A REVIEW APPROACH OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS) IN PEPTIC ULCERS

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ABSTRACT

Peptic ulcers, encompassing both gastric and duodenal ulcers, continue to be a prevalent and challenging gastrointestinal ailment afflicting millions of individuals globally. The treatment of peptic ulcers is often hindered by factors such as short gastric residence time, uneven drug distribution, and potential side effects associated with conventional drug delivery systems. Gastro retentive drug delivery systems (GRDDS) have emerged as a promising approach to address these limitations and enhance the therapeutic efficacy of anti-ulcer medications. This review provides a comprehensive analysis of the evolving landscape of GRDDS in the context of peptic ulcer treatment. It begins by elucidating the pathophysiology of peptic ulcers and the factors influencing drug delivery to the gastric mucosa. Subsequently, it delves into the various approaches employed in GRDDS design, including floating systems, mucoadhesive systems, expandable systems, and magnetic systems. Each approach is critically examined for its mechanisms, advantages, and limitations in achieving prolonged gastric retention. Furthermore, the review presents an in-depth assessment of the prominent anti-ulcer drugs formulated using GRDDS, emphasizing their pharmacokinetic profiles and therapeutic benefits. The comparative evaluation of these formulations highlights their potential to enhance drug bioavailability, prolong drug release, and minimize side effects, thus optimizing peptic ulcer therapy.

Keywords: Peptic, Ulcer, Therapeutic, Gastro, Retentive, Floating

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INTRODUCTION

The widely popular new method known as the "Gastro Retentive -Drug Delivery System" (GRDDS) keeps drugs in the digestive system for a longer time so they can have the desired effects. Drugs formulated and developed as gastro retentive drug delivery systems can be stashed in the stomach for a longer duration as desired. By continuously releasing the drug for a long period, GRDDS can enhance the bioavailability of low bioavailable drugs in stomach (Tripathi *et al.*, 2019). Medicines that get absorbed from the proximal region of the gastrointestinal tract, or having lower solubility, or which gets degraded due to alkaline pH possible gives better efficacy via extending their gastric retention time (GRT). GRDDS are favourable to such medications because they improve their efficacy (Shweta Arora,*et al* 2005). The figure 1.1 indicates the various strategies to formulate the gastro retentive

formulation.

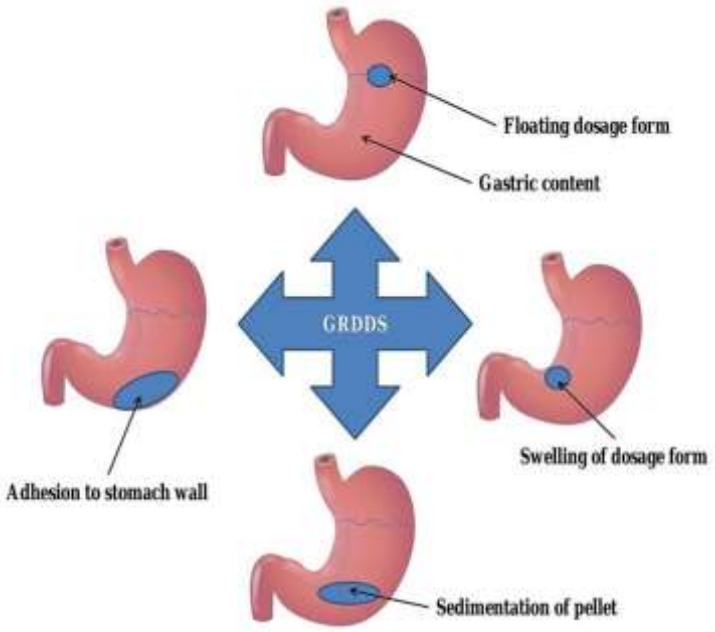

Figure 1.1: Different strategies for formulation of GRDDS

Ingested food is mostly digested in the stomach by creating an acidic environment, adding various enzymes, and then moving the food to the small intestine. Food resides there for a short duration of time and most of the proteins get digested over there. Various gastro retentive formulations covers different regions of GIT including the stomach (Figure 1.2) (Pawar *et al.*, 2011).

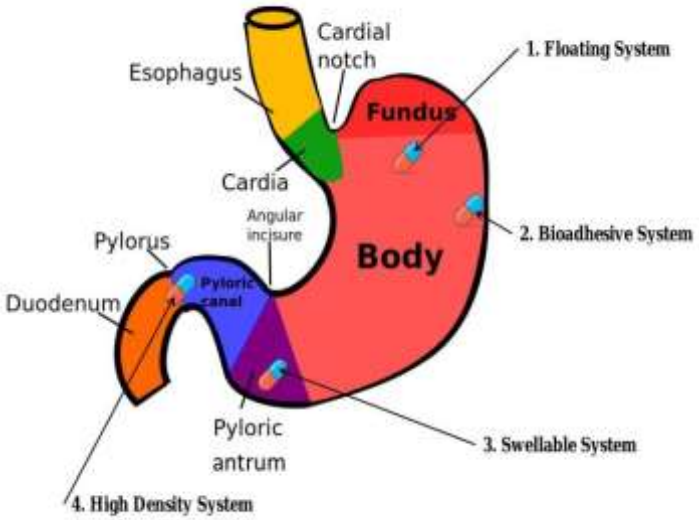

Figure 1.2: Different regions of stomach covered by various formulations ofGRDDS

Stomach has three parts: topmost in continuation to that of the oesophagus is the fundus, followed by the body, and at last, just before duodenum is antrum or pylorus. Inthe region of the fundus along with the body undigested food material is present can be considered as a

reservoir, while pylorus is the primary site where food gets mixed, moreover, its propelling action makes it comparable to pump by which stomach emptying occurs (Kong & Singh, 2008). In fasting as well as in fed condition gastric emptying takes place. During fasting, a sequence of electrical events happens every 2 to 3 h, passing through stomach and intestine (Takahashi, 2013). Later called as migrating myoelectric cycle or interdigestive myoelectric cycle (MMC), this is additionally separated into four different cycles (Figure 1.3) (Washington *et al.*, 2000).

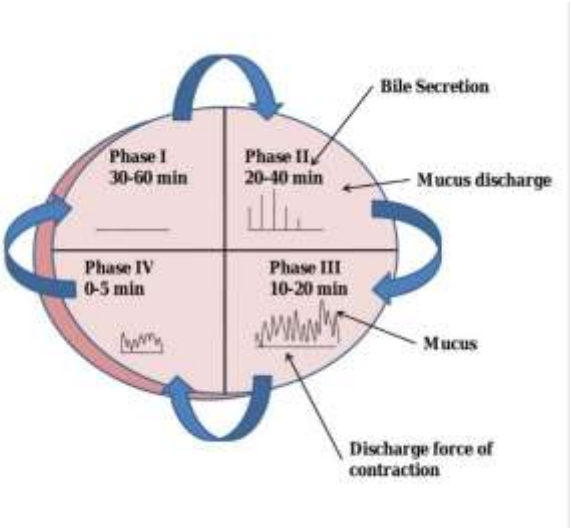

Figure 1.3: Different Phases of gastric emptying

Merits of GRDDS

In the past thirty years, GRDDS have grown in significance and are distinct systems. It has a number of benefits, including site-specific, delayed, and controlled drug release from various gastroretentive dosage forms, which increases patient compliance and reduces side effects by reducing dosing frequency (Vinchurkar *et al.*, 2022).

- **Increased bioavailability**

In contrast to other formulations, the bioavailability of medications is greatly improved in the gastro retentive method. Several mechanisms similar to drug absorption and movement through the GIT affect the degree of drug absorption at the same time.

- **Sustained drug delivery**

Sustained and gradual feedback from the gastro-retentive system reduces dosing frequency for medications with a limited biological half-life, which is related to improved patient compliance.

- **Localized treatment**

The drug's administration from GRDDS to the stomach can be extended and persistent.

- **Decrease variation of drug amount**

Continuous infusion of the drug from GRDDS dosing results in a finer range of blood

medication quantity than rapid dosage.

- **Reduce variability**

Reduction in the fluctuation of systemic concentration of the dose by the maintenance of the gastric content of the drug.

- **Enhancement of the efficacy**

Increasing the solubility of medications increases their effectiveness (Eytan A Klausner, 2003)**.**

APPROACHES FOR GASTRIC RETENTION

Several technological approaches have been put forth to prolong medication residency in the stomach area (Figure 1.4).

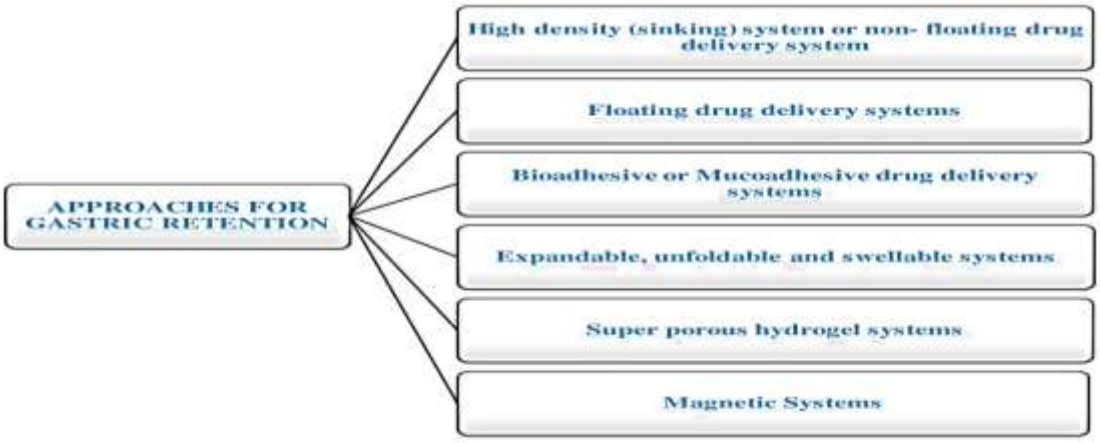

Figure 1.4: Various approaches for gastric retention

Following is an explanation of the many technologies and methods for gastric retention

High density (sinking) system

Comparable to the native stomach contents in density (1.004 g/cm^3) is the major requirement of this system. Dosage forms are created by covering a heavy core with the drug or incorporating it with inert substances like titanium oxide, iron powder, zinc oxide, and barium sulphate (N. K. Jain, 2004). Density can be enhanced by 1.5-2.4 g/cm^3. For a significant increase in gastric retention interval, a density of around 2.5 g/cm^3 appears to be needed (Clarke *et al.*, 1993). However, the feasibility of this method in humans has not been proven (Moes, 1993).

Floating drug delivery system (FDDS)

FDDS are amongst the most efficient process for acquiring gastric retention and appropriate medication bioavailability (B. N. Singh & Kim, 2000). Drugs that have stomach or upper small intestine absorption windows are perfect candidates for FDDS (Sungthongjeen *et al.*, 2006). The medications are released gradually and under regulated conditions thanks to the systems, lower bulk density than gastric fluids, this enables them to float for a longer period

of time in the stomach without preventing gastric emptying. The stomach's residual system is emptied following the release of the medicine. As a result, the GRT is prolonged and the plasma-is better regulated.

Bioadhesive or Mucoadhesive drug delivery system

For increasing absorption at targeted specific sites in humans, bioadhesive drug delivery systems are being used. Bioadhesive drug delivery systems employ polymers having stomach epithelial surface adhering property which in turn help them in acquiring gastric retention. Dosage forms bind to the mucosal surface by several mechanisms (Moes, 1993). The preceding is some of the mucoadhesion pathwayshypothesis.

- The wetting hypothesis postulates that the primary cause of bioadhesion may bedue to the spreadability and close contact potential of bioadhesive polymers with mucosal layers

- The diffusion principle suggests that the physical coupling of mucin strands with elastic polymer chains or mucin strand conceptualization into the porous-structure of the polymer substrate can be one of the factors in bioadhesion.

- Vander Waal forces and hydrogen bonding which acts as secondary forces as per the absorption principle can be held accountable for bioadhesion.

- According to the electron theory, the glycoprotein mucin systems, as well as the bio adhesive material, include electrostatic forces that are attracted to each other.

- Polymers namely polyacrylic acid, sucralfate, chitosan, tragacanth, cholestyramine, dextrin, polylactic acids, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol (PEG), and sodium alginate are used in formulating bioadhesive drug delivery system. Most of these polymers are efficient in formulating bioadhesive drug delivery systems, due to the GIT's fast mucus turnover, retaining them is quite cumbersome (Boddupalli B. M. *et al*, 2010)

Expandable, unfoldable, and swellable system

Formulation, wider than the pyloric sphincter may be able to survive gastric transit. Butthis should not cause any gastric obstruction and can be taken orally with ease when taken alone or in combination. As a result, their configurations have changed (Eytan AKlausner, 2003). A small dosage form for oral intake, an extended gastroretentive type, and one more compact design that allows for evacuation.

To overcome peristalsis and structural contractility of the stomach, gastroretention is achieved by combining significant dimensions with higher stiffness of dosage form. Recently, researchers have been able to build an effective GRDDS using foldable and swellable devices. Unfoldable parts are constructed from biodegradable polymers. This is achieved by compacting biodegradable polymer into a capsule that stretches into the stomach formulated in different shapes and sizes for e.g., planner membrane, a cube, or a tetrahedron (Nayak *et al.*, 2010). Due to their mechanical characteristics, swellable materials can occasionally be kept in the GIT. Osmotic water absorption causes the swelling, and the formulation should be so small that it may be absorbed by gastric fluid (Prinderre *et al.*, 2011). Some drawbacks of stretchable systems include the difficulty of storing easily

hydrolyzable,biodegradable polymers. Blockage, intestinal adhesion, and gastropathy may occur when inflexible, large single-unit expandable systems are retained for an extended amount of time (A. Badoni, *et al* 2011).

Super porous hydrogel system

Super porous hydrogel systems have to be classified separately owing to their unique properties. They function by lengthening the period that food stays in the stomach, allowing for faster water absorption through capillary wetting through many linkedopen pores with an average pore size of >100 µm (J. Chen *et al.*, 2000). In order to survive the strain of gastric contraction, they enlarge to a larger size. The inclusion of hydrophilic particle materials in the formulation lends credence to this (J. Chen & Park,2000).

Magnetic System

The magnetic system works on the principle of magnetism i.e., a small magnet is placed in the formulation and can be targeted by placing an external magnet over the abdomen for increasing the GRT. Although it works, the magnet placed on the abdomen must be positioned precisely, and patient compliance is also needed (Nayak *etal.*, 2010).

Combination of different system

Systems like gas-generating apparatuses integrate many gastro-retentive features or concepts in practise, even if it isn't clearly stated that it does so. Due to their low density, they float while also expanding in size to obstruct transit (as described above). Bioadhesion is frequently stated in conjunction with flopping or even swelling behaviour for systems where dual mode of action is expressly asserted. A few floating- bioadhesive microspheres were made using acetohydroxamic acid. When acetohydroxamic acid is loaded onto microspheres in this technique instead of just using plain acetohydroxamic acid, *H. pylori* development is effectively inhibited (Prinderre *et al.*, 2011).

PEPTIC ULCER

The phrase "peptic ulcer" refers to a variety of digestive tract ulcers, including those in the stomach and duodenum. Previously, it was thought that stress and spicy foods contributed to the development of this type of ulcer. Recent studies, however, have revealed that these are only the exacerbating variables. The *H. pylori* bacterial infection or a reaction to some medications, non-steroidal anti-inflammatory drugs are among the primary cause. Weight loss, a lack of appetite, bloating, nausea, vomiting, and dark faeces that signify gastrointestinal bleeding are all signs of peptic ulcers (Kuna *et al.*, 2019).

Signs and Symptoms of Gastric Ulcers

Signs and symptoms of Gastric ulcers include loss of appetite, nausea & vomiting, melena, hematemesis, chest pain, blotting & abdominal fullness and gastric perforations leading to acute peritonitis, extreme, stabbing pain etc.

Pathophysiology of Peptic Ulcers

Even though they are prevalent and devastating illnesses, *Helicobacter pylori* infection only affects a small percentage of those who develop stomach ulcers and gastric cancer.We need to

know how to focus prophylaxis because mass eradication of *H. pylori* is unfeasible due to the price and danger of drug resistance. It is important to understand the processes that result in stomach cancer or the development of ulcers when *H. pylori* is present. The result of a *H. pylori* infection depends on a number of variables , including the host reaction, the intensity and extent of stomach inflammation as well as how much acid is released by parietal cells. *H. pylori* can increase acid secretion in people who develop duodenal ulcers, decrease acid through gastric atrophy in people who develop either gastric ulcers or cancer, and essentially maintain acid secretion in people who do not experience any of these conditions (Calam & Baron, 2001)

The primary mechanism of NSAID-related harm to the gastroduodenal mucosa is systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is involved in prostaglandin synthesis and is linked to decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. NSAIDs reversibly and in dependence on concentration manner, block the enzyme. Exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs minimise ulcer risk and mucosal damage (Figure 1.19).

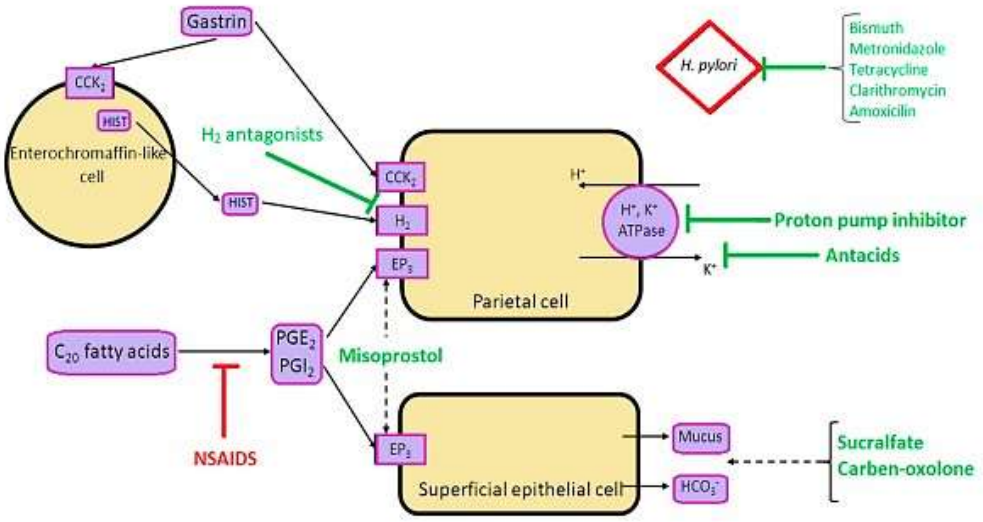

Figure 1.19: Pathophysiological mechanism involved in Peptic ulcers

CONCLUSION

The review discusses the significance of the physiological and pharmacological factors influencing the performance of GRDDS in peptic ulcer treatment. Considerations such as gastric emptying rate, patient variability, and dosing regimens are addressed to offer a holistic perspective on the practical implementation of GRDDS. Moreover, safety concerns and regulatory considerations associated with GRDDS for peptic ulcer treatment are examined, shedding light on the need for thorough preclinical and clinical assessments to ensure patient well-being. In conclusion, this comprehensive review underscores the potential of Gastro Retentive Drug Delivery Systems (GRDDS) as a transformative approach to peptic ulcer therapy. The amalgamation of scientific advancements and innovative drug delivery strategies holds promise for optimizing treatment outcomes, improving patient compliance, and ultimately alleviating the burden of peptic ulcers. Nevertheless, further research and clinical validation are imperative to unlock the full therapeutic potential of GRDDS in the

management of this prevalent gastrointestinal disorder.

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