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A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The aim of this review is to investigate, compile and present the recent as well as past literatures in more concise way with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in recent years in the field of oral drug delivery. It is widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. In order to understand various physiological difficulties to achieve gastric retention, we have summarized factors influencing and various strategies for gastric retention. It also includes invitro evaluation techniques to evaluate the performance of gastro retentive systems.

KEYWORDS: GRDDS, Oral drug delivery, Bioavailability, Gastric retention.

INTRODUCTION

The most popular route of administration for systemic action is oral route. It is probable that at least 90% of all the drugs given by oral route. Solid dosage form represents the preferred class of product among the drugs that are given orally. Oral route is the mostly prescribed route since it has patient compliance, ease of ingestion, pain avoidance & versatility to accommodate various type of drug. The short gastric retention time and unpredictable short gastric emptying time are the two problems of drug delivery systems. Decrease response of dose due to incomplete drug release from the dosage form in the absorption zone.

Drug absorption is unsatisfactory and highly variable among and between individuals due to physiological and usually affected by the GI transit of the form, especially its gastric residence time, which appears to be one of the major causes of the overall transit time variability. In delivery of drugs with narrow absorption windows in the small intestinal region the gastric retention will provide advantages.[1]

Attempts are being made to develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner.[2]

One novel approach in this area is GRDDSs (gastro retentive drug delivery system). Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of the GIT (gastro intestinal tract)or those are less soluble in or are degraded by alkaline pH or they encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their:

- Bioavailability
- Therapeutic efficiency and possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like domperidone, papaverine)

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for

local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.[3]

Gastric Emptying Time (Get) and Motility

GET occurs during both fasting as well as fed states. GET is the time required to pass drug from the stomach to the small intestine. It is the rate limiting step for drug absorption because the intestine is the major site for absorption. In general, bioavailability of the drugs is increased by rapid gastric emptying. For drugs that degrade in gastric environment, faster onset is required. The drugs which are poorly soluble at alkaline pH and are majorly absorbed from the stomach or proximal part of the intestine their dissolution is promoted by delayed gastric emptying.[4]

MERITS[5]

- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such ascyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc.
- Patient compliance by making a once a day therapy. • Improved therapeutic efficacy.
- Reduces frequency of dosing.
- Targeted therapy for local ailments in the upper GI tract.
- The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery.
- Gastro retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
- Prolong the residence time of the dosage form at the site of absorption.
- To avoid the first pass metabolism.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increase in drug bioavailability due to first pass metabolism.
- Site-specific drug delivery.
- Minimizing mucosal irritation by drugs, by drug releasing slowly at a controlled rate.

Demerits

- Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.
- In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- There is also possibility of esophageal binding with bioadhesive drug delivery systems.
- [6]GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.
- Hydrogel based swelling system takes longer time to swell.
- Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach.

Need For Gastric Drug Delivery System

- Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- [7]Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounter at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.

Factors Effecting Gastric Retention Of Dosage Forms[8]

- **Density:** GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
- **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% to 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 unfedstate- under fasting conditions:** GI motility is characterized byperiods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **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 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.
- **[9]Age:** GRT is more in geriatric patients and less in neonates and children. People with age more than 70 have a significant longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Disease State:** Gastric disease such as diabetes, chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc fluctuates the GRT
- **Concomitant Intake of Drug:** Combination of some drugs along with
- Gastric motility enhancers or depressants, affect GRT.

Various Approaches of Grdds

In order to overcome the factors effecting gastric retention, various approaches of GRDDS have been designed which includes the following

A) Floating Systems

An optimised level of drug bioavailability can be reached by judicious gastric retention. The floating drug delivery system is a novel approach for the same. It is needed for drugs that have an absorption window in the stomach or in the upper small intestine. This method does not affect the rate of gastric emptying over a prolonged time. It is a low density approach (lower than gastric fluid). Hence remain buoyant in the stomach releasing the drug slowly. The emptying of residual system is followed by the drug release, from the stomach. Thus occurs an increased gastric retention time (GRT) and improved control over fluctuating plasma drug concentration. The pre-requisites for floating drug delivery system are.[10]

1. Slow content release to act as reservoir.
2. Specific gravity should be maintained lower than gastric contents (1.004 – 1.01gm/cm^3)
3. It must form a cohesive gel barrier.

Mechanism of Floating Drug Delivery Systems: The slow drug release is accompanied with requisite rate during the system flow on the gastric contents. The release is followed by removal of the residual system from the stomach. But, along with the appropriate level of floating force (F), minimum levels of gastric contents are needed to permit achievement of buoyancy retention principle and also to keep dosage form buoyant over meal surface. In the literature an apparatus has been described that measures the kinetics of floating force. Its operation constitutesof measuring a force equivalent to F (with respect to time) which keeps the object submerged.

As depicted in **Fig,** the presence of force F in a higher positive side makes the object flow better. This apparatus optimizes FDDS and prevents its drawbacks unforeseeable intragastric buoyancy capability variations, related to stability and durability.

$F = F_{buoyancy} - F_{gravity}$

$= (D_f - D_s)\, gv$

Where,

F= total vertical force,

D_f = fluid density,

D_s = object density,

v = volume and

g = acceleration due to gravity.

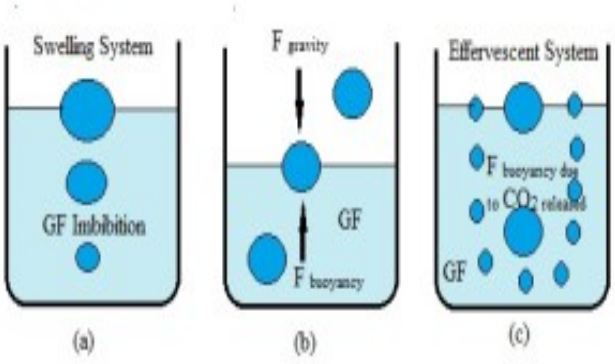

Fig 1: Mechanism of floating drug delivery systems, gf: gastric fluid, co_2: carbon dioxide

Based on the buoyancy mechanism, floating systems are classified as follows

a) Low density systems

1) Non effervescent system

i) Hydrodynamically balanced system

ii) Microporous compartment systems

iii) Alginate beads

iv) Hollow microspheres

2) Effervescent systems
i) Gas generating systems
ii) Volatile Liquid/Vacuum Containing Systems.

B) Non floating systems

Non- floating systems are class of gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are further classified as below :

1. High density systems
2. Swelling and expanding systems
3. Muco adhesive systems
4. Magnetic systems
5. Raft forming systems

Low Density Systems[11]

Low density systems are also known as floating drug delivery systems (FDDS. These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach.

Based on the mechanism of buoyancy, two distinctly different types of systems have been utilized in the development of GRDS:

1) Non effervescent systems
2) Effervescent systems

Non Effervescent Systems

Non-effervescent systems are prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene and polymethacrylate.In these system the floating of dosage forms involves intimate mixing of drug with a gelforming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. These systems can be further classified into the following subtypes:[12]

a) Hydrodynamically balanced systems

These are single-unit dosage forms, which contain one or more gel-forming hydrophilic polymers such as HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenans, or alginic acid thus forming hydrocolloids and remain buoyant on the stomach contents. These polymers are mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to a dosage form for a long period in gastric juice as shown in Figure(Dhiman et al., 2011)[13].The continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and provides buoyancy to dosage form. A fatty excipient can be incorporated to give low density formulations reducing the erosion.

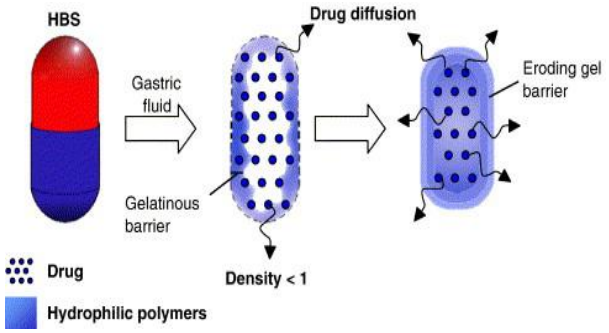

Fig. 1: Mechanism of hydrodynamically balanced systems.

b) Micro porous compartment system[14]

This system involves the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to prevent any direct contact of the undissolved drug with the gastric surface. The floatation chamber in the stomach containing entrapped air causes the delivery system to float in the gastric fluid. The gastric fluid that enters through the aperture dissolves the drug and causes continuous transport of the dissolved drug across the intestine.

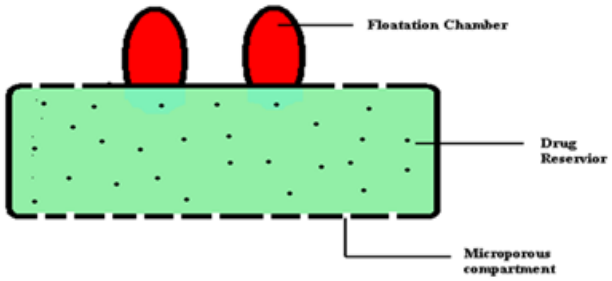

Fig. 2: Microporous compartment system.

b) Alginate beads:[15]

A multi-unit gastroretentive sustained release dosage form of a water-soluble drug (eg: ranitidine hydrochloride) is prepared by emulsion gelation technique. The beads are formed using sodium alginate as the polymer and oil were entrapped in the beads by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. Thus beads are prepared and these beads deliver the drug in stomach for a prolonged duration.

c) Hollow microspheres:[16]

Hollow microspheres are considered as one of the promising buoyantsystems because they combine the advantages of multiple-unit system and good floating. The drug loaded hollow microspheres are prepared by using solvent diffusion technique. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug.

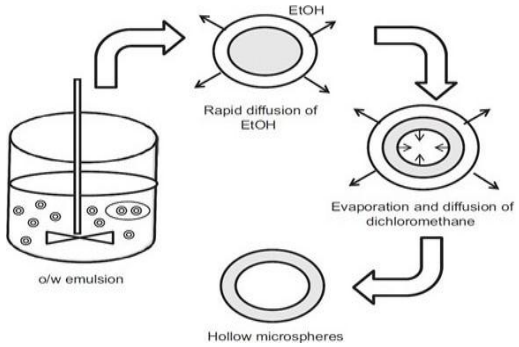

Fig. 3: Solvent diffusion technique.

2) Effervescent Systems:[17]

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types:

1. Gas generating systems,
2. Volatile Liquid/Vacuum Containing Systems.

1) Gas generating systems:[18]

The mechanism involved in this system is production of CO_2 gas due to reaction between sodium bi carbonate, citric acid and tartaric acid.The gas produced gets entrapped in the jellified hydrocolloid layer of the system which decreaseits specific gravity and making it float over gastric contents. The system consist of a sustain release pill as seed surrounded by double layers. The inner layer is an effervescent layer containing sodium bi carbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA shellac etc.

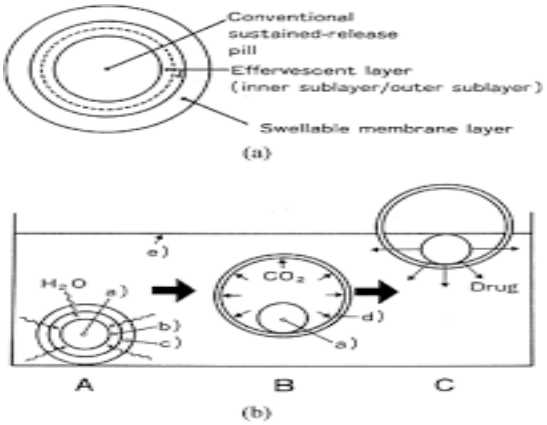

Fig. 4: Gas generating sytems.

These can be further divided into

1) Floating capsule

These are prepared by formulating mixture of sodium bi carbonate and sodium alginate. On exposure to acidic environment, CO_2gas is generated which is trapped in the hydrating gel network and makes the system to float.

2) Floating pills

These are a type of sustained release formulations which are basically multiple types of unit dosage forms. The sustained release pill is surrounded by two layers. Outer layer consists of swellable membrane and the inner layer consists of effervescent agents. The systems swell due to swellable membrane and then sink. Due to presence of effervescent agent, CO2 is released and the system floats.

3) Floating system with ion exchange resin

The most common approach for formulating these systems involves resin beads loaded with bi carbonates. This is then coated with ethyl cellulose which is usually insoluble but permeable to water .this causes carbon di oxide to release and the system to float.

2) Volatile liquid containing systems[19]

This type of system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperatureto cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid. These systems are further classified as below

a) Intragastric floating gastrointestinal drug system[20]

These systems 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 microporouscompartment (fig 1).

b) Inflatable gastrointestinal delivery system

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, then 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 into the gastric fluid.

c) Intragastric-osmotically controlled drug delivery system[21]

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bioerodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release theintragastric-osmotically controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag.

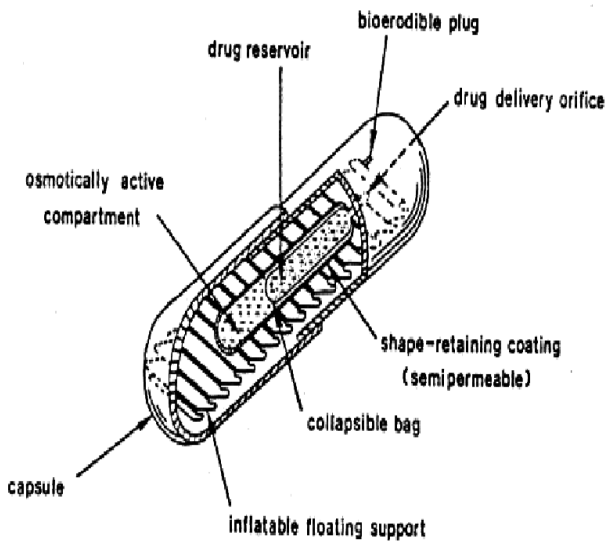

Fig. 5: Intragastric-osmotically controlled drug delivery system.

High Density Systems[22]

High density systems involves the formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3). These 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. The materials increase density by up to 1.5- 2.4 gm/cm3.[23]

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. Dense pellets (approximately 3g/cm^3) that are trapped in rugae tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. A density close to threshold density seems necessary for significant prolongation of gastric residence time.

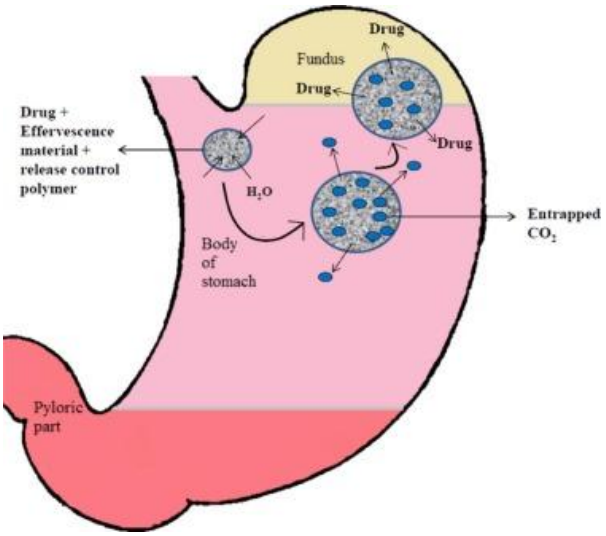

Fig. 6: High density systems.

Swelling and Expanding Systems[24]

These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorus is prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. The swelling usually results from osmotic absorption of water and the dosage form and these systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. The formulations that are designed for gastric retention and controlled delivery remain in the gastric cavities for several hours even in the fed state. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release. On coming in contact with gastric fluid the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross links prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

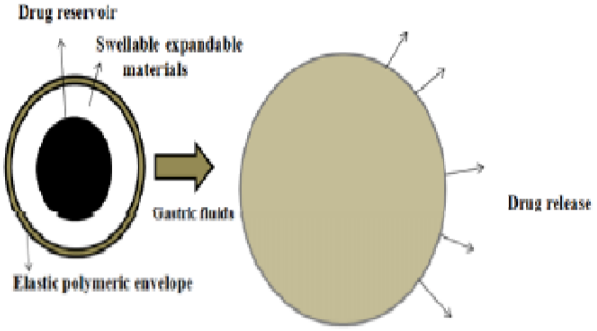

Fig. 6: Swelling and expanding systems.

Muco/Bio-Adhesive Systems[25]

These are developed to perform drug absorption in a site specific manner. In this approach, bioadhesive polymers are used that adhere to mucosal epithelial surface in stomach, thereby increase gastric retention time. These polymers can be cationic or anionic or neutral.The polymers used may be natural such assodium alginate, gelatin, guar gum etc., and semisynthetic polymers such as HPMC, carbopol,sodium carboxy methyl cellulose. There are various mechanisms of adhesion:-

- Wetting theory causes the ability of bioadhesive polymers to spread and cause intimate contact with mucin layers.
- Diffusion theory involves the physical entanglement of mucin strand with soluble polymer or interpenetration of mucin strand into structure of polymer.
- Absorption theory elicitbioadhesiondue to secondary forces such as vanderwaal forces and hydrogen binding.
- Electronic theory proposes attractive electrostatic forces between glycoprotein mucin network and bioadhesive material.

There are various types of adhesion through which polymers adhere to the mucus membrane which includes:[26]

❖ **Hydration mediated adhesion:** In this the hydrophilic polymer become sticky and mucoadhesive upon hydration.

❖ **Bonding mediated adhesion:** It involves mechanical or chemical bonding. chemical bonds may involve ionic or covalent bonds or vanderwaal forces between the polymer molecule and the mucous membrane.

❖ **Receptor mediated adhesion:** It takes place between certain polymers and specific receptors expressed on gastric cells. The polymers can be cationic or anionic or neutral.

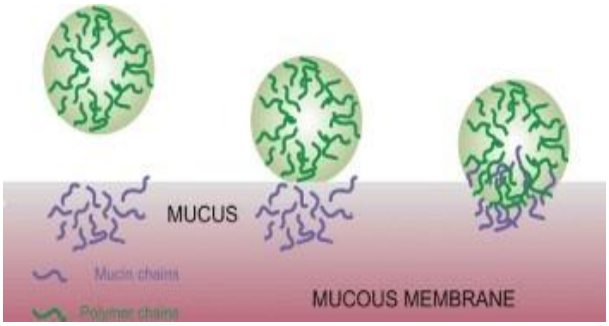

Fig 7: Muco/bio adhesive systems.

Magnetic Systems:[27]

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

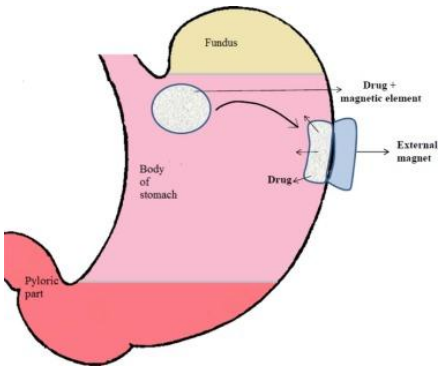

Fig. 8: Magnetic systems.

Raft Forming Systems:[28]

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. Floating raftshave been used in the treatment of Gastric esophageal reflux disease (GERD). The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.

Superporous Hydrogel Systems:[29]

Superporous hydrogels are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states during which the premature evacuation of the dosage

form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size within minutes, due to rapid intake of waterby capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol.

Evaluation of grdds

Pre compression parameters

1) Bulk density:[39]A quantity of drug powder was weighed initially and was introduced in to 10 ml measuring cylinder.The bulk volume was determined and the apparent bulk density in g/ml was calculated using the formula

Bulk density=weight of powder/bulk volume

2) Tapped density:[40] A quantity of drug powder blend from each batch, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to tap under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted.

Tapped density=weight of powder/tapped volume

3) Hausner's ratio (HR):[41] This was calculated as the ratio of tapped density to bulk density of sample

HR=Tapped density/bulk density

4) Carr's compressibility index:[42] The Compressibility Index of the powder blend was determined by the below formula

Carr"s compressibility index = Tapped density-bulk density/tapped density*100

5) Angle of repose:[43] The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

Tan θ = h/r

Where,

h= height of the powder cone and

r= radius of the powder cone.

Standard values of angle of repose.

Angle of repose	Flow property
>250 Excellent	Excellent
250-300	Good
370-400	Fair beyond
400	Poor

Post Compression Parameters

1) Weightvariation test:[30] To study weight variation twenty tablets of the formulation were weighed using a citizen electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Percentage Deviation (PD) $=w_{avg} - w_{initial}/w_{avg}$

Where,

W_{avg} = average weight and

$W_{initial}$= initial weight

Standards for uniformity of weight as per I.P.

Avg. wt. of tablet	% Deviation
80 mg or < 80mg	10
80mg to < 250 mg	7.5
250mg or more	5

2) Hardness test:[32,31] Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined by diametric compression using a Monsanto Hardness Tester. Three tablets were randomly picked and hardness of the tablets was determined. A tablet hardness of about 2-4 Kg/cm^{2}is considered adequate for mechanical stability.

3) Friability test:[33] The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). The tablets were initially weighed and transferred into Friabilator. The Friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by the following formula.

[34]% Friability = initial weight-final weight/initial weight *100

- Percentages Friability of tablets less than 1% are considered acceptable.

4) Floatation studies:[35] The invitro buoyancy is characterized by floating lag time (FLT) and total floating time (TFT). The FLT and TFT are measured by placing the tablets in a 250 ml beaker containing 200ml of 0.1N HCL. The time required by the tablet to rise to the surface and float is known as floating lag time and the time period upto which the tablet remained buoyant is called total floating time.

5) Drug content uniformity:[36,37] Inthis tablets were randomly selected, weighed and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N HCl and sonicated for 20min.The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at λmax of API(nm) using 0.1 N Hydrochloric acid as blank. The tablets contained not less than 85% or not

more than 115% (100±15%) of the labeled drug content can be considered as the test was passed**.**

6) Drug release study:[38] The drug release study for the Floating tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at λmax of API (nm) using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3)

CONCLUSION

Gastro retentive drug delivery system have emerged as an efficient means of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing GRDDS. GRDDs will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which are sustained over a large period. GRDDS is much safer dosage form and have systemic, localized actions as well GRDDS also reduces dose frequency there by minimize contra indication, systemic toxicity, drug dependence. Based on the literature surveyed, it is concluded that Gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability.

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