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Current Approaches on Gastroretentive Drug Delivery Systems

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ABSTRACT:
Over recent years, there have been many efforts to develop the absorption rate of medication and the therapeutic efficacy of oral dosage types. GRDDS for strengthen the pharmacological effects of drugs with small uptake site, are unbalanced at pH greater than 7, are dissolved under acidic region and are effective local region in stomach. There are many criteria for choosing the drug used in gastro-retardant system as drug should be sparingly stable, it should be compatible with gastric region and narrow absorption. The purpose of writing this GRDDS was to compile recent literature with special focus on various Gastroretentive approaches that recently become leading methodologies in field of site specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention.[1,2]

KEYWORDS: Gastroretentive drug delivery system (GRDDS), Floating drug delivery system, Approaches, Application

I. INTRODUCTION:

The oral route is best path for the drug administration for single-dose systems and it is easy for administration and cost-effective for developing a single dos controlled release or extended or sustained release dosage form the extensive research has been performed for making the better patient compliance and avoidance of repeated administration of the drug the highly soluble drug at acidic pH condition and lower solubility at pH higher than 7 resulted as a lower absorption window drug from intestine. The conventional drug delivery system achieves and also maintained the drug concentration in the therapeutically effective range desired for treatment, only when taken numerous times a day. A drug that has a narrow absorption window in the GIT may have poor absorption. For these drugs, GRDDS offer the advantages in extending the gastric emptying time. Many problems are faced in preparing controlled release systems for better absorption and improved bioavailability. Drug absorption from the GIT is a complex process and is subject to several variables.[2]

Current progress in technology has provided feasible dosage alternatives which can administered by different routes of administration like oral, topical, parenteral, rectal, nasal, ocular, vaginal, etc. But out of all these routes, oral route is considered as the best preferred and practiced way of drug delivery, due to the following reasons:[2]

- Ease of administration
- Ease of production
- More flexibility in designing
- Low cost

The proximal stomach, which includes the fundus and body, and the distal stomach, which includes the antrum and pylorus, are both better understood in terms of their anatomy and physiology.

Caloric density, patient-related parameters, the size, shape, and density of the gastro-retentive formulations, and other essential aspects influence the gastro-retentive drug delivery systems. An enlargement of the dosage form can stop the medication from passing through the pyloric antrum. Gastro retentive drug delivery formulations have a higher floating capacity due to their lower density compared to stomach fluids.

The ingested food's increased calorie density contributes to its gastro-retentive quality, which in turn influences how quickly the stomach empties. The administration of gastro retentive formulations is also influenced by various patient-related characteristics, including gender, age, disease, and emotional condition.[3] Diabetes and Parkinson's disease are two more illnesses that affect how quickly the stomach empties. Male and elderly individuals empty their

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stomachs more quickly than female and younger people.

ADVANTAGES OF GRDDS[3]

- Enhances bioavailability.
- Sustained release of drug by prolonged gastric retention time.
- Site specific or targeted delivery of drug.
- Reduction in dosing frequency.
- Improves patient compliance & Suitable for self-administration.
- Minimization of side effects.
- Enhances therapeutic effectiveness.
- Local release of drugs to treat stomach and duodenal ulcers, gastritis and esophagitis.
- Reduced the risk of stomach carcinoma.
- Various antibiotics, antiviral and antifungal agents can be successfully administered: e.g sulphonamides, quinolones, cephalosporin's, aminoglycosides and tetracyclines etc.

DISADVANTAGES OF GRDDS[3]

- Unsuitable for drugs with limited acid solubility.
- Drugs that irritates or cause gastric lesions on slow release.
- Drugs that absorb selectively in colon.
- Drugs that absorb well through the GIT.
- Unsuitable for drugs those are unstable in acidic environment.
- Floating drug delivery systems require high fluid level in stomach to float and work effectively.

DRUG SELECTION CRITERIA FOR GRDDS:[4]

- Ideal candidates for GRDDS are molecules have poor intestinal absorption but have the better absorption in upper part of GIT.
- Primary absorbed in Stomach
- Degrade in the colon.
- It should be absorbed in duodenum and upper jejunum segments.
- Poor solubility in alkaline PH.
- Drugs having short half-life and require frequent dosing.
- Drugs which having required frequent dosing.
- Drugs which undergo first pass metabolism.
- Drugs that are required for local action in stomach.
- Poor solubility in intestinal media and poor bioavailability.

ANATOMY OF THE STOMACH:[3,4]

The most dilated of the gastrointestinal tract is the stomach and it is positioned between theoesophagus and small intestine. The pyloric sphincter governs the opening of stomach in the duodenum. The stomach can be classified into four anatomical part namely;

1) Fundus
2) Body
3) Antrum
4) Pylorus

COMPOSITION OF GASTRIC CONTENT:[4,5]

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rogue. There are 4 major types of secretory an epithelial cell thatcovers the stomach and extends into gastric pits and glands.

a) Mucous cells - secrete alkaline mucus.
b) Parietal cells – secrete HCL.
c) Chief cells – secrete pepsin.
d) G cells -secrete hormone gastrin.

FUNCTION OF STOMACH:[4]

In the both fasting and fed states gastric emptying are obtained. Nevertheless, the motility pattern varies. markedly in the two condition in the fasted condition it is characterized by an inter-digestive 4 phase as shown on figure 1.

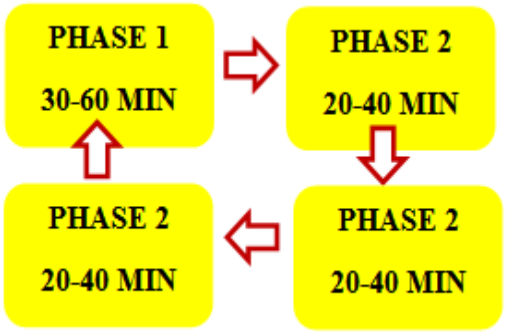

FIG 1: PHASE CYCLE

Phase 1: It is a relatively inactive 40-60-minute period with only occasional contractions.
Phase 2: Increasing numbers of contractions are present in phase2, which has a similar duration to phase1.
Phase 3: This is characterized by strong peristaltic contractions after opening the base of pylorus and clears the stomach of any residual material.

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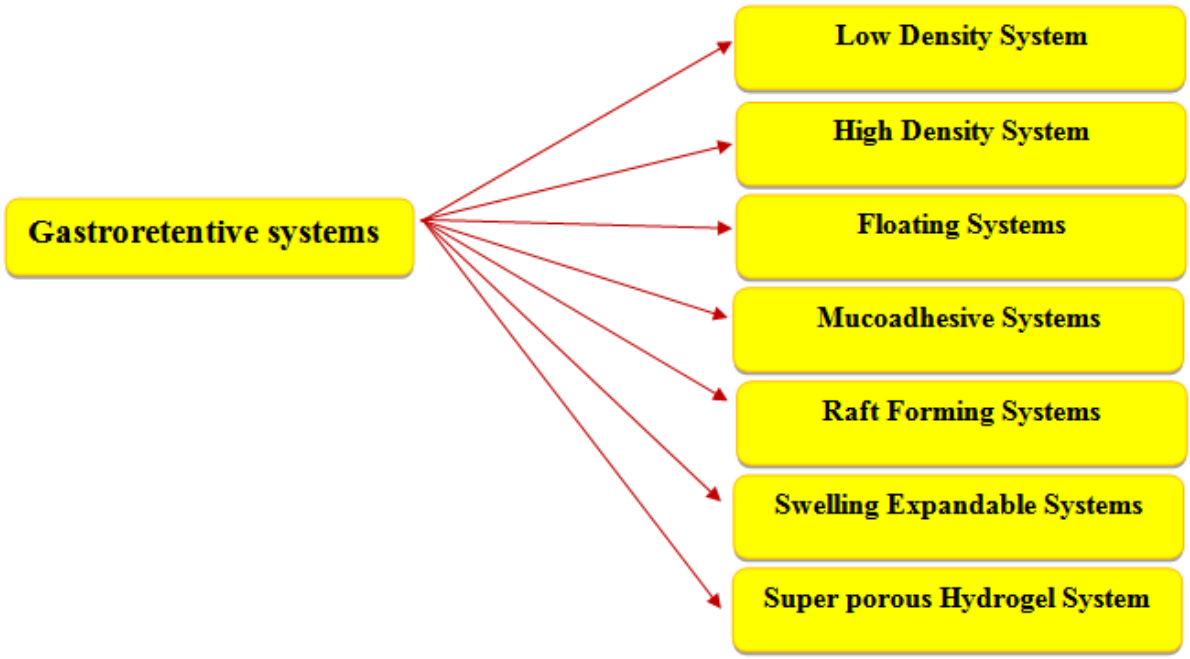
Phase 4: This is a less period of transition among powerful action of phase3 and phase1.The process repeats every 2 hours until the meal is eaten and fed or motility starts.

Approaches for Gastroretentive Drug Delivery System:[3,4,5]



LOW DENSITY SYSTEMS: It is also said as hydro dynamically balanced systems for floating bulk density should be lesser than (1.004 g/cm). Due to this they allow to floated a dosage form for prolonged period time in stomach. They are major approaches to reach longer gastric retention time and shows higher drug bioavailability.
Low density system or floating system are of two types
1.Non-Effervescent system.
2.Effervescent system.

1)Non-Effervescent floating drug delivery system: The main advantages of non-effervescent systems are the stability of acid or base labile drug gastric pH not affected floating lag time.The tablet was designed with a mixture of optimized solid dispersion and action retardant polymers/swellable polymers such as xantham gum and polyethylene oxide in the hydrodynamically balanced system.Polymers help prolong the staying time of GI and improve the absorption of drugs.

2) Effervescent floating drug delivery system: In these preparations including a release retardant polymer, ethylcellulose, eudragit L100, xantham gum, polyethylene oxide (PEO).In that formulation the gas generating agent Makes better the buoyancy of the tablet in gastro-floating systems consists hydrophilic polymers combination as shown in fig 2.

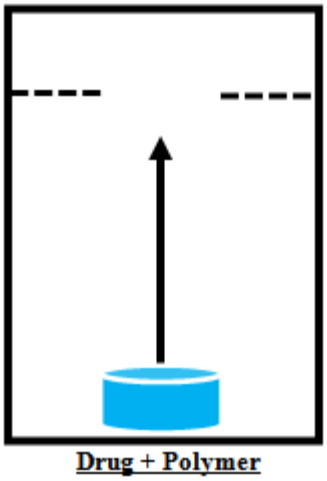


Fig 2: Effervescent systems

1) Gas generating systems: The effervescent reaction among carbonate/bicarbonate salts, citric/tartic acid, CO2 is released in presence of water when the formulation is put in the beaker it will sink with a production of gas it rises up and floats.

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2) Raft forming systems: In this process, a viscous gel containing trapped carbon dioxide bubbles on contact with gastric fluid is created by carbonates or bicarbonates. Formulation often typically contains antacid such as aluminium hydroxide or calcium carbonate to minimize gastric acidity. They create a layer on upper of gastric fluids which are often used in GI treatment as with water**.**

HIGH DENSITY SYSTEM:

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3) shown in fig 3.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. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time.

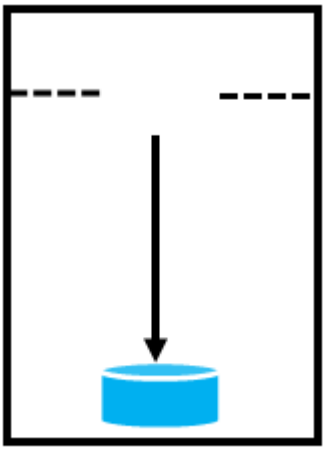

Fig 3: High Density System

EXPANDING SYSTEM: The expandable GRDFs are usually a small configuration depends, which enables for a convenient expanded oral intake in the stomach and thus prohibits the travels through the pyloric sphincter. Dissolution of the polymers and thus maintain the physical integrity of the dosage form. Such cross-linking prevents the polymers from dissolving and thus preserve the physical properties of dosage type. A high degree of cross-linking delays the system's swelling ability to maintain its physical integrity for extended periods of time as shown in fig.4

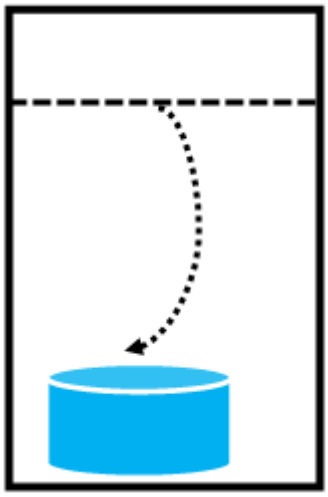

Fig 4: Expanding system

BIO ADHESIVE SYSTEMS: Bioadhesive means adhesion to the biological surface or to the mucosal surface. polymers are interacted with the mucosa and referred to the mucoadhesion. The mucosal layer consists of the high molecular weighted glycoproteins that contain fucose, sialic acid. The thickness of mucin gel layer is between 50-500 micrometer in the stomach and 15-150 micrometer in colon region the thickness depends on the region and adhesive properties are depends on the percentage of the glycoproteins concentartion. the systems that bind to the epithelial cell and they increased the gastric residence time in the stomach as shown in fig 5.

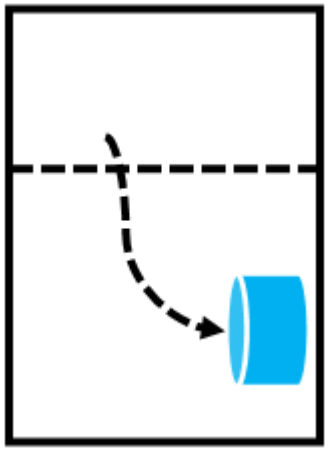

Fig 5: Bio adhesive systems

SUPERPOROUS HYDROGEL SYSTEMS:[6,7] The conventional hydrogels are a very long-term process and it may take several hours to reach the

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equilibrium during which super porous hydrogels of pore size > 100 micrometre swell to balance size may occur prematurely in a minute. Due to the rapid absorption of water by capillary wetting through numerous open pores interconnected Increasingly, they swell to a massive size and are intended to have sufficient mechanical strength to handle the pressure due to gastric contraction, which is attained through the co-formulation of hydrophilic particulate materialsas shown in fig 6.

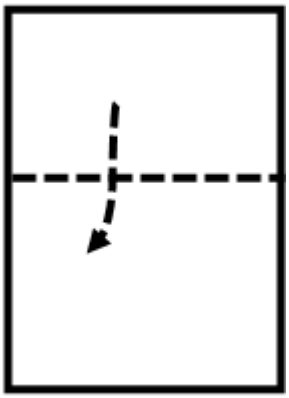

Figure 6: Superporous Hydrogel System

FACTORS AFFECTING GASTRIC RETENTION:[5,6]

Density: Gastric retention time (GRT) is a function of dosage form buoyancy which is dependent on the density. The density of the dosage form must be lower than the gastric contents (1.004 gm/ml).

Size: Dosage form units having a diameter of greater than 7.50 mm are stated to have an improved GRT related with those having a diameter of 9.90 mm.

Shape of the dosage form: Tetrahedron and ring-shaped devices having a flexural modulus of 48 and 22.50 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

Age: Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.

Gender: Mean ambulatory gastric retention time in males (3.4 ± 0.6 hours) is less correlated with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, body surface and height.

EXCIPIENTS USED IN FLOATING SYSTEMS:[7,8]

1) Hydrocolloids: Hydrocolloids are the agent that having the capacity to forming the gel and. It gets swell when the gastric fluids are in contact. e.g.-Pectin, agar, HPMC, ethylcellulose, sodium alginates.

2) Release rate accelerants-

It is an agent that increases the rate of drug release e.g.-lactose, mannitol

3) Release rate retardant-

It is an agent that retards the release action of the drug by decreasing the solubility by using the substance like calcium phosphate, magnesium striate, and talc.

4)Buoyancy increasing agent- For increasing or enhancing the buoyancy by using the low-density materials like ethylcellulose.

5)Effervescent agent-

This is the agents that produce carbon dioxide by contact with the acidic medium.in floating systems, the gas generating agent like citric acid, sodium bicarbonate is used.

POLYMERS USED IN GASTRIC RETARDANT SYSTEMS:[5]

Chitosan

Chitosan is the natural swellable polymers. chitosan is the N-deacetylated derivatives of chitin. chitosan that contains the primary amino group and these primary amino group are shows controlled release action, mucoadhesive properties.

Eudragit

Eudragit is amorphous. it is non-biodegradable, non-absorbent, and non -toxic in nature are of the two grades of the polymer as L and S. L is dissolved at pH6 for coating grade S dissolved at pH 7 used for colon targeted systems. RS and RL containing a quaternary amino group and they used for sustained release.

HPMC

HPMC contains methoxy and hydrolpropoxy groups having the molecular weight 10000-1500000 Dalton. It is dissolving in the water they form colloidal solution. Certain grades are soluble in acetone. It is acts as a bioadhesive, coating activity, controlled release capacity, emulsifying agent, thickening agent.

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SR.NO.	Dosage Form	Polymer used
1.	Tablets	Xanthan Gum, Guar Gum, HPMC K4M, HPMC K100M
2.	Microspheres	Ethylcellulose, Eudragit RL 100
3.	Matrix Tablet	HPMC K4M, HPMC K15M, Ethyl cellulose

EVALUATION PARAMETERS:[3,4,5,6]

1. Size and Shape: The particle size and shape play a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation was determined using Sieve analysis, Sedimentation techniques.

2.Floating Properties: Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.

3.Buoyancy Lag Time: It is determined in order to know the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium.

4. Determination of Moisture Content: A product intended for trade and production has standard properties such as,

1. Flow properties
2. Dry substance content
3. Concentration or purity
4. Agglomeration

5. Swelling Studies: The swelling studies by using Dissolution apparatus USP dissolution apparatus was calculated by formula,

Swelling ratio = weight of wet formulation/weight of formulation.

6. In vitro release studies: In vitro release studies were performed to provide amount of drug that is released at a definite time period.

II. CONCLUSION :

Gastro retentive is the most favourable approach for delivery of the specific quality and quantity of the drug for some long term disease treatments on these many approaches has been developed in these delivery systems for the site-specific and disease-specific action of the molecules in these technologies using the many polymeric condition that according to the site-specificity and their effectiveness. According to type of systems and their dosage forms the polymer selection and their concentration is to be different. If the high-density polymer used then the technology or approaches in GRDDS is change. Many synthetic, non-synthetic, and naturally occurring intermediates are to be used. Many of the formulation are involved in market according to the systems and dosage form which are they are in may be tablet, beads, gel, capsule forms.

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