

A Review on Gastro Retentive Drug Delivery System

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ABSTRACT :Gastroretentive drug delivery with oral controlled drug delivery is advantageous to many drugs having low absorption window and therefore poor bioavailability. Oral controlled release is the most favorable approach to gastroretentive drug delivery system by increase the duration of gastric residence and continuous release of the drug to the upper part of Gastro intestinal tract (GIT) for local or systemic effects and this significantly extend the duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. These involve floating drug delivery system , modified shape systems or unfolding systems, bioadhesive systems/mucoadhesive systems, high density system or non floating drug delivery systems. The purpose of this review is briefly describe the gastroretentive drug delivery, factors affecting, advantages and disadvantages, approaches ,application of gastroretentive drug delivery system.

Key words : gastroretentive, physiology of stomach, floating Drug delivery system.

I. INTRODUCTION

Oral administration of drugs is the most convenient and commonly used, over the past two to three decades. because its easy to administer and low cost of therapy and high level of patient acceptance . most drugs administered by the oral route have a bioavailability when administered as a solid dose shape, that is the speed and range of drugs are absorbed less than desirable, are difficult to predict controlled oral release in real time in

vivo dosage form, administration of gastroretentive drugs delivery system (GRDD) to improve the bioavailability of the drug , therapeutic efficacy to reduce the frequency of dosing .[1,2]

Absorption of the drug in the GIT is a highly variable procedure and such dependence on factors such as absorption of the drug on the spot , release of the drug from the dosage form gastrointestinal transit time of dosage forms and gastric emptying process gastroretentive dosage the permanence of forms in the gastric region for longer periods and prolonged gastric drug retention time.

Drug release into the stomach will be monitored that is why the drug is continuously supplied to absorption site of gastrointestinal tract .

Stomach one of the important approach of gastroretentive drug delivery system such as prolong gastric residence time, thus targeting specific sites release of drugs in the stomach when mechanism floating gastro-retentive drug delivery system as the formulation are before administration in solution form after the contacts of the administrative solution gastric fluid in the stomach forms a gel and floats in the gastric fluid. The gel flats in gastric fluid in the longest period.

GRDD devices are mainly site specific drugs delivery systems , which are kept in the stomach for a longer period of time .this in turn improves the Bioavailability , Reduce the waste of drugs and Improve the solubility of drugs less soluble in a high pH environment (e.g papaverine, domperidone) , It also helps ensue local delivery of drug to the stomach and proximal small intestine.[3]

Physiology Of Stomach [4,5]

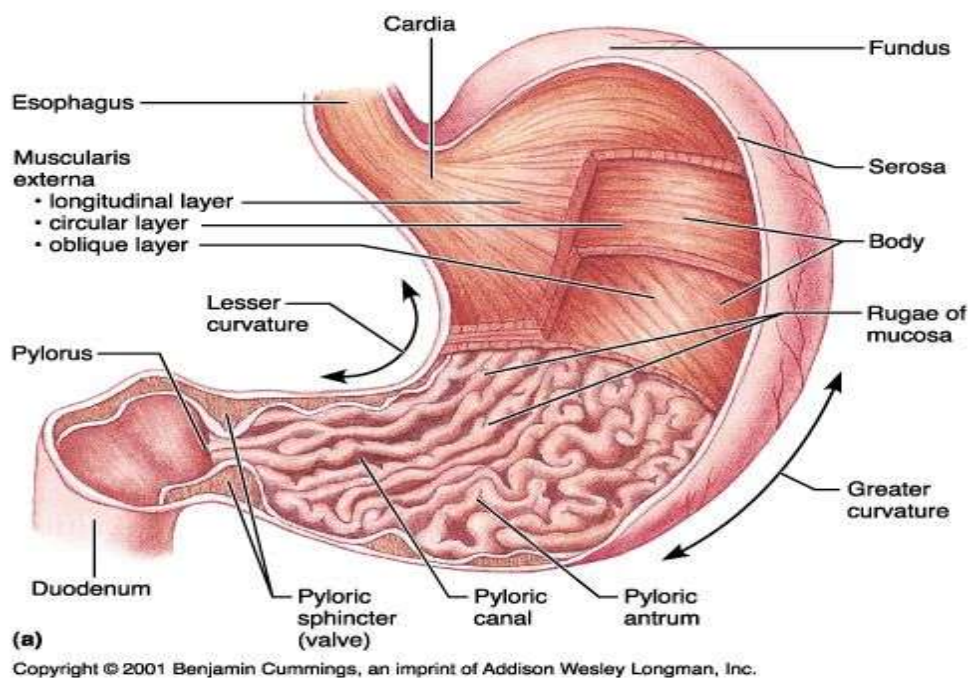


Figure (1) diagrammatic representation of internal view of stomach

The stomach is a muscular organ, J-shaped hollow and dilated part of the digestive tract. The main function of the stomach temporarily stores food, and mix food with the stomach secretion and then slowly release it into the duodenum. when the stomach is empty occupies a volume of about 50ml , but this can increase to 1 liter when full.

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus).

The proximal part formed by the fundus and the body act as a deposit of undigested material, while, the antrum is the main place to mix movements and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs both during fasting and during eating states. The pattern of motility is however different in the 2 states.

During the fast, an interdigestive series of electrical events take place, passing through both in the stomach and in the intestine every 2 to 3 hours. This is called the interdigestive myoelectric Cycle or migrating mylo-electric cycle (MMC), which is divided into the following 4 phases.

Phase I (basal phase): period that lasts from 30 to 60 min with no contractions .

Phase II (pre-burst phase): this phase mainly increases frequency and intensity for phase progression and period about 40-60 min. gastric

discharge of fluid and very small particles begins later in this phase.

Phase III (burst phase): this phase is short intense period, major distal and proximal period of gastric contractions (4 to 5 per minute) about 4-6 min. It is also called "House keeper wave", burst phase the undigested gastric contents is swept out of the stomach down to the small intestine .

Phase IV: this is a short transitory period of about 0 to 5 min, this phase occurs between the last part of phase III and beginning of phase I. After feeding the phase IV cycle leads to change in the pattern of contraction, may last for many min. increase gastric retention time due to the frequent administration of mixtures meal .

After ingestion of a compound meal, the pattern of The contractions change from fasting to fed State. This is also known as digestive motility pattern and comprises continuous contractions such as in phase 2 of the fasting state. These contractions cause the size of food particles to be reduced (a less than 1 mm), which are pushed towards the pylorus in suspension During the fed state the onset of MMC is delayed, resulting in slowing gastric emptying rate.

Scintigraphic studies determination of the gastric emptying rate revealed that oral controlled release dose the forms are subject to such short

complications unpredictable gastric and gastric residence time.[6]

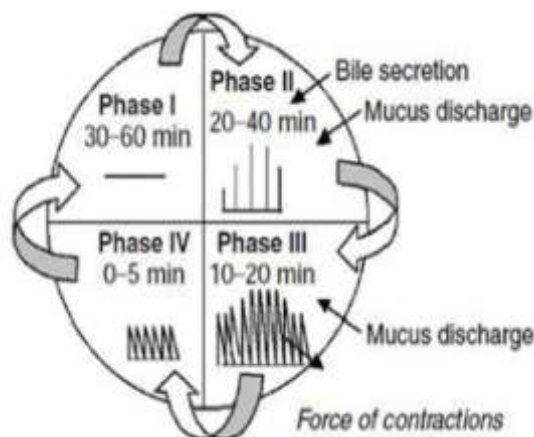


Figure (2) mobility pattern in gastrointestinal tract

Advantages Of Gastroretentive Drug Delivery Systems [7]

1. Enhanced bioavailability
2. Enhanced first pass biotransformation
3. Targeted therapy for local ailments in the upper GIT
4. Sustained drug delivery/reduced frequency of dosing
5. Minimized adverse activity at the colon
6. Reduced fluctuations of drug concentration
7. Reduced counter – activity of the body
8. Extended time over critical (effective) concentration
9. Minimized adverse activity at the colon
10. Site specific drug delivery to stomach can be achieved
11. Gastric irritation can be avoided by designing sustained release.

Disadvantages Of Gastroretentive Drug Delivery Systems

1. Drugs that absorb equally well through GI e.g. isosorbide dinitrate, Nifedipine
2. Drugs that absorb selectively in colon, e.g. corticosteroid
3. Not suitable for drugs with limited acid solubility e.g. phenytoin
4. Not suitable for drugs unstable in acid environment e.g. erythromycin
5. Drugs that irritate or cause gastric damage slow release. E.g. aspirin and NSAIDs

6. Floating drug delivery systems require a large amount of fluid level in the stomach to float

APPROACHES TO ACHIEVE GASTRIC RETENTION

1. High density (sinking) system or non-floating drug delivery system.
2. Floating drug delivery systems
3. Modified shape systems or unfolding systems
4. Bio adhesive systems/mucoadhesive systems

Drugs that are formulated in gastroretentive drug delivery systems [8]

1. Drugs acting locally in the stomach. For example, Antacids and drugs for H. pylori, namely Misoprostol
2. Drugs which are rapidly absorbed from the gastrointestinal tract for example tetracycline, metronidazole
3. Drugs poorly soluble at alkaline pH, for example Furosemide, diazepam, verapamil, etc
4. Drugs which have a narrow absorption window. For example, cyclosporine, levodopa, methotrexate...etc
5. Drugs that are primarily absorbed in the stomach for example Amoxicillin
6. Drugs that interfere with normal microbes in the colon for example Antibiotics against Helicobacter pylori
7. Drugs that break down in the colon for example, ranitidine, Metformine HCL.

Table (1)Gastroretentive drug delivery system vs. conventional drug delivery systems [9]

S.No	Conventional DDs	GRDDs
1	Drug acting locally in the stomach	Drugs having rapid absorption through GIT
2	Not much advantageous Drugs which are poorly soluble at an alkaline ph	Very much advantageous Drugs which are poorly soluble at an alkaline ph
3	Not suitable for Drug with narrow absorption window in small intestine	suitable for Drug with narrow absorption window in small intestine
4	Not much advantageous for Drug having rapid absorption through GIT	Very much advantageous for Drug acting locally in the stomach
5	Not much advantageous for Drugs which degrades in the colon	Very much advantageous for Drugs which degrades in the colon
6	High risk of toxicity	Very low risk of toxicity
7	No risk of Dose dumping	Possibly of dose dumping
8	Less Patient compliance	Improve patient compliance

Factors affecting gastric retention[1,10]

There are many factors affecting gastric emptying of an oral dosage form:

1. Particle size: It must be between 1 and 2 mm to pass through the pyloric valves in the small intestine.

2. Density : The density of the dosage form should be between from 1 g / cm³ to 2.5 g / cm³

3. Dimensions: The size should be over 7.5mm diameter.

4. Form of dosage forms : Ring and tetrahedron devices with bending 22.5-48 KSI modulus (keto / inch²have 90-100% gastric retention times (GRT).

5. Single unit / multiple unit : Multiple units are preferred due to predictable release profile, multiple unit co-administration, plus safety margins.

6. Food intake: GRT is longer in powered states.

7. Nature, calorie content : Non-digestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, fat and protein flour GRT is increasing.

8. Frequency of recruitment: GRT increases 400 times due to the low MMC frequency

9. Posture: Varies between spine and standing position ambulatory states.

10. Gender: Females have a shorter GRT than males.

11. Age: An age > 70 shows a longer GRT.

12. Nature of the drug: Drugs Affecting the Gastrointestinal Tract transit time, for example. Codeine and pharmacokinetic agents, eg. metoclopramide, cisapride can increases GRT.

13. Other factors:

Pathological states of the individual (disease, diabetes, etc.), Body mass index, Physical activity
 Molecular weight and lipophilicity of drug according to its state of ionization.

Gastroretentive Dosage Form

Gastro-retentive dosage forms are systems that can stay in the gastric region for several hours and therefore prolong the gastric residence time of drugs. Then oral administration, such a dosage form is stored in stomach and releases the medicine in a controlled manner and sustained so that the drug can be administered continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug waste and improves the solubility of drugs that are less soluble in a high pH environment.

Approach of Gastro retentive Drug Delivery System[11]

- 1..Floating drug delivery systems
 - a. effervescent system
 1. volatile liquid containing system
 2. gas generation system
 3. ion exchange region
 - b. Non effervescent system
 1. colloidal gel barrier system(hydrodynamically balance system)
 2. intragastric / micro porous compartment system
 3. alginate beds
 4. hollow microspheres
- 2.High density system or non- floating drug delivery system.
- 3.Modified shape systems or unfolding systems
- 4.Bio adhesive systems/mucoadhesive systems



Figure (3) approach of gastric retention

Floating Drug Delivery Systems [12]

Floating Drug Delivery Systems (FDDS) or hydrodynamically balanced systems have a volume density less than that of gastric fluids and therefore remain floating in the stomach without affecting the rate of gastric emptying over an extended period of time. While the system floats in the stomach contained, the drug is slowly released at a stomach rate. After the release of the drug, the residual system is emptied from the stomach.

Floating drug delivery system can be divided into :

- a-non effervescent system
- b-Gas generation (Effervescent)

a. Non Effervescent System

The One of the methods of formulating such a dosage forms involves mixing of the drug with a gel, which swells on contact with gastric fluid after oral administration and maintains the relative integrity of shape and bulk density less than one in the external gelatinous barrier. The air trapped by The swollen polymer provides buoyancy at these dosage forms.

Ex: hydroxyl propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be divided into four subtypes

1. Hydrodynamically Balanced System(HBS)

Contains drugs containing hydrocolloid gelling agents to remain floating in the contents of the stomach. This prolongs GI residence time and maximizes the amount of drug that reaches their absorption sites as a solution for easy

absorption This system incorporates a high level (20 to 75% w/w)of one or more highly gelling agents soluble cellulose-type hydrocolloid, e.g Hydroxy propyl cellulose(HPC), hydroxyethyl cellulose(HEC), hydroxyl propylmethyl cellulose (HPMC), polysaccharides and a polymer forming a matrix such as a polycarbophil, polyacrylate and polystyrene. By getting in touch with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface.

2. **Micro-porous Compartments System** This technology is based on the encapsulation of a drug reservoir in a micro-porous compartment with pores along its upper and lower surface. The peripheral walls of the drug reservoir compartment they are completely sealed to avoid direct contact of the gastric surface with the undissolved drug In the stomach, the flotation chamber containing entrapped air floats the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolve the drug and carried the dissolved drug for continuous transport through the intestine for absorption.

3. **Alginate beads** Multiple unit float dosage forms have been. developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm in Diameter were prepared by dropping sodium alginate solution in aqueous calcium chloride solution, causing a precipitation of calcium alginate, these beads were then separated, snap frozen in liquid nitrogen and freeze dried at 40°C for 24hrs leading to the formation of a porous system that maintained floating force for over 12hrs.

4. **Hollow Microspheres / Microballons** Hollow microspheres loaded with drugs in their the outer polymer shelf have been prepared by a new

emulsion solvent diffusion method . The ethanol /dichloromethane solution of the drug and a enteric acrylic polymer was poured into a shake polyvinyl alcohol solution (PVA) that was thermally controlled at 40 ° C 18. The gas phase was generated in the polymer droplet dispersed by the evaporation of the formed and internal dichloromethane cavity in the microsphere of the drug polymer. The microballon continually floated above the surface of an acidic dissolution medium containing surfactant for more than 24 hours.

b..Gas generation systems (effervescent)

These floating systems use prepared matrices with swellable polymers such as methocel, polysaccharides (eg, chitosan), effervescent components (for example, baking soda, citric acid or tartaric acid). The system is prepared so that when reaching the stomach, carbon dioxide is released, floating the formulation in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and baking soda, multi-unit floating pills generate

carbon dioxide when ingested, floating capsules with a core of sodium bicarbonate, lactose and hydroxylated polyvinylpyrrolidone propylmethylcellulose (HPMC) and floating system based on an ion exchange resin system.

1. **volatile liquids containing Systems** These devices are osmotically controlled floating systems that contain a hollow deformable unit that can be converted from a collapsed to an expanded position and returned again to collapse position after a prolonged period. A deformable system consists of two chambers separated by an impermeable, mobile bladder pressure responsive . The first chamber contains the drug and the second chamber contains a volatile liquid. The device is inflated and the medicine is continuously released from the reservoir into gastric fluid. The apparatus may also consist of Bio-erodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing inflatable chamber to release gas and collapse after a predetermined time to allow Spontaneous expulsion of the inflatable system of the stomach.

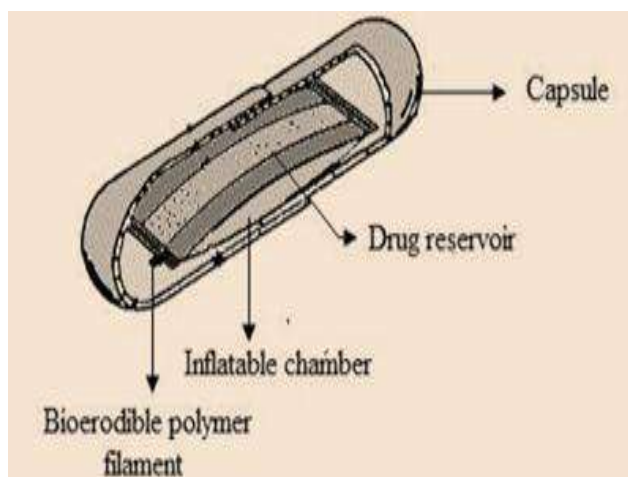


Figure (4)gastro inflatable drug delivery devices

2. **Gas Generation Systems:** These floating fuel systems use an effervescent reaction. between carbonate / bicarbonate salts and citric / Tartary acid for the release of CO₂ it is trapped in the gelatinous hydrochloride layer of the system, thus decreasing its specificity gravity and the fact that it float above chyme. These tablets may either single layer in which CO₂ generating components are intimately mixed within the tablet matrix or can be bilayer in which the gas-generating components are compressed into a hydrocolloid containing the layer and the drug in the outer layer for a sustained release. Multiple unit type Floating pellets that

generate CO₂ have also been developed. These kinds of systems float completely in 10 minutes and remain buoyant for an extended period of 5 to 6 hours.

3. **Ion exchange resins** the formulation of the coated ion exchange resin beads has been shown to have gastroretentive properties, that have been loaded with bicarbonates. Ion exchange resins are being loaded with bicarbonate and a drug that is negatively charged is bound to the resin, where the resulting beads are then bound encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. By reaching the acidic

environment of the stomach and the exchange of chloride and bicarbonate ions are taking place. As a result of this reaction, carbon dioxide has been released and trapped in the membrane carrying the beads to the top of the

gastric contents and producing a floating layer of resin beads in contrast to uncoated beads, which will sink quickly.

Table (2)Drugs explored for various floating dosage forms:

Dosage forms	Drugs
Microspheres	Ibuprofen, Aspirin , Tranilast
Granules	Indomthacine,Prednisolone
Capsules	Diazepam, Furosemide
Tablets/pills	Amoxicillin Trihydrate,Ampicillin Diltiazem , Theophyline

High Density System or non floating drug delivery system[13,14]

The density of a drug delivery system is an important factor that influences gastric residence time. High density devices use their weight as a retention mechanism. When the density of the system is greater than that of the gastric juice, the device settle down to the bottom of the stomach, remaining located below the pylorus .These systems with a density of about 3 g / cm3 are retained in the antrum part of the stomach and are able of withstanding its peristaltic movements. The only major drawbacks of such systems is that it is technically difficult to manufacture such formulations in large quantities drug (> 50%) and to achieve a specific gravity of 2.8 g / cm3. Formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc .

Bio/Muco Adhesive Systems

Bioadhesive drug delivery system (BDDS) used as a delivery device to the lumen , enhance the absorption of drugs in a site specific manner . this approach involved the use of bioadhesives polymers that can adhere to the epithelial surface in the stomach, gastric mucoadhesion does not tend to be strong enough to give to the dosage forms ability to resist the strong propulsion forces of the stomach wall. continuous production the mucosa of the gastric mucosa to replace the mucus that is lost due to peristaltic contractions and the dilution of the contents of the stomach also tend to be limit the capacity of mucoadhesion as a gastro retentive force. A few of the most promising ones excipients that have widely been used in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

Table (3)Mucoadhesive polymers used in GRDDS [2,15]

Anionic polymers	Nonionic polymers	Cationic polymers
Hyaluronic acid	Polyoxyethylene	Polylysine
Polyacrylic acid	Poly(vinyl alcohol)	Polybrene
Dextran sodium	Guar gum	Polyvinyl methyl imidazole
Sodium alginate	Poly(ethylene oxide)	Chitosan
Carboxymethyl cellulose	Poly (vinyl pyrrolidone)	
Pectins	Hydroxypropylmethyl cellulose	
Poly-L-aspartic acid	Hydroxyethyl cellulose	
Chitosan	Hydroxypropyl cellulose	

Modified shape systems or unfolding systems

Modified shape systems are non-disintegrating geometric shapes like tetrahedron, disc, spiral, which can be packed tightly into a

gelatin capsule and unfolds after dissolution of capsule shell. System consists of one erodible polymer, non erodible polymer and drug dispersed within polymer matrix.

Table (4) Marketed products of Gastroretentive drug delivery system. [2]

Sr. No.	Brand Name	Drug	Company, Country	Technology
1	CifranOD®	Ciprofloxacin (1 g)	Ranbaxy, India	Gas-generating ® floating tablet
2	Valrelease®	Diazepam (15 mg)	Hoffman-Laroche, USA	Floating capsule
3	Topalkan®	Al-Mg antacid	Pierre Fabre drug, France	Floating liquid alginate preparation
4	Madopar®	Levodopa (100 mg), Benserazide (25 mg)	Roche products, USA	Floating capsule
5	Cytotec®	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
6	Oflin OD®	Ofloxacin (400 mg)	Ranbaxy, India	Gas generating floating tablet
7	Liquid gaviscon®	Al. Hydroxide (95 mg), Mg. Carbonate (358mg)	Glaxo smith kline, India	Effervescent floating Liquid alginate preparation
8	Conviron®	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
9	Glumetza ®	Metformine HCL	Depomad, USA	Acuform
10	ProQuin® XR	Ciprofloxacin Hydrochloride	Depomad, USA	Acuform

Evaluation of gastroretentive dosage form

A) in vitro method of evaluation

Differential scanning calorimetry

DSC is performed to classify water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained by using DSC instrument equipped with an inter cooler zinc standards are used to calibrate the DSC temperature and enthalpy scale. The sample preparations are sealed in aluminium pan and heated at a constant rate of 10 °C/min over a temp range 25°C-65°C.

Fourier transform infrared analysis

The main application of Fourier transform infrared spectroscopy is identification of organic, polymeric, functional groups, and even certain inorganic materials. FT-IR measurement of pure drug, polymer and drug loaded formulations are obtained by the use of this technique. The pellets are prepared on kbr press under hydraulic pressure of 150kg/cm² and the spectra are scanned over the wave number range of 3600-400cm⁻¹ at ambient temperature.

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

The particle size and size distribution of beads or microspheres are determined in the dry state using optical microscopy method. The external and cross sectional morphology is accomplished by scanning electron microscope.

Swelling studies

The swelling of the excipient particles in the tablet involves the fluid absorption causing weight gain and volume. The absorption of liquid by particles may be due to the saturation of the capillary spaces within the particles or hydration of macromolecules. The liquid enters particles through the pores and bind to large molecules, break the hydrogen bond and cause the swelling of particles. The tablet is weighed and placed in a beaker containing 200 ml of 0.1 N HCl after each interval during which the tablet is withdrawn from the beaker, soaked using filter paper and reweighing.

$$\text{Swelling index (SI)} = \frac{(W_t - W_0)}{W_0} \times 100$$

Wt - tablet weight at time t

WO - initial tablet weight

Determination of drug content

The percentage of drug content indicates the amount of the drug is present in the formulation. Must not exceed the limit acquired by the monographic content of the drug is determined using HPLC, HPTLC, microtitrimetric methods, and also using spectroscopy techniques . To determine the drug content 10 tablets are crushed in the mortar .10 mg of tablet powder dissolved in 10 ml of 0.1 N HCL and after the drug sample is analyzed under ultraviolet spectrum photometer.

Dissolution studies

Dissolution tests are generally performed to calculate amount of drug released using USP Dissolution apparatus . The test is performed using 900 ml of 0.1N HCL, at 37 ° C and 100 rpm . A 10 ml sample is taken every hour and analyzed under u.v and absorbance is measured. The sample is replaced by the dissolution medium Cumulative the percentage is calculated using the equation obtained from standard curve.

Flotation studies

In vitro buoyancy is characterized by a floating lag time and total floating time . FLT and TFT are measured by placing the tablets in a 250 ml beaker containing 200 ml of 0.1N HCL. The time required by rise to the surface and float is called floating lag time and the period during which the tablet remained floating is called total floating time.

B) In vivo evaluation

X-ray method

X-rays are a very popular evaluation for the floating dosage form today. Help to locate the dosage form on the GIT and by which the stomach can be predicted and correlated the emptying time and the passage of the pharmaceutical form in the TGI. Here, the inclusion of a radiopaque material in a solid dosage form allows it to be visualized by x-rays.

Gastroscopy

It consists of a peroral endoscopy used with a fiber optic and video system. Used to inspect visually the effect of a prolonged stay in the environment of the stomach in the FDSS.

Ultrasonography

Ultrasonic waves reflect significantly different acoustic impedances at the interface images of certain abdominal organs. Most DFs do not have clear acoustic imbalances through its interface with the physiological environment. Therefore, ultrasonography is not commonly used

for FDSS evaluation. The characterization included the evaluation of intragastric localization of hydrogels, penetration of the solvent into the gel and interactions between the gastric wall and FDSS during peristalsis.

II. CONCLUSION:

Gastroretentive drug delivery system offer a several potential advantages for the drug with low bioavailability . drug absorption in the gastro intestinal tract is a highly variable process and prolonging the gastric retention of the dosage form and improve bioavailability of drug. different approaches for gastroretentive drug delivery system have their own advantages and disadvantages due to the unpredictability of the human GIT .to avoid the disadvantages of the gastroretentive approaches combinational gastroretentive approaches are appear to be beneficial for gastric retention and increase the efficiency of medical treatment .

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