Gastro-retentive drug delivery system for treatment of Ulcer

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ABSTRACT

Due to the comfort of administration, economical and extensibility in formulation, the most adopted route to the systemic circulation is the oral route regardless of the astounding elevation in the drug delivery. Oral drug delivery is the most comforting method of delivery due to its better solubility, accurate dosage and simpler production. Approximately 90% of the drugs are administered orally of which solid oral dosage form is the most chosen class of medicaments. Conventional dosage forms usually exhibit the serum drug concentration fluctuations and irregularities in drug concentration in the tissues with resultant toxicity, low bioavailability and thus low therapeutic effects. Accordingly, the concept of the oral sustained release drug delivery system has gained popularity in advancement. Sustained release drug delivery systems have steady concentration for a longer course. However, if the system doesn’t achieve the constant drug release but shows the drug release over the longer duration compared to the conventional system, it is prolonged release systems. These systems are hot in the recent trend as they offer huge designing and adaptability range during formulation.

KEYWORDS

Sustained Release, Pharmacodynamics, Solid Dosage Form

Mostly discover yet 17 essential nutrients for the plants to their growth, Zinc is an essential micronutrient out of total. Oral sustained – controlled release systems have been developed to overcome the limitation regarding the drug which are well absorbed from GIT but have short half-lives and are quickly eliminated from the systemic circulation, by releasing drug slowly into the GIT and maintaining an effective drug serum concentration for a longer course. However, these systems face two obstacles: short GRT and unpredictable short GET which causes incomplete drug release at the absorption site (GIT) and thus, the efficacy of the system diminish.

Thereby, a new and recent approach came into enlightenment i.e. GRRDS that focuses on the site targeted drug release in the prime GIT for both local and systemic effects, by remaining in the stomach region for extended time and thus increasing the GIT of the medicaments (Awasthy et al., 2014)

Need for GRDDS

- Though conventional dosage forms are widely used in treating diseases, yet it has limitation of non-site specificity.
- Drugs which are site specific in absorption requires maximum release of drug at the site thus, GRDDS is needed.

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Thus, Pharmaceutical field is currently concentrating towards the drugs which are site specific by nature.

GRDDS refers to the drug delivery at specific sites i.e. stomach or intestine which is achieved by restraining the dosage form into stomach for controlled release of drug to the specific site viz. stomach, duodenum and intestine.

Merits

- Delivery of drug having low absorption window i.e. the small intestine have been possible by GRDDS.
- They can increase longer residence time thus giving local action. Bioavailability is enhanced for drugs which are readily absorbed in the GIT.
- Patient compliance has increased with these systems.
- Enhanced therapeutic efficiency and efficacy is possible by GRDDS.
- GRDDS reduce the P-glycoprotein activity enhances the bioavailability in the duodenum.
- Reduced dosing frequency and targeted therapy.

Limitations

- Acid unstable drugs are not desirable candidate.
- The drugs which are dominantly absorbed throughout GIT but metabolism through first metabolism are the suitable candidate.
- High fluid level in the stomach is needed for floating systems.
- Adequate water (200-250 ml) is required to be taken while taking such dosage forms.
- Drug having stability or solubility problem in GIT is not preferred for such delivery systems.
- Drugs which causes gastro-irritation isn’t preferred class of drugs for such dosage forms.
- The patient is required to maintain a straight position after having such dosage forms so as to prevent the sweeping away of the dosage form from the stomach. Hence, patients are suggested to take the drug during day time and not before sleeping at night.
- This system doesn’t provide over the top merits for the drugs which have wide absorption window throughout the GIT.

Mechanism of Controlled Gastric Retention of Dosage Forms

- Sedimentation
- Floatation
- Mucoadhesion
- Expansion
- Modification in shape etc.

Gastrointestinal Dynamics

An inter-digestive series of electrical events occur and cycles in every 2-3 hours, through stomach to intestine known as inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC) which has in total 4 phases ongoing throughout the series.

Different Approaches of the GRDDS

Recently, new techniques have been developed solely for the prolonged retention time of oral dosage forms in the gastric region. Both unit component and multi-component solid dosage forms have been designed and developed. They are broadly sorted into two major systems viz. floating and non-floating system.

A. Floating Drug Delivery System

These are the systems which have prolonged floating tendency in the gastric fluid. Thus, are also termed as low density systems. The buoyant behavior can be as a result of various mechanisms as:

- Effervescent system
- Non-effervescent system
  - Hydrodynamically balanced system
  - Microballoons or hollow microspheres
  - Alginate beads
  - Microporous compartment

B. Non-Floating

They don’t show any floating behavior in the stomach but stay for prolonged duration in the stomach by different mechanisms.

- High density (sinking) drug delivery system
- Bioadhesive or mucoadhesive system
- Magnetic system
- Unfoldable system
Beads

One of the latest approach for targeted delivery of drug for sustained release is based on “the concept of magic bullets” given by Dr. Paul Ehrlich is the microbeads, are solid beads like particle act as drug carriers of size varying from 50nm to 2mm\(^{[10]}\). Also known as microbeads are drug containing small, solid and free flowing particles \([11]\). The magic bullets concept deals with the design of systems which focuses the drug to its specific site of action and hence, the maximum therapeutic activity is achieved along with least adverse effects as the drugs distribution is negligible at other body tissues (Gulia et al., 2011). They can show multiple release profiles and the drug is released by a continuous double mechanism \textit{i.e.} diffusion and/or erosion of polymer. Depending on the biocompatibility of the microbeads, they can be used for long-lasting medications. The coated microbeads can be prepared using a coating substance having a property which ability of dissolving in different parts of GIT as per the pH or the enzymes present their and thus providing a site focused and time dependent drug release.

Alginate Beads

Alginate bead is an effective approach for GRDDS. Floating alginate beads can be prepared from sodium alginate or calcium alginate usually by ionotropic gelation method or oil emulsion method. Multi-unit floating dosage forms was prepared with freeze dried calcium alginate. Alginate beads of spherical shape and size 2.5 mm is prepared by dropping alginate polymer into CaCl\(_2\) solution and thus, the calcium alginate gets precipitated. The beads are filtered, washed and frozen in liquid nitrogen. The beads are dried freeze in -40\(^\circ\)C for 24 hours. In this way, the beads are formed with pores which induce the floating force to the beads to float for more than 12 hours.

Mechanism of Floating Multi-particulate System

Firstly, multi-particulates are buoyant in the stomach fluids, but when the stomach empties, the drug get deposited onto the mucous linings and then the drug is absorbed through it continuously. The drug release gets monitored such that it overlaps with the half-life emptying of the system from the stomach.

Floating microbeads can be prepared by incorporating polymers like HPMC and sodium alginate or by incorporating gas generating agents (Kare et al., 2010 and Karthik et al., 2016). Such beads swell when they come in with water and start floating as a result of buoyancy properties of the polymer and the drug release is dependent on the time duration of buoyancy (Karthikeyan D., Karthikeyan M., Ramasamy C., 2008).

Gelling Agent for Preparation of Microbeads

Microbeads are prepared from gelling agent such as Natural polymer, synthetic polymer and semi- synthetic polymers. Natural polymers are gaining importance as carriers of drug in recent times. The advantages of these polymers over commercially available polymer are that, they are biodegradable, biocompatible, nontoxic, and low cost and environment friendly and locally available, better patient tolerated and edible (Kumar et al., 2015).

Polymer

\[
\begin{array}{ccc}
\text{Natural Polymer} & \text{Synthetic Polymer} & \text{Semi-Synthetic Polymer} \\
\text{Sodium alginate} & \text{Carbomers (carbopol)} & \text{Cellulose derivatives} \\
\text{Chitosan} & \text{HPMC} & \\
\text{Pectin} & \text{Agar} / \text{agarose} & \\
\text{\textit{\textalpha}-carrageenan (Lachman et al., 1986)} & \\
\end{array}
\]

Method of Preparation of Microbeads

- Ionotropic gelation method: a natural polymer like sodium alginate or pectin is used as gelling agent for therapeutic agent and a rigiding agent is used for the precipitation of beads by rigidization of gelling polymer. A gas generating agent like NaHCO\(_3\) or CaCO\(_3\) can be used to aid the floating properties to the microbeads (Marinaganti et al., 2013).
- Oil emulsion method: a natural oil like sunflower oil or liquid paraffin have been used along with gelling polymer so as to entrap drug and prepare floating microbeads by two phase emulsion preparation (Mustafa et al., 2015).
- Solvent preparation method: A volatile solvent is usually used which latter evaporates on drying of the prepared beads and leaves the porous structures on the beads surface which induces floating force to the beads (Nagai, T., Machida, Y., 1985).
Cell Immobilization by Electrostatic Method: Micron size beads can be developed by the use of electrical fields and the size can be varied by varying applied electrical potential (Nagai T., Machida Y., 1985).

Table. Phases of migrating myoelectric complex

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Phase</th>
<th>Phase name</th>
<th>Description</th>
<th>Avg. time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phase I</td>
<td>Basal phase</td>
<td>Period of no contractions</td>
<td>30-60 mins</td>
</tr>
<tr>
<td>2</td>
<td>Phase II</td>
<td>Preburst phase</td>
<td>Period of intermittent contractions</td>
<td>20-40 mins</td>
</tr>
<tr>
<td>3</td>
<td>Phase III</td>
<td>Burst phase</td>
<td>Period of regular contraction at the maximal frequency that migrate distally</td>
<td>10-20 mins</td>
</tr>
<tr>
<td>4</td>
<td>Phase IV</td>
<td>transit phase</td>
<td>Period of transition between burst phase and basal phase</td>
<td>0-5 mins</td>
</tr>
</tbody>
</table>

Fig. 1. A schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time period for each period (Chun et al., 2001).

Fig. 2. The mechanism of floating system

Table 2. Classification of anti-peptic ulcer drugs
Ideal Properties for Microbeads

Ideal Microbeads should have following abilities:
- They should prolong the systemic circulation of drug and thus should potentiate their action.
- The drug concentration is specially localized at its site of action by incorporating drug in microbeads like drug carriers.
- They must have reduced toxicity.
- They safeguard the drug from metabolic degradation.
- They are capable of releasing the drug only at the site of action at a desirable rate.

Advantages of Microbeads Formulation

- Beneficial for drug with narrow therapeutic index as it prevents the fluctuations in serum drug concentration by slow and sustained release of drug.
- Complete absorption of drug can be expected firstly from stomach followed by small intestine.
- Site specific drug release inducing maximum efficacy.
- Flexibility in design.
- Improve patient compliance.
- Easily manufactured and lower cost
- Improve bioavailability or by pass first pass metabolism.
- Reduce dose frequency.

Therapeutic Applications of Beads

- Beads can be used for targeting drugs to the tumor cells as they can deliver an effective drug dose to the site and avoids the normal tissue from the exposure of such cytotoxic drugs.
- They can also focus the anti-tubercular drugs to the causative microorganisms which are present inside the cell.
- Drugs or other substances can be incorporated in the cosmetic oil care of the beads and then can be developed into cosmetic products.
- Beads can also be formulated in the suspension dosage forms where in pilocarpine or other miotic drugs can be used for the ophthalmic delivery.
- The peptides and the proteins which are unstable in the GIT can also be delivered successfully orally.
- Radio nucleotides can be incorporated into beads and used for diagnostic agents.

Evaluation Parameter for the Microbeads

- Morphological study
- Particle size determination
- Micromeretics study (Bulk density, Tapped density, Carr’s index, Hausner’s Ratio, Angle of repose)
- Percentage Yield
- Floating lag time and Buoyancy test
- Drug content
- Entrapment Efficiency
- Loose Surface Crystal Study
- Swelling index
- In vitro dissolution

Disease Profile

Peptic Ulcer

A gastric ulcer also known as peptic ulcer is an open sore in the stomach lining. This is a more common term for ulcers that may be in the stomach or the upper part of the small intestine [27]. Peptic ulcer (gastric or duodenal ulcer) is one of the most prevailed disorders affecting the GI system.[28]

Types of Ulcer

1. According to the Location
- Gastric ulcer: the stomach lining or portion is contradictorily influenced and very prevailing in geriatrics.
- Duodenal ulcer: the duodenum portion is contradictorily influenced and very prevailing in juvenile to adults.
2. According to the Severity
- Acute ulcer: is the lower degree ulceration occurring in deep mucosa tissues.
- Chronic peptic ulcer: is the ulcer penetrating through epithelial to muscle layer of stomach to adjacent pancreas and liver. They majorly occur in the pyloric antrum of the stomach and in the duodenum. They are highly severe.

Pathophysiology of Peptic Ulcer

Ulcer occurs as a result of imbalance between aggressive factors (gastric acid and pepsin) and defensive factors (gastric mucus, bicarbonate, prostaglandins) and the mucosal defense becomes incapable and the flow of blood with gets slower thus decreasing the GET. *H. pylori* are a curved or S-shaped gram negative bacterium.

Mechanism of *H. pylori* Infection

*H. pylori* bind to the mucous and epithelial cells of the stomach lining and attaches tightly to the cells by forming “attachment pedestal” causing localized cell damage. They also cause elevation of certain enzymes which causes increases secretion of acid and pepsin thus causes imbalance of aggressive agents. *H. pylori* is capable of producing toxins like chemo toxins also known as “vacuolating cytotoxin” (VacA) which adversely acts on epithelia leading to damage of defense system by inducing cell injury on the lining and tissue damage inside the stomach. Hence, peptic ulcer or gastric ulcer is caused successive to the *H. pylori* infections.

Associated Symptoms
- Epigastric pain for several days–usually after 2 to 3 hours of basic meal–When stomach is empty.
- Anaemia as a result of blood loss
- Weight loss
- Poor appetite
- Bloating
- Burping and oral flatulence
- Nausea and vomiting and intolerance fatty foods.

Advanced Symptoms
- Sharp or sudden but persistent stomach pain heartburn
- Bloody and black stools
- Blood in vomit

Aetiolog for Peptic Ulcer

- *H. pylori*
- NSAIDs
- Pepsin
- Alcohol and smoking
- Bile acids
- Steroids
- Stress
- Changes in gastric mucin consistency
- Past gastric ulcer and family history

Treatment/ Medication

The management and prevention of these acid-related disorders are possible either by decreasing the level of gastric acidity or by enhancing mucosal protection.
- To prevent extreme elevation of gastric acid secretion and direct irritation of gastric mucosa, avoid the foods that cause them.
- Avoid smoking and alcohol.
- In case of NSAIDs induced or positive *H. pylori*, discontinue NSAIDs. In case, it is must to continue NSAIDs, a COX-2 selective inhibitor should be selected as far as possible.
- PPI maintenance is recommended in preventing recurrences even after *H. pylori* eradication.
- In bleeding ulcer, treatment with prostaglandin analogue or a PPI for 6-8 weeks for complete healing.
- Surgical care for perforated peptic ulcer
  - Emergency lapratomy in peritonitis
  - Simple closure, truncal vagotomy and pyloroplasty and gastrectomy.

Therapy

Following regimens are proven to have 80 % eradication rate and are majorly used for the treatment of *H. pylori* infection:
1. PPI in standard dose + Clarithromycin 500 mg + Amoxicillin 1000 mg= twice a day each
2. PPI in standard dose + clarithromycin 500 mg + Metronidazole 400 mg= twice a day each
3. Ranitidine bismuth citrate (RBC) 400mg + Clarithromycin 500 mg + Amoxicillin 1000 mg = twice a day each.
4. RBC 400 mg + Clarithromycin 500 mg + Metronidazole 400mg = twice a day each

**Anti- Ulcer Drugs**

**Preventive Care**

1. Don’t smoke.
2. Drink alcohol only in moderation limit alcohol – 2 drinks for man per day– 1 drinks for man per day.
3. Changes should be made to the diet like eating smaller but frequent meal.

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