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Gastro retentive drug delivery systems

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ABSTRACT :
Most preferable route of drug delivery is oral administration . Gastro retentive drug delivery is one of the site - specific delivery of the drugs at stomach . This route have a high patient acceptance, comfort of administration . Effectiveness of oral drug delivery depend upon the various factors such as the process of gastric emptying . Gastricintenstinal transit the time of the dosage form, the drug release rate from the particular dosage form , and site of drug absorption . In the order of various physiological barrier to achieving the gastric retention for prolonged time . Afterwards, we have review the various approaches of gastro retentive drug it is designed and developed. i.e Sinking system (High density), bio adhesive, expandable, unfoldable, swellable system, super hydrogel system and magnetic system , and floating with high porosity ,and advantages and disadvantages of gastroretentive drug delivery system (GRDDS) . To formulate for the gastroretentive drug delivery systems (GRDDS) , factors controlling gastric retention time.

Keywords: Gastroretentive drug delivery systems, floating system, Non - floating system, Gastric retention time.

INTRODUCTION:

the most benificial and preferred method of oral administration of any drug delivery to the systemic circulation. In the pharmaceutical field the interest is developed towards oral controlled release drug delivery to achieve improved therapeutic benefits, such as of dosing administration, patient compliance and Pliability in formulation. Drugs that are without effort absorbed from gastrointestinal tract (GIT) and have half-lives very short are remove fastly from the systemic circulation(1). These drug delivery systems suffering from divided into mainly two adversity : the Unpredictable Short Gastric Emptying Time (GET)and Short Gastric Retention Time (GRT)(2). orally administered to formulate a site - specific controlled release dosage form, its the desirable to achieve of a prolonged gastric residence time by the drug delivery (3). As well as prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine.
e.g.: Treatment of peptic ulcer.
Gastroretentive dosage form can remains in the gastric region for long periods and significant prolong the gastric retention time (GRT) of drugs (4).
Low density (Floating systems) that caused in gastric fluid (5,6,7).
Mucoadhesive systems are causes bio adhesive to stomach mucosa(8).

Advantages of gastroretentive drug delivery systems :

1. It increases the patient compliance by reduce dosing frequency .
2. It Improve Curative result of small - half life drugs.
3. Buoyancy increase gastric residence time.
4. The site specific drug delivery to stomach can be achieved.
5. In this drug release in a controlled manner. (9)

Disadvantage of gastroretentive drug delivery systems :-

1. Medicine that are absorbed selective in colon such as corticosteroids.
2. Unsuitable for drug with limited acid solubility . E.g. phenytoin .
3. Unsuitable for drugs those are unstable in acidic environment E.g. Erythromycin .
4. Drugs that irritated or causes gastric lesions on slow release . E.g. Aspirin .

Anatomyofthestomach:
The gastrointestinal tract divide into three main parts

- Stomach
- Small intestine :duodenum, Jejunum and ileum
- Large intestine

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Parts of stomach

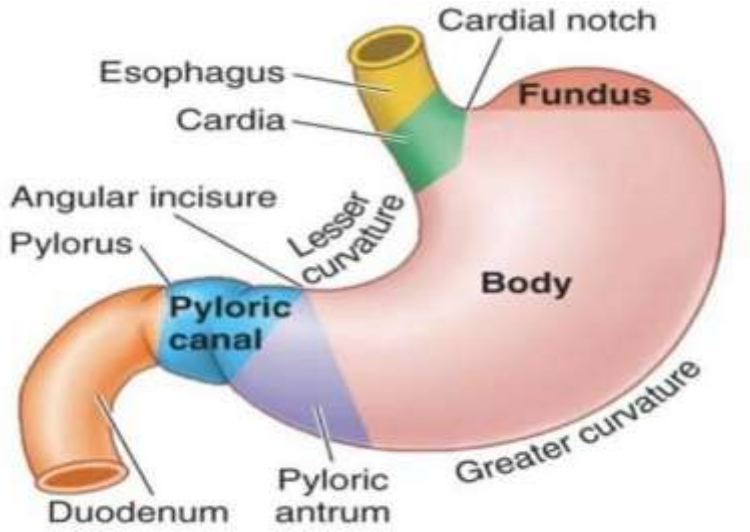

Figure 1: Parts of stomach

The gastrointestinal tract is muscular tube of about 9 m which extends from mouth to anus . Main function of stomach to take nutrients and remove out waste products by physiological process Such as absorption, digestion ,secretion and excretion .

Three muscle layer of stomach called oblique muscle and it is situated in the proximal part of the stomach branching over the fundus and higher region of the gastric body . stomach divided into fundus, body and pylorus (10). The stomach is a J shaped organ located in the upper left hand portion of abdomen and main function of the stomach to store the food temporarily .

Physiology of stomach

The stomach is an expanded section of the digestive tube between oesophagus and small intestine.

There are four major types

1. Mucous cells - secrete alkaline mucus
2. Parietal cells - secrete HCL
3. Chief cells - secrete pepsin
4. G cells – secrete hormone gastrin (11).

Gastric motility and gastric empty rate

The orally administered drug of bioavailability is depending upon the state of the feeding. The fasted state it is interdigestive series of electric event called interdigestive myoelectric cycle .

It is divided into 4 phases

- Phase 1 (basal phase) from 40 – 60 min with rare contraction.
- Phase 2 (Preburust phase) from 40 – 60 min with intermittent potential.
- Phase 3 (burst phase) for 4 – 6 min it is a regular contraction occur for short period .
- Phase 4 it lasts for 0 – 5 min and occurs between phase 3 and phase 1.

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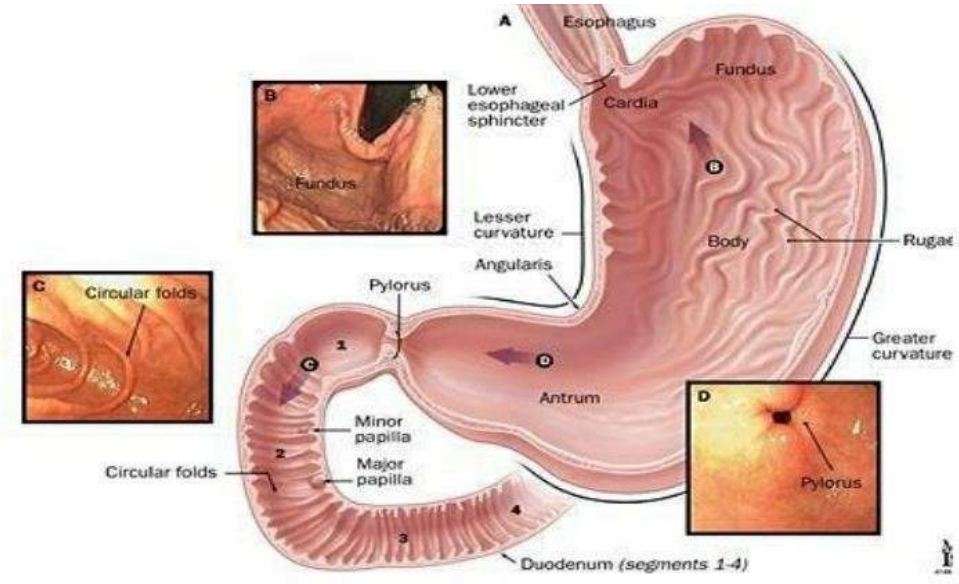

Figure 2 : Shows physiology of stomach

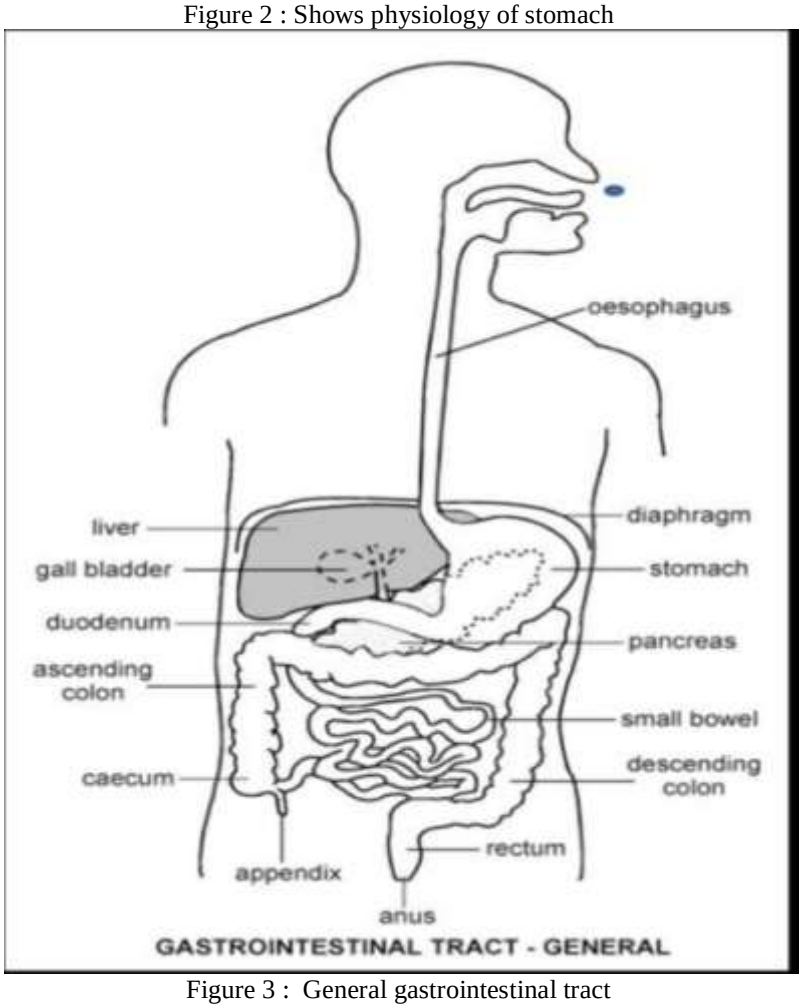

Figure 3 : General gastrointestinal tract

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Factors affecting Gastric Retention Of Dosage Forms :

In the developing of Gastroretentive dosage forms the stomach anatomy and physiology contain parameters to be taken in consideration . To pass from the pyloric valve into the small intestine and the particle size ranges in between of 1 to 2 mm (12). The most essential parameters controlling the gastric retention time (GRT) Of important factors of oral dosage forms is density, size and shape of the dosage form and the manner food intake nature, caloric content and frequency by which of intake, age , sleep , body mass index ,(e.g. . Diabetes etc.) (13).

DensityOfDosageForms :

The density of dosage form also influenced by the rate of gastric emptying and determine the exactly location of the system in the stomach (14). The density of range is less than 1.0 gm / cm^3 is needed to show property of the Floating (15).

Size And Shape Of The Dosage Form

The most important factor in dosage form Size and shape of dosage forms are helpful in the designing indigestible single unit solid dosage preparation. The gastric residence time of non – Floating dosage forms are highly different and greatly dependent on their size , it is large , medium and small . the larger the dosage form the higher will be the gastric retention time (GRT) because to the larger size of the dosage form (16).

The dosage form with a diameter of greater than 7.5 mm show the longer gastric residence time in contrast with the one having 9.9 mm (15). Gastric residence time as contrast with the other different shapes of ring shaped and tetrahedral shaped (17) .

FoodIntakeAndItsNature.

Food intake , viscosity and food volume , caloric value and feeding frequency of have a profound impact on the gastric retention of drug . The drugs absorption Inhanced by allowing its stay at the site of absorption for a longer period(18) .

Effect Of Posture , Gender And Age

Generally female have poor gastric emptying rates than male . The effect of posture does not affect any significant in the mean gastric retention time (GRT) for persons in upright , ambulatory and supine state (19) .

Possible drug substances for gastroretentive drug delivery systems.

1. Narrow absorption window drugs in the gastrointestinal tract (GIT) .e.g. : L – DOPA , Furosemide etc.
2. Drugs are locally efficient in the stomach e.g. Antacids etc.
3. Drugs that affect normal colonic microbes e.g. antimicrobic opposite to Helicobacter pylori.
4. Drugs are exhibition poor solubility at most pH value e.g. diazepam , verapamil HCL .

To Achieve Gastric Retention following approaches as follows

Approaches of gastroretentive drug delivery systems :-

Sinking system(High density) or non – floating drug delivery systems.

This approach including formulate dosage form with the density that must exceed density of normal stomach content (~ 1.004 gm / cm^3) .

These preparation are prepared by the layer of drug on a heavy core or added with inert material such as barium sulphate etc. (20) .

The material are inhancing density by up to 1.5 – 2.4 gm / cm^3 . density close to 2.5 gm / cm seems essential for significant inhancing of gastric residence time (21) . but efficacy of this system in human beings was not noticed (22). and no system has been available in market.

Floatingdrugdeliverysystems :

Floating drug delivery system is one of the efficatious approaches to achieve gastric retention to obtain good drug bioavailability (23) . This delivery system is helpful for drug with an absorption site in the stomach or in the upper small intestine (24) . a bulk density lower than gastric fluid and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system . The major requirements for floating drug delivery system are

- It must release content slowly to serve as a reservoir
- It must maintain specific gravity lower than gastric content (1.004 – 1.01 gm / cm^3) .
- It must from a cohesive gel barrier .

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) (25). Or by the incorporation of low density materials (e.g. fatty materials or oils or foam powder)(26,27) . a single unit floating system was proposed consisting of polypropylene foam powder matrix forming polymerase drug and filter (28). Various multiple unit floating system like air compartment multiple – unit system , Hollow

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microsphere (microballoons) prepared by the emulsion solvent diffusion method (29) . microparticles based on the low density foam powder beads prepared by emulsion gelating method (30) . Based on the mechanism of the buoyancy two distributed different technologies i.e. non – effervescent and effervescent systems has been utilized in the development of the floating drug delivery system.

Non – effervescentsystem:-

Non – effervescent floating drug delivery systems are generally prepared from the gel – forming or highly swellable cellulose type hydrocolloids.

In one approach , intimated mix of drug with a gel forming hydrocolloid which effect in contact with gastric fluid after the oral administration and maintaining relatives honesty of the shape and a bulk density is less than the unity within the gastric environment (31). This systems divided into the sub – types.

Hydrodynamicallybalancedsystems:-

Sheth and Tossounion (32) . 1st designed these ‘ Hydrodynamically balanced systems ‘ . These stomach contain medicine with gel creating hydrocolloids meaning to staying buoyancy on the abdomen containing. This are single unit indefinite quantity dosage forms , containing one or a lot of gel – forming hydrophilic polymers . hydroxethyl cellulose , (HEC) , sodium carboxymethyl cellulose (NaCMC) , agar , carrageenans or alginic acid are commonly used recipient to develop these systems (33 , 34) . The polymer is mixed with drugs and usually administered in the Hydrodynamically balanced system capsule . The capsule shell dissolved in contact of with water and mixture swell to form a gelatinous barrier, which imparts of the buoyancy to dosage form in gastric juice for a long period . because continuously erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form (34) . Incorporation of fatty excipients gives low – density formulation reducing the erosion madopor LP (Ŕ) , based on the system was marketed during the 1980 ‘s (35) . impactive drug delivers depend on the balance of the drug loading and the effective of polymer on its release profile several strategies have been tried and investigated to improved efficiency the floating Hydrodynamically balanced systems .

Hollowmicrosphere / Microballoons :-

Hollow microsphere / Microballoons filled with drugs in their other polymers shelf were ready by the simple solvent evaporation or solvent evaporation or spreading methods (36) . (figure 4) to lengthy the gastric retention time (GRT) of the dosage form . In generally used polymers to developed these systems are polypropylene , cellulose acetate , calcium alginate , agar drug released from the dosage form are dependent on the quantity of polymers , the plasticizer polymers ratio and the solvents are used for formulation . Microballoons floated continuous over the surface of an acidic dissolution media contain surfactant for > twelve hrs. .At present in hollow microsphere are consider to be one of the most promising buoyant systems because they are combine the benefit of multiple - unit system and benefit floating .

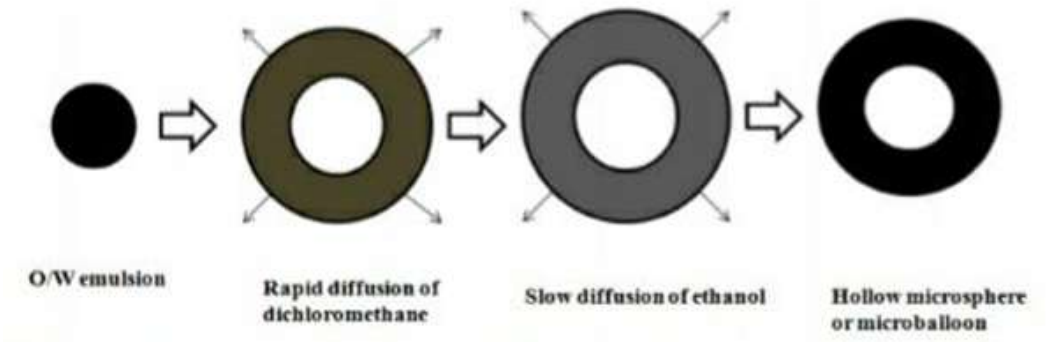

Figure 4: Formulation of floating Hollow Microballoons or Microsphere

Alginatebeads :-

Talukdar and Fassihi (30) . recently development a multiple – unit floating system based on cross – linked beads . They were made by using Ca^{2+} and low methoxylate pectin or Ca^{2+} low methoxylate pectin and Na alginate . in this approach generally sodium alginate solution is drop into aqueous solution of calcium chloride and

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causes the precipitation of calcium alginate. These bead are separating and dried by air convective and freeze drying , leading to the formulation of a porous system , it is maintain floating force for over 12 hrs. it improving (GRT) gastric retention time most than 5.5 hours. (37).

Microporouscompartmentsystem :-

This approaches based on the principle of the encapsulate of a drug reservoired interior a microporous compartment with pores beside its bottom walls and top (38). gastric fluid penetrate through the apertures , melt the drug and causes the dissolve drug for continuously transport across the intestine for drug absorption.

Effervescent (gasgenerating) systems:-

Floatability care often achieved by generation of gas bubbles . The optimum stoicheometric magnitude ratio of citric acid and bicarbonate for gas generation is report to be 0.76:1 .In this system carbon dioxide is discharged and causes the formation to float in the stomach (figure 5 and figure 6) . Materials that are the report area of mixture of Na alginate and bicarbonate , multiple – unit floating indefinite quantity forms that generating gas. (carbon dioxide) . Once eaten, floating mini capsule with a core of bicarbonate , milk sugar and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl alkyl group polyose (HPMC) , and floating system supported ion exchange resin technology etc. Bilayer or multilayer system has additionally been designed (39,40). The matrix with the chemical compound that is leaky to water, however to not carbon dioxide. The most difficulty of those formulations is finding a honest compromise between physical property, malleability and porosity of the polymers.

Bioadhesive or Mucoadhesive drug delivery systems

The Bioadhesive drug delivery systems are use as the delivery appliance within the human to enhancing drug absorption in a site of specific manner. During this approach , bio adhesive polymers are used and they can adhere to the epithelial surface in the abdomen (41).

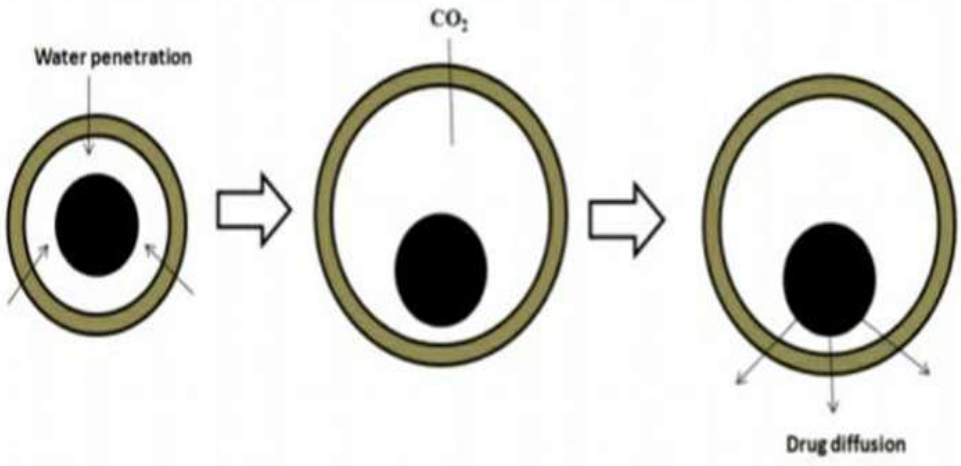

Figure 5: Effervescent gas generating systems

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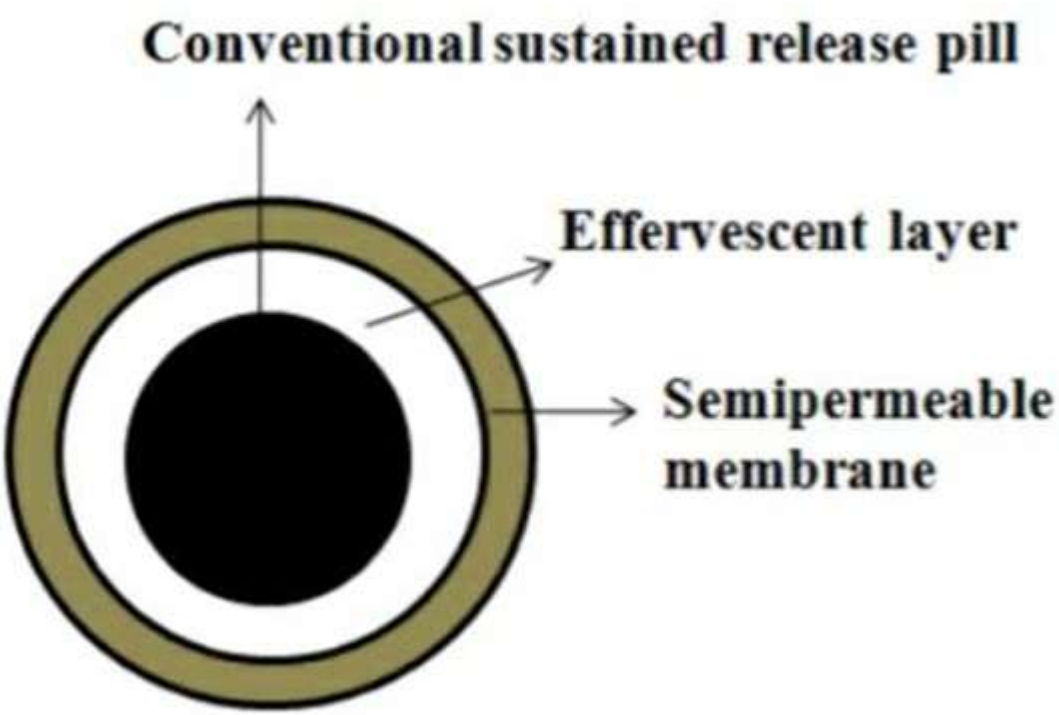

Figure 6: The Drug Release From Effervescent Gas Generating Systems

In they improve the prolongation of gastric retention . Basic of adhesive in that a dosage form can stick to the mucosal surface by completely different mechanism . These mechanisms are (42 , 43) .

1) The wetting theory, which is based on the capability of bioadhesive polymers to spreads and develop intimate contact with the mucous layers .
2) The diffusion theory which proposes physical entanglement of mucin strands the flexible polymer chains or an interpenetration of mucin strands into porous structure of the polymer substrate.
3) The absorption theory indicate that bioadhesion is due to secondary forces like Vander Wall forces and Hydrogen bonding.
4) The electron theory which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive materials.

Materials ordinarily used for bioadhesive are poly acrylic acid , chitosan , sodium alginate etc. tract (GIT) .

Expandable , unfoldable and swellable systems

The dosage forms in the stomach will with stand gastric transit if it biggest than pyloric sphincters . However , the dosage form must be smallenough to be swallowed and must not cause gastric obstruction either single or by accumulation . Thus their configuration (44 ,45).

1) A small configuration for the oral intake .
2) An expanded gastroretentive form and drug release from device.

Thus , gastroretentive is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach . The bioerodible polymer compressed within a capsule which extends in the stomach (46 ,47) . The swelling is usually result from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (figure 7) . Expandable systems have some drawbacks like problematical storage of much easily hydrolysable , biodegradable polymer relatively short – lived mechanical shape memory for the unfolding system most difficult to industrialized and not cost effective (48) .

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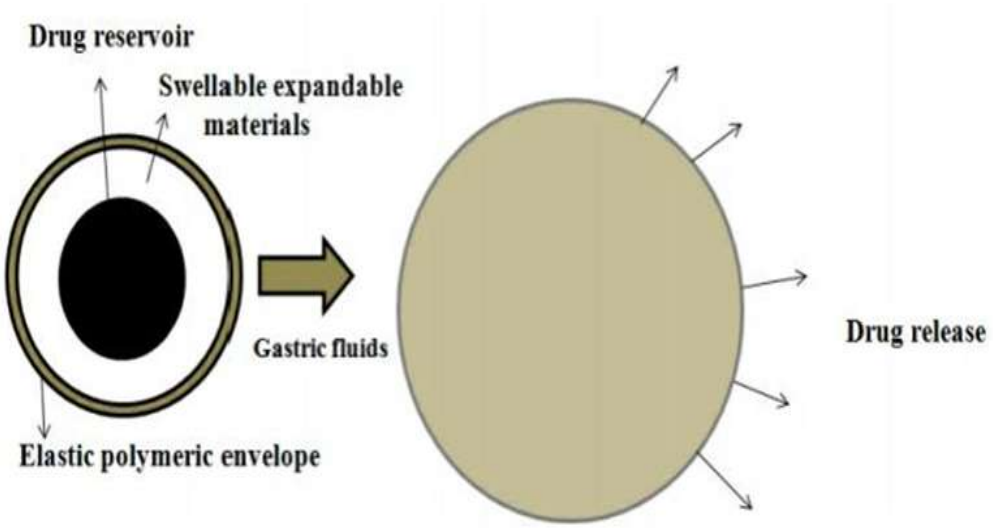

Figure 7: Drugs release from Swellable Systems

Superporoushydrogelsystems

These swellable systems differ adequately from the traditional types to warrant separate classifying . in the gastric retention time to improve (GRT) super porous hydrogel of average pore size >100 micro miter , swell to balance size inside a minute due to fast water uptake by capillary welting through numerous interconnected open pores (49) . They swell to a big size (swelling ratio : 100 or more) . and are intended to have adequately mechanical strength to withstand pressure by gastric contraction . This is advised by co – formulation of hydrophilic particulate material (50) .

Magneticsystems

This approaches to increase the (GRT) gastric retention time is found on the plain principle that the dosage form contains a little internal magnet , and a magnet placed on the abdomen over the position of the stomach .

CONCLUSION:

The Gastroretentive drug delivery system offers various advantages of drug with poor bioavailability due to their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered there by maximizing their absorption and enhancing the absolute bioavailability .

In vivo studies are required of established the optional dosage form For a particular medicine. .Another area of research gastroretentive drug delivery systems are elimination of Helicobacter pylori, this micro organisms is most sensitiveness to antibiotics . It complete required of highly concentration of antibiotics be maintain within a gastric mucosa for prolonged time period. An important characteristic to take into a stomach physiology . The time when drug is taken is an major parameters .To develop the gastroretentive dosage form is a actual challenge to the pharmaceutical technology and the drug delivery systems should remains the adequate time in the stomach .which is not corresponding with its generally physiology. All these gastroretentive drug delivery systems (High density, floating expandable or unfoldable or swelling ,super porous ,bioadhesive ,magnetic systems) are present their own benefits .

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