GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Oral route has been the most convenient and accepted route of drug delivery. Owing to tremendous curative benefits of the oral controlled release dosage forms are preferred as the interesting topic in pharmaceutical field to achieved improved therapeutics advantages. Gastroretentive drug delivery system is novel drug delivery systems which has an upper hand owing to its ability of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. Attempt has been made to summarize important factors controlling gastroretentive drug delivery systems. This review covers the advantages, disadvantages, marketed preparation and some patents of gastroretentive drug delivery system and represents the floating and non-floating gastroretentive system and also highlights some of the current gastroretentive approaches. Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems), magnetic systems, swelling systems, unflodable and expandable systems. Raft forming systems and superporous systems, biodegradable hydrogel systems.

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INTRODUCTION

Recently, various routes of drug administration have been explored for the effective delivery of the drug. However, the oral route of drug administration is most widely acceptable by the patient as it is most convenient. Today, a wide range of gastrointestinal controlled delivery systems are available in the market. These systems can release the drug predetermined rate and over a defined period of time. The oral controlled delivery is advantageous for reduction in drugs blood level fluctuations, dosing frequency and adverse side effect as well as improved overall healthcare costs, patient convenience and compliance. However per-oral drug preparations show considerable differences in bioavailability is markedly decreased area of absorption and the possible degradation of drug by intestinal bacteria. Although, attempts have been made to develop controlled release delivery systems for oral route, yet certain limitations like unsatisfactory and variable drug absorption, uncontrolled gastric transit time etc. have established the urgent need of the more intelligent drug delivery system, which can either prolong the transit time, or provide effective concentration locally. The two approaches of gastro retentive and colon based controlled delivery have been widely utilized to overcome these barriers.[1]

Oral drug delivery is widely used in pharmaceutical field to treat the diseases some drugs are absorbed at specific site only these require release at that specific site.

Gastro retentive drug delivery system (GRDDS) is one of the site specific drug delivery for the delivery of the drug at stomach. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner at specific site.[2] oral drug administration has been the predominant route for drug delivery gastric residence time is time which a drug resides in stomach. Depends upon fluid and food intake GRDDS are designed to delay gastric emptying.[3] it may lead to incomplete and non uniform absorption of the drugs having absorption window in upper part of GIT as once the DF passes down the absorption site, the remaining quantity goes unabsorbed beneficial DDS would be one which exhibits the ability to control and prolong the gastric emptying time and can deliver drug in maximum concentration the absorption site.[4] however, this approach has not been suitable for a variety of important drug, characterized by a narrow absorption window in the upper part of the gastrointestinal tract i.e. stomach and small intestine. The drug is released in non-absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bio availability.
The medications that are included in the category of narrow absorption window drugs are mostly associated with improved absorption at the jejunum and ileum due to their enhanced solubility of the drug in the stomach as opposed to more distal parts of the gastrointestinal tract. [5]

Additionally, large intestine (colon) is also considered for development of alternative oral controlled delivery system. It is required to deliver an effective concentration at the large intestine for the treatment of colonic diseases i.e. inflammatory bowel diseases (IBD), ulcerative colitis and crohn’s disease. In addition to the local delivery, the large intestine or colon is useful as a site where these poorly absorbed drug molecules (peptides and proteins) may have an improved bioavailability. This region of the GI tract is recognized as having a somewhat less hostile environment (with less diversity and intensity of enzymatic activities) than the stomach and large intestine. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drug. Further, drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of those diseases that have peak symptoms in the early morning such as nocturnal asthma, angina or arthritis. Although, this region has such drawbacks as impaction of faces (which might act to entrap drug) and the presence of bacterial enzymes and toxins yet these problems are less important compared with exhaustive destruction that the drug may experience in the stomach and small intestine. [1]

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration patient compliance and flexibility in formulation. Drug that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. [6]

**Physiology of Stomach:**

Anatomically the stomach is divided into three regions fundus, body and antrum the proximal part made one novel approach in this area is GRDDS. Dosage forms that can be retained in the stomach are called GRDDS.

- Bioavailability
- Therapeutic efficiency
- 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
- Improve solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine).[7]

Figure 1: The Human GI Tract

The 4 phases as are enumerated below and also shown in figure 2.

Figure 2. Schematic Representation of Inter Digestive Motility
**Phase 1** is basal phase, which is silent period of 30-60 minutes and characterized by lack of secretory, electrical and contractile activity and there is no contractions.

**Phase 2** is pre-burst phase, which exhibit intermittent action for 20-40 minutes. Some bile secretion started and contractile motions increases frequency. Mucus discharge is started during later part of phases 2.

**Phase 3** is burst phase, which is characterized by intense and large regular contractions termed as “house keeper waves”. These waves sweep off undigested food by maximizing the pyloric opening and last for 10-20 minutes. Thus, this phase enables efficient evacuation of the stomach contains.

**Phase 4** is transition period up to 5 minute, between phases 3 and 1. [8]

**Advantages of GRDDS [15]**

1. Increase in bioavailability and curative efficiency of drugs and economic usage of dosage.
2. Minimized factor of risk in resistance in antibiotics owing to stabilized therapeutic levels over prolonged periods removing fluctuation.
3. Optimized release in case of short half-life drugs causes flip flop pharmacokinetics and also ensures patient compliance with reduced dosage frequency.
4. They are advantageous against drawbacks of the gastric retention time (GRT) as well as the gastric emptying time (GET). The system remains buoyant on gastric fluid because of lower bulk density than gastric fluids.
5. These are efficient in repairing stomach and small intestine related problems. Its attributed to the fact that gastroretentive drug delivery sustains drug release and hence, avail local therapy in these organs.
6. This method provides with a systematic and controlled drug delivery system which minimizes chances of drug over exposure at the diseasedsite.
7. Providing a narrow curative index, the gastroretentive dosage form minimizes variance in concentrations of drugs and effects.
8. This system provides higher efficiency due to reduced counter activity by body.
9. As the system provides with controlled rates of fluctuation, a wider array is provided for selectivity in receptor activation.

**Disadvantages of GRDDS [16,17,18]**:-

1. Need for increased level of fluids in the stomach.
2. Problematic with solubility in gastric fluid.
3. Drugs intended for selective release in the colon.
4. Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.
5. GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.
6. The ability of the drug to remain in the stomach depends upon the subject being positioned upright.
7. Hydro gel based swelling system takes longer time to swell.
8. Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach.

**Factors Affecting Gastric Retention:**
These factors include density, size and shape of dosage form, concomitant intake of food and drugs such as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide) and biological factors such as gender, posture, age, body mass index and disease state (e.g. diabetes).

1. Physical form of dosage form.
2. Size and shape of dosage form.
3. Density of a dosage form.
4. Formulation parameters.
5. Volume of liquids administered.
6. Viscosity, volume and caloric content of meals.[1]

**Suitable and Unsuitable Drugs Candidates for GRDDS**
Suitable and unsuitable drugs candidates for GRDDS are listed in Table 1 and Suitable and unsuitable drugs candidates for GRDDS: Suitable and unsuitable drugs candidates for GRDDS are listed in Table 1 and Table 2 respectively

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Suitable Drug candidates</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Drugs acting locally in the stomach.</td>
<td>Antacids, Anti-ulcer drugs, drugs against H</td>
</tr>
<tr>
<td>2.</td>
<td>Drugs with narrow absorption</td>
<td>Misoprostol, Clarithromycin, Amoxicillin</td>
</tr>
</tbody>
</table>
3. Drugs having unstable properties in the intestinal or colonic environment

Cyclosporine, Methotrexate, Levodopa, Repaglinide, Riboflavin, Furosemide, Para-aminobenzoic Acid, Atenolol, Theophyllin

4. Drugs caused imbalance of normal colonic microbes.

Captopril, Ranitidine HCl, Metronidazole, Metformin HCl, Antibiotics against H. Pylori, Amoxicillin Trihydrate, Diazepam

5. Drugs having low solubility at high pH values.

Chlordiazepoxide, Furosemide, Verapamil HCl

Table 2: Unsuitable drug candidates for GRDDS (19, 20)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Unsuitable Drug Candidates</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drugs having very limited acid solubility.</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>2</td>
<td>Drugs that exhibits instability in the gastric environment.</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>3</td>
<td>Drugs that are used for selective release in the colon.</td>
<td>5-amino salicylic acid and corticosteroids</td>
</tr>
</tbody>
</table>

Approaches of GRDDS:

The GRDDS are broadly classified into four classes viz. high density, floating, bioadhesive and swelling/expanding systems. The following approaches are employed in designing GRDDS.
1) Swelling and Expanding Systems:

One way to retain a dosage form in stomach is by increasing its size. The stomach discharges its constituents through the pylorus into intestine. Thus if a dosages from attain a size larger than that of the pylorus, it can be retained in the stomach for a longer time. It is not possible to shallow a dosage from a such a large size. Thus it should attain this large size only after reaching the stomach. This large size should be archived fairly quickly failing which the dosage form is emptied through the pylorus. [1] 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. These systems are called as plug-type system as they have the tendency to remain lodged at the pyloric sphincter. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release. [9]

2) Mucoadhesive System:

Mucoadhesions a pharmaceutically important novel solution to solve bioavailability problems that result from a too short length of stay of a dosage form at the absorption site within the GI tract bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and thus extend the gastro retentive time in the stomach. The mucoadhesive drug delivery provides a means of promoting residence time of a dosage from as well as improving the intimacy of contact with various absorptive membranes of biological system. Besides acting as platforms for sustained release dosage forms. Bioadhesive polymers can themselves exert some control over the rate and amount of drug release. and thus facilitate the therapeutic advantage of such systems. Stability problems in the intestinal fluid can also be overcome. Mucoadhesive drug delivery systems contain a mucoadhesive polymer that adheres to the gastric mucosal surface and prolong its gastric retention in the gut. The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful excipients in the GRRDS. The polymers can be natural such as sodium alginate, gelatin, guar gum etc. semi synthetic polymers such as HPMC, carbopol, sodium carboxy methyl cellulose. [10]

3) Floating system:
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 constitutes of measuring a force equivalent to F (with respect to time) which keeps the object submerged. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler.[12] The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation.

On the other hand multiple-unit floating system may be an attractive alternative since they have been shown to reduce the intermolecular and intermolecular subject availabilities in drug absorption as well as to lower the possibility of dose dumping.[13] based on the buoyancy mechanism, floating system are classified as follows.

1. Effervescent system
2. Non-effervescent system

1) Effervescent system [gas generating system] :-
Gas bubble generation helps to achieve floatability. The swellable polymers viz. methylcellulose and chitosan and various Effervescent compounds, e.g. Sodium bicarbonate, tartaric acid and citric acid, helps in creating matrix types of such system. They are created in manner. They upon contact with gastric contact CO2 is released finally entrapping in swollen hydrocolloids, that makes dosage forms buoyant.[14]

These Systems Are Further Classified As Below:

- **Gas Generating Component:** - this may consist of a single substance that will produce gas upon contact with gastric fluid. Commonly used gas generating components are hydrogen carbonate or potassium hydrogen carbonate, sodium sulfate, sodium bisulphate or sodium metabisulfate etc. the gas generating component such as carbonate and bicarbonates may be present in amounts about 10% to 30% by weight of total weight of
composition. These salts can be used alone or in combination with an acidosource.[1]

- **Swelling Agent:** - effervescent system may contain a swelling agent, which is capable of swelling to greater than its original volume and preferably to at least twice its original volume, upon contact with an aqueous (gastrointestinal) fluid. Examples of swelling agents include cross-linked polyvinyl pyrrolidone, cross-linked carboxymethyl cellulose sodium and sodium starch glycoalate. These compounds belong to the class of compounds known as superdisintegrants. The swelling amount may be present about 5-50% by weight of total weight of the composition.[1]

- **Viscolyzing Agents:** - effervescent system may also contain a viscolyzing agent which, upon contact with gastrointestinal fluid, instantaneouslyviscolyzes to trap the gas generated by the gasgenerating components. Preferably, the vicolyzing agent comprises of a carbohydrate gum, for example xanthum gum. Tragacanth gum, gum karaya, guar and acacia. They can be used in concentration range of 3-10% per cent by weight.[1]

- **Gel Forming Polymer:** - the floating system optionally contains a gel forming polymer, which is preferably a water soluble salt of one or more polyuronic acid such as alginic acid. Generally, the gel forming polymer is used in amount from 0.1% to about 20% by weight.[1]

- **Hydrophilic Water-Soluble Polymer:** - the floating system may also contain a hydrophilic water soluble polymer in addition to salt of polyuronic acid. Examples of commonly used hydrophilic water soluble polymers include hydroxy propyl methyl cellulose, hydroxypropylcellulose and polyacrylic acid (carbopol). These polymers modify the rate of release of the drug from the dosageform.[1]

**Non- Effervescent Systems :**-Hydrodynamically balanced systems (HBS), also known as get forming systems is one good example of non effervescent systems. Such systems contain drug with gel forming hydrocolloids meant to remain buoyant in the stomach. This systems comprise of hydrocolloids such as hydroxy ethyl cellulose (HSE), hydroxyl propyl methyl cellulose (HPMC), various other polysaccharides etc, with very high content (20-75%) in the form of tablets or capsule.[1]

- **Ideal HBSTM should have following properties:**
  1. It must have sufficient structure to form a cohesive gelbarrier.
  2. It must maintain an over allspacific density lower than that of gastriccontents.
  3. It should dissolve slowly enough to serve as reservoir for dellivertsystem.
Other examples of such systems are alginate beads, hollow microspheres and other microporous systems.[1]

4) High Density System: -

Systems with a density of about 3 g/cm³ are retained in the range of stomach and are capable of withstanding its peristaltic moment. There is a threshold density limit (2.6-2.8 g/cm³) to retain a system in the lower part of stomach. Various materials such as zinc oxide, titanium dioxide, iron powder etc. are used to manufacture.

**Table 3: Marketed products of GRDDS**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dosage forms</th>
<th>Dose</th>
<th>Indications</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cifran O.D</td>
<td>Ciprofloxacin</td>
<td>Tablet</td>
<td>500mg, 1 gm</td>
<td>Systemic</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Liquid Gavison</td>
<td>Al hydroxide and Mg carbonate</td>
<td>Liquid</td>
<td>95mg and</td>
<td>Antacid</td>
<td>Glaxo Smith Kline, India</td>
</tr>
<tr>
<td>Madopar</td>
<td>Levodopa And Benserazide</td>
<td>Capsule</td>
<td>100mg and 25mg respectively</td>
<td>Parkinson’s disease</td>
<td>Roche Products, USA</td>
</tr>
<tr>
<td>Glumetza</td>
<td>Metformin Hydrochloride</td>
<td>Tablet</td>
<td>500mg and 1000mg</td>
<td>Type 2 diabetes</td>
<td>Depomed, Canada</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam</td>
<td>Capsule</td>
<td>15 mg</td>
<td>Anxiety</td>
<td>Hoffmann</td>
</tr>
</tbody>
</table>
CONCLUSION:

Gastroretentive drug delivery systems have emerged as an efficient means of prolonged retention ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. In spite of number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. Number of commercial products and patents issued in this field are evident of it.

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