The other methods used are Thermo gravimetric methods, Vacuum drying, Air oven method, Freeze drying, and Moisture Meters.

Determination of the Drug Content:

The amount of drug that was present in the formulation is informed by percentage drug content. It should not exceed the limits acquired by the standard monographs. The drug content is determined by using Near infrared spectroscopy (NIRS), Micro titrimetric methods, HPLC, HPTLC methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques.

Percentage Entrapment Efficiency:

The three methods used to determine entrapment efficiency include pressure Ultra filtration, Ultra centrifugation and Micro dialysis method. Percentage entrapment efficiency is reliable for quantifying the phase distribution of drug in the prepared formulations.

In-vitro Release Studies:

In vitro release studies (USP dissolution apparatus (usp-24) are performed to determine the amount of the drug that is released at a definite time period. Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus are used to perform release studies.

Future prospects:

In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery system by overcoming physiological adversities such as short GRT and unpredictable GET. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydrodynamically balanced system (HBS), swelling and expanding system, polymeric bioadhesive system, modified-shape system, high-density system and other delayed gastric emptying devices. FDDS has emerged as an efficient means of controlling release of many drugs. The control of GI transit profiles could be the focus for the next two decades and this might result in the availability of new products with new therapeutic possibilities and substantial benefit for patients. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, large numbers of companies are focusing toward commercializing this technique

CONCLUSION

Drug absorption in the gastrointestinal tract is variable, and prolonging dosage form gastric retention can extend absorption time. FDDS is a potential approach to improve drug bioavailability and narrow absorption window in the gastrointestinal tract. This prolongs drug resident time, improves solubility, reduces drug waste, and reduces plasma level fluctuations. Despite challenges in achieving prolonged gastric retention, many companies are focusing on commercializing this technique, despite the numerous commercial products and patents in these fields.

Aim:

An overview on floating Tablets and Microballoons: Gastro RetentionFloating drug delivery system (FDDS)

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