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COMPARISON OF VARIOUS APPROACHES TO INCREASE THE GASTRIC RESIDENSE TIME

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ABSTRACT: Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which lead to better patient compliance. So, oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Extended release drug delivery system which reduce the dosing frequency of certain drugs by releasing the drug slowly over an extended period of time. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract. The purpose of writing this review was to compile recent literature on pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT). Enhancing the GRT may explore new potentials of stomach as drug-absorbing organ. Several approaches are currently used including Floating drug delivery system, Matrix tablet, pulsatile drug delivery, In situ gel, Stomach specific Mucoadhesive tablets and Microsponge.

INTRODUCTION: Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration. [1]

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However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8- 12h), and the existence of an absorption window in the upper small intestine for several drugs. These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. 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]

During the past three decades, numerous oral delivery systems have been developed to act as

drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. The oral controlled release formulation have been developed for those drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation. As these will release the drug slowly into the GIT and maintain a constant drug concentration in the plasma for a longer period of time. [1]

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS 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 thus ensuring its optimal bioavailability. [3]

The sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and respiratory dosage forms are terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [1]

Anatomy of Stomach:

The stomach is J-shaped dilated portion of the alimentary tract situated in the abdominal cavity. The stomach is divided into three regions: (**Fig. 1**)

i. Fundus
ii. Body
iii. Pylorus(antrum)

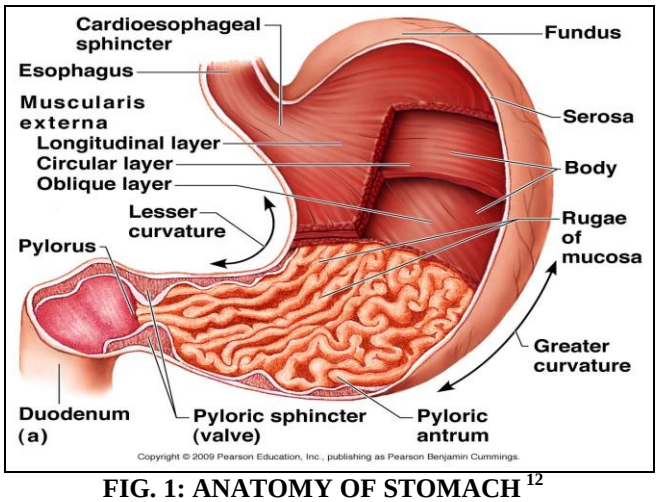

FIG. 1: ANATOMY OF STOMACH [12]

At the distal end of the pylorus is the pyloric sphincter, guarding the opening between stomach and the duodenum. [10]

The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs. Which is called as interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided in to four phases. [10] **Fig. 2**

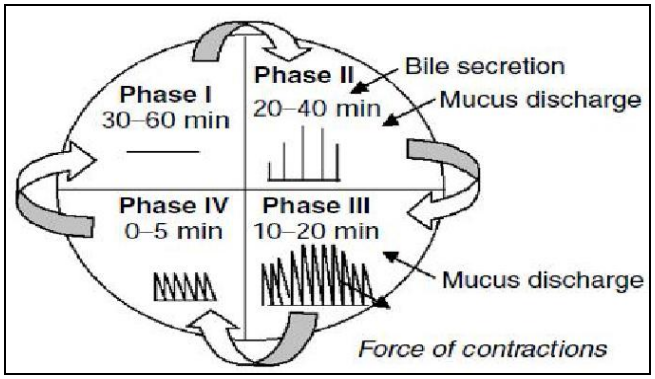

FIG. 2: MOTILITY PATTERN OF GIT

Gatrointestinal Retention: Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities & substantial benefits for patients. [4, 5]

Requirements for gastric retention: One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease. [6]

Advantages of Gastroretentive Drug Delivery System: [6]

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

Approaches to Enhance GRT: [6] Fig. 3

1. Floating drug delivery system
2. Matrix tablet
3. Microsponge & Nano sponges
4. Pulsatile drug delivery system
5. In situ gel
6. Stomach specific mucoadhesive system
7. Swelling & expandable system
8. Low density system
9. High density system
10. Raft forming system

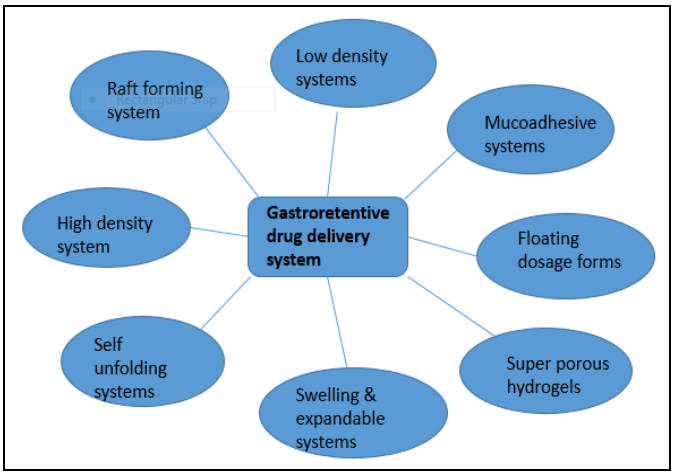

FIG. 3: APPROACHES TO ENHANCE GIT

Floating Drug Delivery System:

Classification of floating system: [13]

1). Single Unit Floating Dosage Systems:

a. Effervescent system
b. Non effervescent Systems

2). Multiple Unit Floating Dosage Systems:

a. Effervescent Systems
b. Non-effervescent Systems
c. Hollow microspheres

3). Raft forming system:

A. Single Unit Dosage Forms:

a) Effervescent Systems (Gas-generating Systems): These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonate. [4]

b) Non-Effervescent Systems: This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the „plug-type systems" since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier, micro porous compartment system, alginate beads, and hollow microspheres. Another type is a Fluid- filled floating chamber which includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir.

Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein.

The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolonged time and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. A newer self-correcting floatable asymmetric configuration drug delivery system has a 3- layermatrix to control the drug release. This 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process.

The system was designed in such a manner that it floated to prolong gastric residence time *in vivo*, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine. [4]

B. Multiple Unit Floating Systems: In spite of extensive research and development in the area of hydro dynamically balanced systems and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or- nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose- dumping. Much research has been focused and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties. [4]

a) Non-effervescent Systems: No much report was found in the literature on non- effervescent multiple unit systems, as compared to the effervescent systems. [4]

b) Effervescent Systems (Gas-generating Systems): A new multiple type of floating dosage system had developed having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills. [4]

c) Hollow microspheres: Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® Sand cellulose acetate were used in the preparation of hollow microspheres. [4]

C. Raft Forming System: The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO_2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.[4]

Matrix Tablet: Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion - controlled

mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. [7]

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. [7]

Advantages offered by matrix tablets: [7]

1. Maintains therapeutic concentrations over prolonged periods.
2. Avoids the high blood concentration.
3. Reduction in toxicity by slowing drug absorption.
4. Minimize the local and systemic side effects.
5. Improvement in treatment efficacy.
6. Better drug utilization.
7. Minimize drug accumulation with chronic dosing.
8. Can be made to release high molecular weight compounds.
9. Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
10. Reduction in health care cost.
11. Usage of less total drug.
12. Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
13. Improved patient compliance.

Disadvantages of Matrix Tablets: [7]

1. The remaining matrix must be removed after the drug has been released.
2. Greater dependence on GI residence time of dosage form.
3. Increased potential for first-pass metabolism.
4. Delay in onset of drug action.
5. Release rates are affected by food and the rate transit through the gut.
6. Release rate continuously diminishes due to increased diffusional resistance and decrease in effective area at the diffusion front.

In Situ Gel: In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner.[8] **Fig. 4**

Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-coglycolide) and poly-caprolactone etc. are used in the preparation of in situ gelling system. Mainly in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. [8]

FIG. 4: IN SITU FORMATION OF FLOATING GEL

These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of in situ gels.[8]

Advantages of in situ forming polymeric delivery: [8]

a. Ease of administration
b. To increase local bioavailability
c. Reduced dose frequency
d. Improved patient compliance
e. Its production is less complex and so lowers the investment

Stomach Specific Mucoadhsive Tablets: [9]
Stomach-specific mucoadhesive tablets as a controlled drug delivery system have been developed to increase gastric retention time of the dosage forms. [11]

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs.

The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action. Mucoadhesive tablets are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve the patient compliance. [9]

The mucoadhesive drug delivery system may include the following: [9]

- Gastrointestinal delivery system
- Sublingual delivery system
- Vaginal delivery system
- Nasal delivery system
- Ocular delivery system
- Rectal delivery system
- Buccal delivery system

Microsponges:

Defining Microsponge: The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner.[14] (**Fig. 5**)

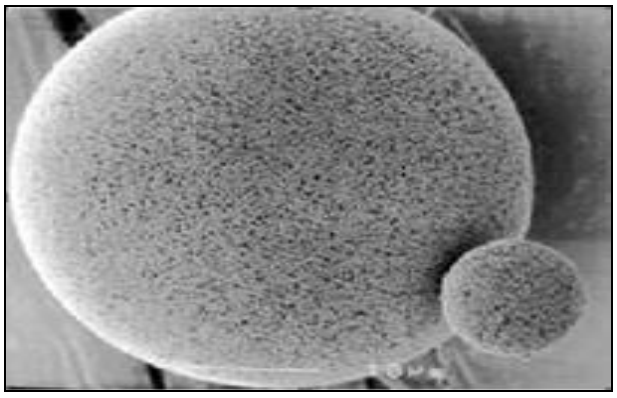

FIG. 5: VIEW OF MICROSPONGE

The size of the microsponges ranges from 5-300µm in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention. The surface can be varied from 20 to 500 m /g and 2 pore volume range from 0.1 to 0.3cm /g. [14]

Characteristics of microsponges: [15]

- Microsponge formulations are stable over range of pH 1 to 11;
- Microsponge formulations are stable at the temperature up to 130 °C;
- Microsponge formulations are compatible with most vehicles and ingredients;
- Microsponge formulations are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate;
- Microsponge formulations have higher payload (50 to 60%), still free flowing and cost effective.

Preparation of microsponges: [15]

1. Liquid liquid suspension polymerization
2. Double emulsion solvent diffusion method

i. Liquid-liquid suspension polymerization: The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc.). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation.

ii. Quasi-emulsion solvent diffusion method: This is a two-step process where the microsponges can be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultra-sonication at 35 °C. The inner phase was

poured into the PVA solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40 ^{0}C for 12 Hrs. and weighed to determine production yield (PY).

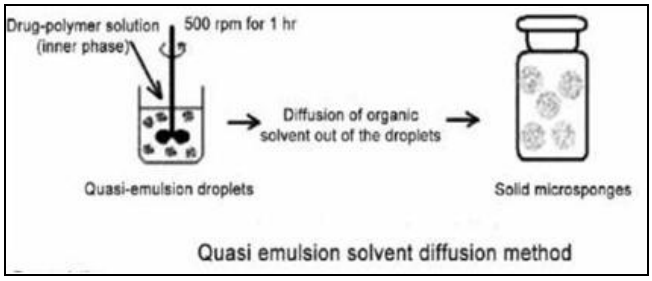

FIG. 6: QUASI EMULSION SOLVENT DIFFUSION METHOD

Characteristics of materials that is entrapped in Microsponges: [15] Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements:

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

CONCLUSION: The real challenge in the development of gastro retentive drug delivery systems is to overcome normal physiology of stomach either in the fed state or in the fasted state. Enhancement in the gastric residence time of the drug improves bioavailability of the drugs with narrow absorption window in gastrointestinal tract region. The various approaches for enhancing GRT also improve the solubility of drug that is having solubility, reduces drug waste and minimizes fluctuations in the drug plasma concentration.

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