International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 165-170 www.ijprajournal.com ISSN: 2249-7781

Peptic Ulcer Therapeutic Treatment by Gastroretentive Drug Delivery Systems – A Review

Peter Kunze[1], Manuela Brock[1], Sabine Pestke[1], Kerstin Fromm[1]
1. University of Greifswald, Greifswald, Germany

Date of Submission: 31-1-2021 Date of Acceptance: 15-01-2021

ABSTRACT: In the recent times lot of research work is being done on oral drug delivery systems which are controlled, in order to overcome some issues with short gastric residence time, gastric emptying time being very varying factor, absorption window being different in different cases. To treat peptic ulcers several approaches like floating drug delivery systems were researched in order to extend the GRT and delayed gastric emptying devices. We will talk about different Gastroretentive drug delivery systems and how they are effective in treating peptic ulcers**.**

INTRODUCTION:

Peptic ulcer is a common disorder that is caused due to damage to the stomach lining in the stomach. Factors that cause peptic ulcers are gastric acid, Pylori, blood flow to mucosa, mucus, bicarbonate. peptic ulcer is also called gastric ulcer or stomach ulcer.There are three types of peptic ulcers.

Gastric Ulcer: This type of ulcer develops in the stomach

Esophageal ulcers: This type of ulcers develop in the esophagus

Duodenal ulcers: this type of peptic ulcers develop in the upper stomach of small intestine, which is called duodenum.

Symptoms of peptic ulcers are change in appetite, nausea, weight loss, vomiting and indigestionGastroretentiveDrug Delivery system:The dosage forma which can be retained in the stomach are calledGastroretentive Drug Delivery Forms [1]. Gastroretentive Drug Delivery Forms deliver the drug for a prolonged period of time continuously and improve the absorption window of drugs by delivering them in a controlled way.The main aim of stomach is transporting and processing food. It quickly process the consumption of a large meal. The main metabolism of substances is promoted by proteins in stomach. Stomach will mix up and grind the food with the secretions of stomach and turn food in to simple liquid form. This liquid form of food will then be moved to small intestine for further digestion. Human anatomy of stomach has three parts fundus, body and antrum. Fundus acts as a storage for the undigested food. By propeller actions antrum mainly acts as gastric emptying pump. Fed state and fasting state cause gastric emptying. Every two to three hours series of events takes place in stomach [2]. Indigestive cycle which happens takes place in four phases [3]. The four phases areas below:

Phase 1: The first phase is Basal phase which will last about 30 to 60 minutes, and this phase is due to lake of secretory, electrical and contractile activity with rare contractions.

Phase 2: This is the second phase pre burst phase and last about 20 to 40 minutes, and during this phase motions increase in frequency and size with intermittent contraction.

Phase 3: This phase is called burst phase, and this is the third phase which will have intense contractions which live for a short period of time.

Phase 4: This is the last phase which will last only for up to 5 minutes.

In the stomach, which is gastrointestinal tract, to deliver the drug various polymers are employed in floating drug delivery system. IN the formation of the raft forming drug system various natural and synthetic polymersare used. Some of the natural polymers are gellan gum, alginic gum, guar gum etc.., and some of the synthetic polymers are HPMC, poly (DLlactide-co-glycolide) and poly-caprolactone etc., In situ gels the polymers used should have the following characteristics:

1. Biocompatibility should exist.
2. pseudoplastic behavior should be there.
3. Along with increase in shear rate polymer should be capable of increasing viscosity.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 165-170 www.ijprajournal.com ISSN: 2249-7781

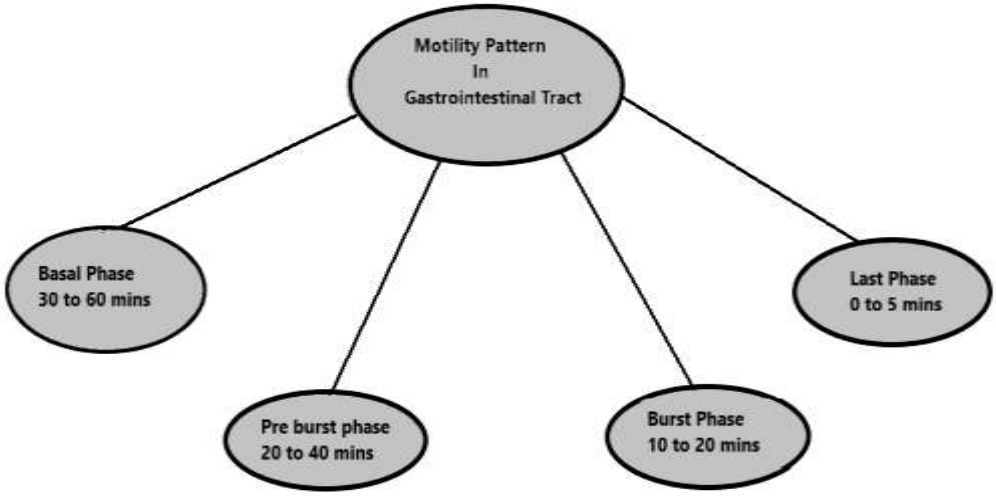

Fig 1: Phases of Motility in GIT

These motility patterns will affect the dosage form and retention. Orally administered dosage forms are affected by complex anatomy and physiology of GIT, including variations in acidity, enzyme content, also significantly influence the release and dissolution and absorption. Continuous pattern of spike potentials and contractions are set off by feeding and are called postprandial motility. The dosage form administered is influenced by a particular phase, and the performance of peroral CR and GRDFs [4]. When controlled systems (CRs) are administered in the fasted state the MMC may be in one of its phases and there is a possibility that this might influence Gastric Residence Time. There should be more significance for drugs which has a particular absorption window as it will affect the amount of time and the dosage forms spend around the particular window. Therefore design of GRDDS should take into consideration about the resistance of dosage form to emptying gastric dosage form in phase 3 of MMC. There are several techniques like Raft Forming system [6], floating,[5], swelling, Effervescent or non-effervescent systems are explained below [7-10].

Floating Systems: Davis in 1968 first described floating system has the sufficient buoyancy to remain in the stomach for the prolonged period of time and floats over gastric contents [11,12]. The drug will be released at the desired rate ,as the system floats over gastric contents, the drug is released at desired rate slowly and also fluctuation in plasma drug concentration is reduced [13]. Floating system is again classified into effervescent and non-effervescent systems.

By incorporating a floating chamber filled with vacuum or air ,drug delivery system flotation can be achieved in stomach. In to the floating chamber gas can be introduced by volatilizing organic solvent [14].

Raft Forming Systems: In this a gel forming solution on contact with gastric fluid forms a viscous gel which contains entrapped CO2 bubbles. Antacids like aluminum hydroxide or calcium carbonate are also contained in the formulation.As it forma a layer on the gastric fluids they are used for various treatments for example amoxicillin Raft forming system is used for H. pylori infection [6].

Mucoadhesive system: In oral drug delivery mucoadhesive drug delivery systems promise prolonged gastric or small intestinal residence time , an intimate contact delivery basis for interactions of multifunctional polymers with mucosa such as enzyme inhibition.If the bond involves mucous coating and adhesive polymeric device the term mucoadhesion is used and the cell specific to bio adhesion is cytoadhesion. This system will bind the gastric epithelial cell surface / mucin and by increasing the duration and intimacy of contact

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 165-170 www.ijprajournal.com ISSN: 2249-7781

between biological membrane and dosage form, it increases and extend the GRT. This concept is based on self-protecting mechanism of GIT. Mucus is of glycoproteins and is gel like stingy slime. Mucus serves as barrier to bacteria and antigens and also acts as passage for solids.

A mucoadhesive is a synthetic or natural polymer which is capable of adhering to mucus lining of the GIT. Specific molecular weight, chain length, molecular flexibility are the characteristics of these polymers. They should be **non**-absorbable and nontoxic, be able to form noncovalent bonds with mucin epithelial surfaces, should be quick to adhere to moist surfaces, should be able to easily incorporate the drug, should not hinder the drug release. Binding of mucin epithelial surface to polymers can be divided into 3 categories [15]:

- Hydration mediated adhesion
- Receptor mediated adhesion
- Bonding-mediated adhesion

Magnetic System: Dosage forms contain a small internal magnet and a also a magnet is placed in abdomen over the position of stomach that retains the dosage forms.Disadvantage of this system:

- With a degree of precision, a magnet needs to be placed.
- Patients noncompliance
- not used in multiple cases and by multiple people.

Swelling systems: These dosage forms swell to bigger size which will prevent their passage through the pylorus after swallowing it [16]. Because of this the dosage form is retained in the stomach for long period of time. They sometimes remain lodged at the pyloric sphincter and are referred to as plug systems. Even in the fed state these polymeric matrices remain in gastric cavity for several hours.BY selecting a polymer with proper molecular weight and swelling properties-controlled drug release will be achieved. When it comes to contact with gastric fluid polymer imbibes water and swell. The presence of physical chemical crosslink in the hydrophilic polymer network cause the extensive swelling of these polymers. The extent to which this swelling happens**,** and duration is balanced by the degree of cross linking between polymeric chains. The swelling ability can be retarted using high degree crosslinking, and then its able to maintain its physical integrity for a prolonged period. while extensive selling is caused by low degree crosslinking which is followed by rapid dissolution of the polymer [17]. To maintain the balance between dissolution and swelling an optimum amount of cross linking is necessary. Due to loss of mechanical strength the swollen system will eventually loose its integrity and it will burst into small fragments [18].

Advantages of Gastroretentive Drug Delivery System:

- They help with gastric retention time GRT, as well as gastric emptying time GET. This system has lower bulk density than gastric fluids so it remains buoyant on gastric fluids.
- This system is efficient in repairing in small intestine and stomach related problems. Gastroretentive drug delivery sustains drug release and so it will avail local therapy in these organs.
- This system reduces the chance of drug exposure to the diseased site as it provides systematic and controlled drug delivery system.
- Minimize risk factor in antibiotics, remove fluctuations, by stabilizing therapeutic levels over prolonged periods.
- This system ensures patient compliance with reduced dosage frequency, with optimized release in case of short half life drugs.
- The gastroretentive dosage forms minimizes variance in concentrations of drugs and effects by providing narrow curative index.
- Due to reduced counter activity by body this system provides higher efficiency.
- Increase in bioavailability and curative efficiency of drugs and economic usage of dosage.
- Due to controlled rates of fluctuation provided by system a wider array is provided for selectivity in receptor activation.

Disadvantages of Gastroretentive Drug Delivery System:

- This system is not suitable for drugs which has limited acid solubility like Phenytoin.
- This system is not suitable for drugs that are not stable in acidic environments like Erythromycin.
- Not suitable for drugs that cause gastric lesions on slow release like Aspirin.
- Hydrogen based swelling systems will take longer time to swell.
- By administrating multiple doses, drug delivery systems pose threat to life.
- Not suitable for drugs which gets absorbed selectively in colon.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 165-170 www.ijprajournal.com ISSN: 2249-7781

- For drugs that are absorbed equally through GIT like nifedipine.
- Floating drug delivery systems require high fluid levels in stomach to float and work effectively.
- Need for increased levels of fluid in the stomach.

Factors that control Gastric Retention of Dosage Forms:

- Several factors of stomach anatomy and physiology need to be considered in the development of gastrorententive dosage forms
- Size of the Particle: Particle should be of size 1 to 2 mm in order to pass through the pyloric values into small intestine [19].
- Density of Dosage Form: Density of dosage form should be in range 1g/cm3 to 2.5g/cm3.
- Food Intake: Gastric retention Time GRT should not be in fed state.
- Gender and Age: Females have short Gastric retention Time GRT than males [21], and age greater than 70 shows longer Gastric retention Time GRT.
- Shape of Dosage Form: Ring and tetrahedron with 22.5 to 48 KSI flexural modulus show 90% of Gastric retention Time GRT.
- Size: Size should be greater than 7.5 mm in diameter [22].
- Posture and Nature of Drug: Posture should be between spine and upright ambulatory states.Drugs with impact on GRT time like Codeine.
- Frequency of Intake: Due to low frequency of MMC, GRT increases 40 times more.

Some other factors that control gastric retention of dosage forms are individual's physical activity, body mas index, and diseased state of the patient, molecular weight of the drug depending on ionization state [23].

Floating drug delivery system remain in the stomach for a longer period of time as the floating drug delivery systems have a bulk density less than gastric fluids. As soon as drug is released the residual system is removed from the stomach. This results in control of fluctuations in plasma levels and increased GRT.A minimum level of floating force is required to keep the dosage from being buoyant. In order to measure floating force the following formula is used.

$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gV$

Where, F= total vertical force, Df = fluid density, Ds = object density, V = volume and g = acceleration due to gravity.

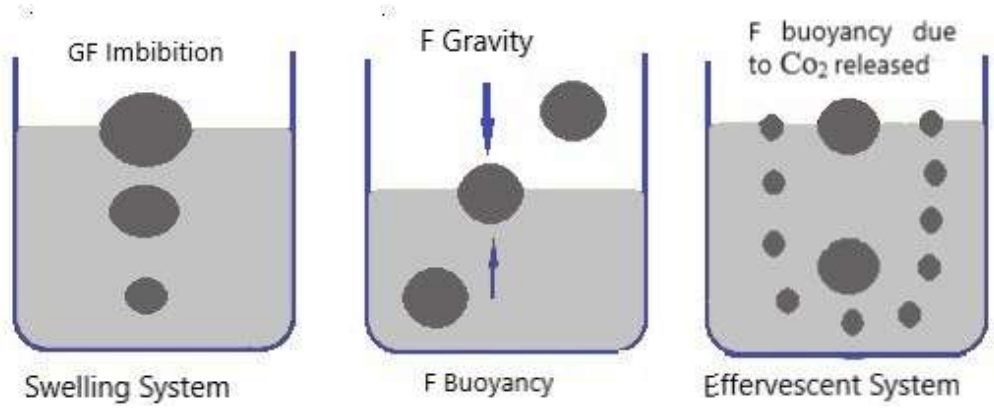

Fig 2: Floating Drug Delivery System Mechanism

Peptic Ulcer Treatments:

Helicobacter pylori has changed our approach to peptic ulcer disease. There are several environmental factors and bacteria playsvery important role in peptic ulcer disease. H. pylori infection and the use of nonsteroidal anti-inflammatory drugs are the causes of peptic ulcer disease. There are also other infections and comorbidities that are associated with risk of peptic ulcer disease. smoking increases the risk of ulcer occurrence and slows down the healing.

History and clinical representation of protic ulcer disease differ in individual population. In about 30 percent of older population abdominal pain is absent [24]. Ulcer symptoms may increase during pregnancy in women. IN patients with ulcer, some of them may have breakdown of mucosal protectants as a result of stress and will lead to splanchnic hypoperfusion. The risk factors in this case are mechanical ventilation which lasts longer than 48 hours, burns, and moderate to severe trauma. In patients of older age who has peptic

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 165-170 www.ijprajournal.com ISSN: 2249-7781

ulcer will likely have painless ulcers, complications int his case are mortality which rate being three times more than younger patients. And these patients more likely will have continuous bleeding and need transfusions and surgery. And in children between the ages 8 to 17, ulcers happen 30 times more common than gastric ulcer.

Antacids like sodium bicarbonate, aluminum hydroxide or them combined provides effective pain relief via neutralization. The time for which these antacids will remain in the stomach is too short for it to create neutralizing effect. In patients with H pylori infection PPI therapy causes corpus predominant gastritis which is frequently found in the patients with gastric cancer. Some studies suggest that during nighttime gastric acidity is not controlled effectively by proton pump inhibitors.Esophagitis is a type of peptic ulcer, and the treatments for healing esophagitis are high doses and frequent doses of H2RAs.Degree of esophagitis is inversely related to heling esophagitis [25]. Combining H2Ras and daily PPIs may prevent nocturnal decrease in pH [26], and this helps patients who have nocturnal symptoms. Cimetidine, the potent of H2Ras like RNT, famotidine (FMT) by modifying these chemical structures,treatment for acid related disease. These compounds will later used to inhibit gastric acid secretion stimulated by not only histamine but also carbachol and gastrin in both humans and animals. These findings suggest that for the effect of secretagogues H2R stimulation is required. In multiple countries There is a risk of four time more in occurrence of gastric cancer in people with H. pylori infection, which means majority of the gastric carcinomas are related to H. pylori infection. Because of patient compliance being poor and antibiotic resistance being high a logical way to improve the effectiveness of therapeutics is to develop gastroprotective dosage forms in order to keep the drugs and release them as long as possible. Amoxicillin is orally absorbed semi synthetic antibiotic, and it is widely used in treating gastric ulcers which are associated with H. pylori [6,27,28]. The treatment time of such a disease may be reduced by increase in residence time. So few researchers had researched new amoxicillin formulations like mucoadhesive tablets , float tablets which can reside in GIT for more period of time which can treat effectively [29].

REFERENCES:

[1]. Cremer K. Drug Delivery: Gastro-Remaining Dosage Forms, Pharm J, 1997; 259:108

[2]. Prajapati S and Dharamsi A: Floating drug delivery for prolonging gastric retention of dosage form. Indian Journal of Novel Drug Delivery 2013; 5:15-27.

[3]. Wilson CG and Washington N: The Stomach: its role in oral drug delivery. In: Rubinstein, M.H., (Ed.). Physiological pharmaceutics: biological barriers to drug absorption. Ellis Harwood. Chechester 1989: 47- 70.

[4]. Khosla R, Feely LC, Davis SS, Gastrointestinal Transit of Non Disintegrating Tablets in Fed Subjects, Int J Pharm, 1989; 53(1):107–117.

[5]. Machida Y, Inouye K, Tokumura T. Preparation and Evaluation of Intragastric Buoyant Preparations, Drug Des Del, 1989; 4:155– 161

[6]. Kamsali, Akhil; et al. Development and Optimization of Amoxicillin Floating Raft System to effectively treat Helicobacter pylori infection. Ars Pharm, 61(3): 163-168 (2020). http://dx.doi.org/10.30827/ars.v61i3.13718

[7]. Sheth PR, Tossounian J. The Hydrodynamically Balanced System: A Novel Drug Delivery System for Oral Use, Drug Dev Ind Pharm, 1984; 10(2):313–339.

[8]. Watanabe S. Solid Therapeutic Preparation Remaining in Stomach, US Patent 3976764, 24 August, 1976.

[9]. Michaels AS, Bashwa JD and Zaffaroni A. Integrated Device for Administering Beneficial Drug at Programmed Rate, US Patent 3901232, 26 August, 1975.

[10]. Ch'ng HS. Bioadhesive Polymers as Platforms for Oral Controlled Drug Delivery II: Synthesis and Evaluation of Some Swelling, Water Insoluble Bioadhesive Polymers, J Pharm Sci, 1985; 74(4):399–405.

[11]. Davis DW. Method of Swallowing a Pill, US Patent 3418999, 31 December, 1968.

[12]. Ichikawa M, Watanabe S, Miyake Y. A New Multiple-Unit Oral Floating Dosage Systems I: Preparation and In Vitro Evaluation of Floating and Sustained-Release Characteristics, J Pharm Sci, 1991; 80:1062–1066.

[13]. Fell JT, Whitehead L, Collett JH. Prolonged Gastric Retention Using Floating Dosage Forms, Pharm Technol, 2000:82–90.
[14]. Reddy LH, Murthy RS. Floating dosage systems in drug delivery, Crit Rev Ther Drug Carr Syst, 2002; 19(6):553 – 585.
[15]. Hilton AK, Deasy PB. In Vitro and In Vivo Evaluation of an Oral Sustained Release Floating Dosage Form of Amoxycillin Trihydrate, Int J Pharm, 1992; 86(1):79–88.
[16]. Caldwell LJ, Gardner CR, Cargill RC. Drug Delivery Device Which Can Be Retained in the Stomach for a Controlled Period of Time, US Patent 4735804, 5 April, 1988
[17]. Gupta P, Vermani K, Garg S. Hydrogels: From Controlled Release to pH Responsive Drug Delivery, Drug Discov Today, 2002; 7(10):569–579.
[18]. Deshpande AA. Development of a Novel Controlled Release System for Gastric Retention, Pharm Res, 1997; 14(6):815–819
[19]. Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Rubinstein, MH, editors. Physiological Pharmaceutical: Biological barriers to the drug absorption. Chichester, U.K: Ellis Horwood. 1989. P. 47-70
[20]. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003: 160-166
[21]. Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr ML. Effects of gender, posture, and age on gastric residence time of an indigestible solid: Pharmaceutical consideration. Pharm. Res. 1988; 10: 639-44.
[22]. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using Gastroretentive technologies. CurrOpinPharmacol 2006; 6: 501-508.
[23]. Larhed AW, Artursson P, Grasjo J, Bjork K. Diffusion of drugs in native and purified gastrointestinal mucus. J Pharm Sci 1997; 86(6): 660-665.
[24]. Hilton D, Iman N, Burke GJ, Moore A, O'Mara G, Signorini D, et al. Absence of abdominal pain in older persons with endoscopic ulcers: a prospective study. Am J Gastroenterol. 2001;96:380–4.
[25]. Younes Z, Johnson A. Diagnostic evaluation in gastroesophageal reflux disease, Gastroesophageal reflux disease, Gastroenterology Clinics of North America, 1999; 28(4):809–30.
[26]. Katz PO, Anderson C, Khoury R. Gastroesophageal reflux associated with nocturnal acid breakthrough with omeprazole, Gastroenteroloy, 2001; 120:A-441.
[27]. Suleymanlar I, Tuncer M, Tugrul MS. Response to triple treatment with omeprazole, amoxicillin and clarithromycin for Helicobacter pylori infections in continuous ambulatory peritoneal dialysis patients, Adv Perit Dial, 1999; 15:79-81.
[28]. Vakil N, Cutler A. Ten day triple therapy with ranitidine, bismuthcitrate, amoxicillin and clarithromycin in eradicating Helicobacter pylori, Am J Gastroenterol, 1999;94: 1197-1199.
[29]. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate, Int J Pharm, 1992; 86:79-88.