EJTAS
ISSN 2786-7447
EUROPEAN JOURNAL OF THEORETICAL AND APPLIED SCIENCES
OPEN ACCESS
PEER REVIEWED

Recent Advances in Gastro Retentive Drug Delivery Systems

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Suggested Citation
Wafa, A., Raihan, R. & Tyagi, S. (2024). Recent Advances in Gastro Retentive Drug Delivery Systems. *European Journal of Theoretical and Applied Sciences, 2*(2), 702-710.
DOI: 10.59324/ejtas.2024.2(2).61

Abstract:

The issues with oral conventional dose forms can be resolved with the use of gastroretentive drug delivery systems (GRDDS). GRDDS is a way to prolong the stomach residence time, which allows for the release of drugs and the possibility of local or systemic effects in the upper gastrointestinal tract. To enhance treatment, some potent medications are employed with gastro-retentive dose forms for longer. By producing a high concentration of medication in the stomach that can be sustained for an extended amount of time, gastroretentive formulations (GRFs) greatly improve stomach pharmacotherapy. As a result, a wide range of dosage forms have been developed for medications that break down at alkaline pH but remain stable at acidic pH. Therefore, medications have limited absorption.

Keywords: *GRDDS, Factors affecting the GRDDS, Type of GRDDS, and Marketed formulations of GRDDS.*

Introduction

The study and development of rate-controlled release oral drug delivery systems have advanced logically and technically in recent years despite persistent physiological challenges, such as low gastric resident time and irregular gastric discharging periods. With traditional formulations like tablets, granules, and capsules, the oral availability of medications with a larger absorption window in the upper part of the GIT is typically insufficient (Gupta et al., 2018). When used to treat stomach ailments including ulcers and H. pylori infections, these treatments have a predictable level of efficacy and can be administered with gradual release in the stomach to have a localized effect at the site of action (Bardonnet et al., 2006). Consequently, insufficient gastric residence time complicates traditional oral formulations. Since most drugs are absorbed in the larger portion of the small intestine, rapid gastrointestinal transit can prevent full drug release in the absorption site and reduce the efficiency of the administered dosage. The oral route is the most popular and efficient medication delivery method; nonetheless, there are several physiological problems. These include a variable degree of stomach emptying that varies from person to person, an insufficient gastrointestinal transit time (eight to twelve hours), and the existence of an absorption site for many medications in the larger gastrointestinal tract. Researchers are working on a delivery system that can stay in the GI for a long, predictable period as a result of these issues (Kshirsagar et al., 2011). Gastro-retentive drug delivery system is a revolutionary

delivery method that can prolong stomach retention, increase the length of time that pharmaceuticals are in the stomach, and improve the bioavailability of drugs (Gopal et al., 2020).

Physiology of Stomach

There are three main components of the stomach: the fundus, the body, and the pylorus. When on a fast, the stomach shrinks to the size of a collapsible bag, holding 50 milliliters. When fasting, the stomach's pH is between 1-3, and its typical gastric residual time is between 1.5 and 3 hours. The pyloric sphincter's diameter is 12±7 mm. The GIT displays continuous motility in two phases, namely the pattern of inter-digestion and digestion motility. A migrating motor complex is the pattern of inter-digestion motilities (CMC). It is repeated every two to three hours and is broken down into four sections (Schubert 2016).

Phase I: Basal phase, without contractions and silent.

Phase II: The contraction intensifies in this pre-burst period.

Phase III: Explosion phase, large-scale, highly organized contraction, and effective contents evacuation.

Phase IV: Transitional period, during which the contractions from Phase III's latter half dissolve into Phase I's stillness. Phases depicted in Figure 1.

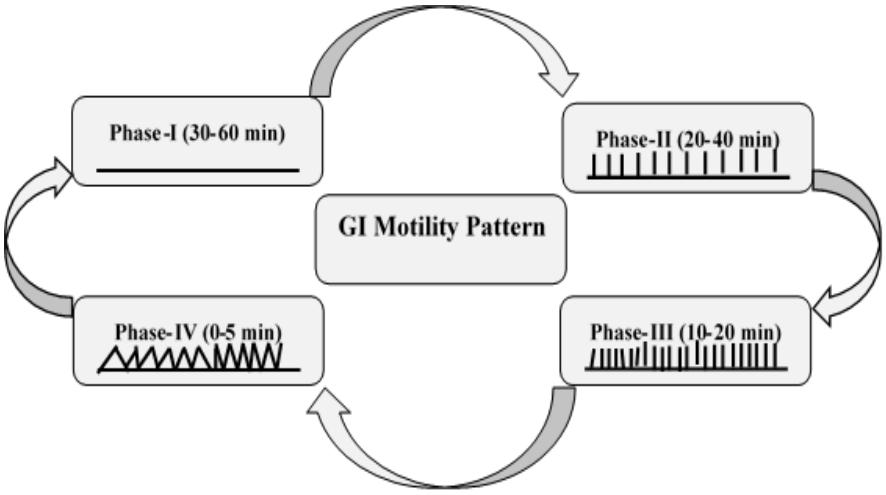

Figure 1. GI Motility Pattern

There are three activities connected with stomach motility:

1. Peristaltic Wave: Only when the distal intestine region is sufficiently relaxed can the longitudinal layer rhythmically shrink and the peristalsis wave occur forward.

2. Segmentation: Rounded muscle layer atrophy that occurs rhythmically.

3. Ancillary Movements: The auxiliary movement is known as stomach rest because it allows the stomach to rest and reserves the food that has been swallowed. A food bolus is transferred from the esophagus into the stomach via the lower esophageal sphincter (LES) (Tobias et al., 2020).

Function of Stomach

- Restricted absorption of certain lipid-soluble medications, alcohol, and water.
- Understand a particular defense against microorganisms and supply the stomach juice with HCl.
- Ileum produces and secretes the intrinsic factor required for Vi-B12 absorption.

- Food storage, mixing, chime creation, and regulated emptying.
- Control of the stomach's contents as they flow into the duodenum.
- Production of gastric hormones.

Ideal Drugs Candidate for Gastro Retentive Drug Delivery Systems

- Medication that acts on the stomach environment, such as antacids and misoprostol.
- Medication with restricted absorption in the gastrointestinal tract, such as L-DOPA, riboflavin, furosemide, and para-aminobenzoic acid.
- Medications like metronidazole and ranitidine that are broken down in the environment of the colon and small intestine.
- Drugs that interfere with the colon's natural flora, such as antibiotics used to treat Helicobacter pylori.
- Drugs including verapamil, chlordiazepoxide, and diazepam are not well soluble at high pH levels.
- Substances with a bulk density below one.
- Medicines that have a specific absorption location in the majority of the GIT.

Unsuitable Drugs for Gastro-Retentive Drug Delivery Systems

- Medication that is not well soluble in acidic conditions, such as phenytoin
- Medications such as erythromycin that are unstable in the stomach environment
- Medications such as corticosteroids are suggested for optional colonic release (Vyas and Khar 2006).

Factors Affecting the Gastro Retentive Drug Delivery Systems

1. Density

The drug's and the dose form's density affects the rate at which the stomach empties and determines where the delivery system is placed. Formulations with a density smaller than the contents of the stomach can float on the surface of the stomach, whereas high-density dosage forms submerge into the stomach; as a result, both dosage forms stay in the stomach and do not pass the pyloric acid. To obtain the floating property, the dosage form's density must be less than 1.0 gm/cm3, (Arora et al. (2005).

2. Shape and Size of Dosage Form

Shape and size play a crucial role in the construction of appropriate and indigestible dosage forms. The stomach residence duration for non-floating dosage forms varies greatly and is influenced by the unit dosage form size. Larger dosage forms will require longer gastric maintenance times since they may not be able to cross the pyloric valve. Larger dosage forms (diameters greater than 7.5 mm) have been found to have a preferred stomach residence period (Garg and Sharma 2003).

3. Food Intake and Its Disposition

The type, quantity, viscosity, calories, and frequency of feeding all have a significant impact on how long a dose form stays in the stomach. Food's presence or absence in the GI affects the dosage form's stomach residency duration; as a result, medication absorption is improved by allowing the medication to remain at the absorption site for a longer time. Elevating the acidity and caloric valence can shorten the stomach emptying time, hence raising the dosage form's GRT (Khosla et al., 1989).

4. Gender, Posture, and Age

Usually, males have higher gastric emptying rates than females, and the outcome of posture does not have any important alteration on gastro retention time for individuals. The gastric emptying time in elderly persons is slowed.

5. Calorie Content

Meals with high fat and protein content raised GRT for four to ten hours.

6. Fed or Hungry State

GI motility is typified by episodes of motility that happen every 1.5–2 hours, as it happens during fasting.

7. Nature of Food

Fatty acids or indigestible polymers may change the stomach's motility, slowing down the rate of stomach emptying and prolonging the time that medications escape from the stomach.

8. Type of Drugs

The duration of gastro retention can be prolonged by medications like codeine, propantheline, and atropine.

9. Stress & Depression

The stomach emptying time is shortened by depression but rises with stress.

10. Amount of Fluid

There is a corresponding rise in the gastric emptying time with an increase in stomach fluid (Mojaverian et al. 1988).

Classification of GRDDS

A. Magnetic Systems

B. Mucoadhesive Drug Delivery Systems

C. Floating Drug Delivery Systems

D. High-Density Drug Delivery Systems

E. Expandable Systems

A. Magnetic Systems

The mechanism of magnetic systems is based on a straightforward idea; it is possible to increase the gastric retention duration. Figure 5 illustrates this. An external magnet is positioned above the position of the stomach, and a small internal magnet is enclosed in the dosage form. It is necessary to position the external magnet to an exact degree to ensure patient compliance. The external magnet, which requires careful placement and is the system's primary flaw, is why it is utilized a lot (Huang et al., 2000).

B. Mucoadhesive Drug Delivery Systems

Both BDDS and MDDS can be used as human delivery systems to enhance medication absorption. Bioadhesive polymers are useful in this technique because they adhere to the GI stomach's (as depicted in Figure 2) epithelial surface. As a result, they lengthen the duration of stomach retention. There are several ways that the formulation can stick to the mucosal surface (Faivre and Pirot 2004).

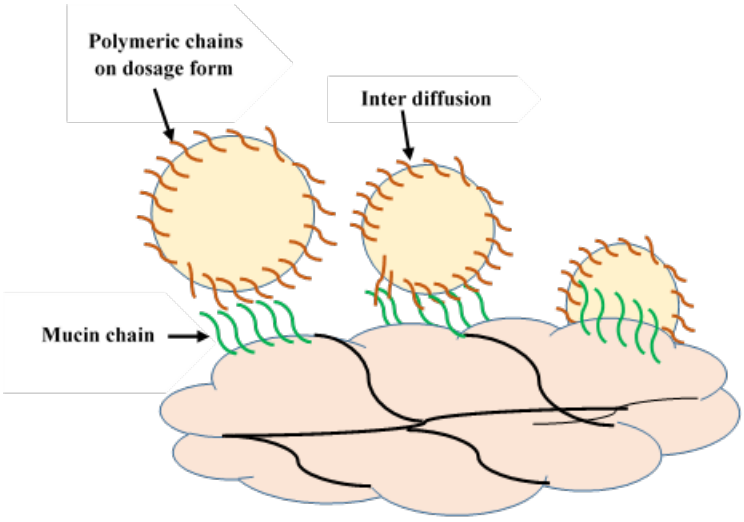

Figure 2. Ischemic Diagram of Mucoadhesive Drug Delivery System

Factors Affecting Mucoadhesion

- The polymer's molecular weight
- Flexibility of its chains
- Concentration,
- pH at the polymer-substrate interface
- Mucin turnover rate
- Swelling, and stereochemistry

C. Floating Drug Delivery Systems

One important technique for increasing the stomach GRT of a dose form and achieving sufficient drug absorption and bioavailability is FDDS. FDDS is appropriate for medications that are absorbed in the upper duodenum and stomach region. This system has a lower bulk density than GI fluid. As a result, the medicine is released more slowly over a longer period and the dosage form floats in GI fluid without influencing gastric emptying rate. Following the drug's release, the residual portion moved the stomach; as a result, the GRT increased and was able to regulate the drug's fluctuating concentration in the plasma (Sharma and Pawar 2006). One type of gastro-retentive employed to achieve delayed gastric living arrangement time is the floating gastro-retentive medication delivery system (Sneha et al., 2015).

Necessities for FDDS

- The system must release content very slowly.
- The specific gravity of the system should be lesser than the gastric contents (1.004-1.01 gm/cm^3).
- The system must form a sticky gel barrier.

Types of Floating Drug Delivery Systems

1. Effervescence Delivery Systems

Gas generation can help ensure that a dosage form is floatable. This method is made of effervescent substances (like sodium bicarbonate and citric or tartaric acid) and swelling-able polymers (like polysaccharides, like chitosan). As the formulation reacts with the gastric liquid, sodium bicarbonate and tartaric acid react, producing carbon dioxide. The carbon dioxide then pushes against the polymer, causing it to swell and expand. Ultimately, this increases buoyancy, causing the dosage form to float.

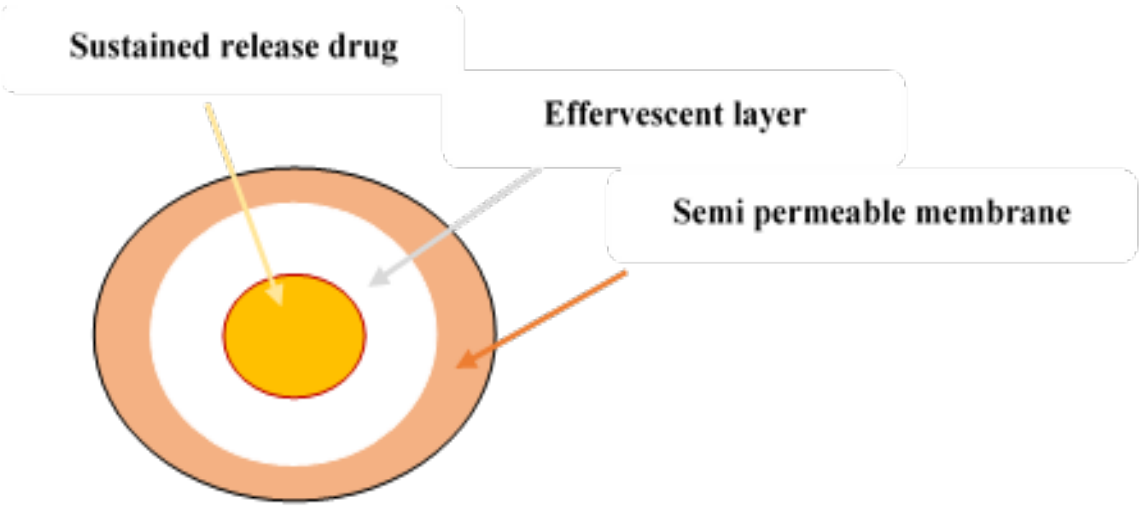

Figure 3. Effervescent (Gas Generation) System

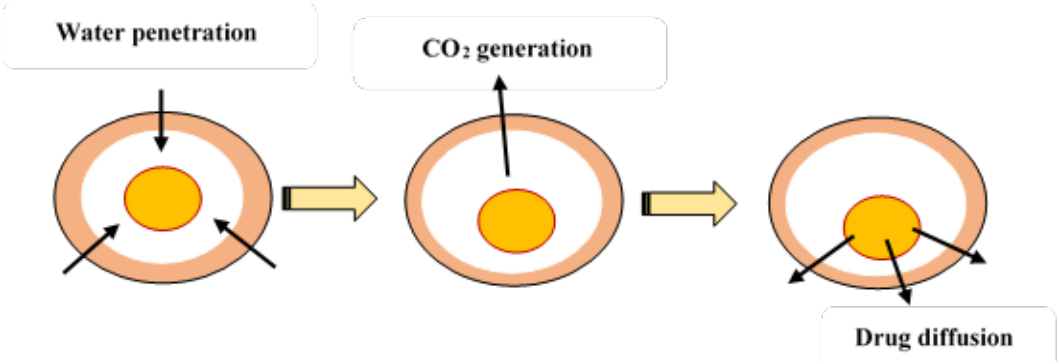

Figure 4. Drug Release (Gas Generation) System

2. Non-Effervescent Delivery Systems

Non-effervescent systems are usually designed from gel-forming or extremely swellable cellulose such as hydrocolloids, polysaccharides, or matrix-forming polymers such as polycarbonate, polystyrene, polyacrylate, and polymethacrylate. In this method, close mixing of the drug with a gel-making hydrocolloid occurs. When the mixed form of the drug interacted with gastric liquid, the bulk density was less than gastric fluid (Hilton and Deasy 1992). The most common excipients used included hydroxypropyl methylcellulose (HPMC) polyacrylates, carbopol, polyvinyl acetate, agar, calcium chloride, sodium alginate, polyethylene oxide, and polycarbonates (Garg and Gupta 2008).

D. High-Density Drug Delivery Systems

The dosage form density in this system needs to be higher than the typical stomach fluid density (1.004 gm/cm3). As seen in Figure 5, high-density formulations are made by either coating the medication with a heavy core or combining it with inert components such as iron powder, zinc oxide, barium sulfate, and titanium oxide these additives increase the density of formulations to 1.5–2.4 gm/cm^3 (Moes, 2003).

E. Expandable Systems

The dosage form in this delivery method is smaller at first, but it expands and grows larger when it interacts with gastric fluids, making it unable to move the pylorus. As a result, the dosage form stays in the stomach for a longer period, and the gastric residency time increases. The dosage form stays in the stomach for a considerable amount of time when it is enlarged, as illustrated in Figure 5, by simply growing and reaching a noticeably greater size in the stomach.

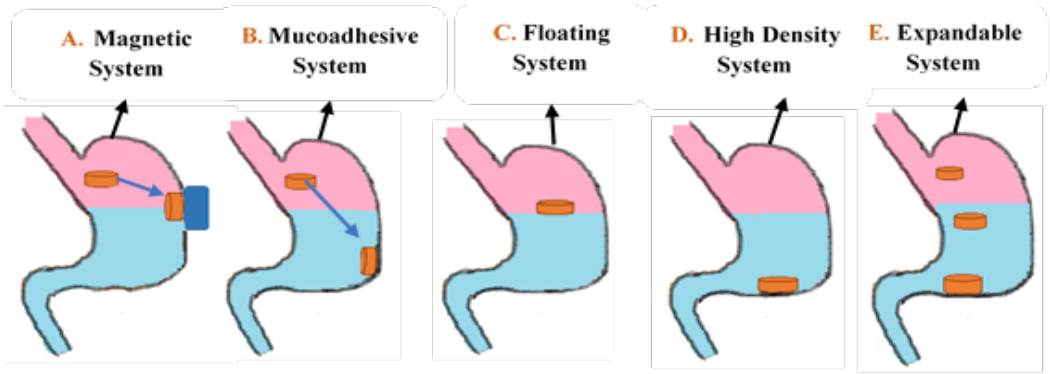

Figure 5. Types of Gastro Retentive Drug Delivery System

Certain medications with a narrow window of absorption can be made into a gastroretentive drug delivery system, which improves the drug's in vivo absorption capabilities (Klausner et al., 2003).

Application of GRDDS

1. Nanoparticle Delivery

The idea behind the nanoparticle medication delivery method was to completely eradicate Helicobacter pylori (H. pylori), which had deeply penetrated the mucosal lining of the stomach. By combining the heparin solution with the chitosan solution and magnetically stirring at room temperature, the enhanced pH-responsive chitosan/heparin nanoparticles demonstrated a dual action of adhesion and drug absorption into the mucous layer. The medication protects against harmful stomach acids because the particles, which have a positive surface charge and are stable at pH 1.2–2.5, have a particle size of 130–300 nm. By adhering to and penetrating cell-cell junctions and engaging in localized interactions, nanoparticles were able to significantly reduce the Helicobacter pylori infection. Currently has a patent on medication delivery methods for stomach retention that are suitable for treating Helicobacter pylori infections (Lin et al., 2009).

2. Vaccine Delivery

The inability of antibiotic therapy to prevent reinfection and the rise in resistant strains of the infection are major problems, which is why developing an infection vaccine is motivated by these issues. The mucosal membrane provides the body with increased access to microorganisms that are the target of mucosal vaccination. Mucosal vaccination has several advantages, including as high patient compliance, convenience of administration, affordability, and a decreased risk of undesirable needle-borne illnesses (AIDS, hepatitis, etc.). Consequently, vaccination at the mucosal surfaces may encourage both mucosal and systemic immunity. By rendering the microbe inactive at the point of entrance, it can help prevent infections. Because chitosan may open tight junctions and promote the paracellular transport of antigens through the mucosal membrane, it is a suitable drug delivery strategy for mucosal vaccination (Van et al., 2001).

Excipients Used in Formulation of GRDDS

- Effervescent agents (tartaric acid)
- Release rate accelerators (lactose, mannitol)
- Release rate retarders (magnesium stearate & talc)
- Buoyancy-increasing agents (ethyl cellulose)
- Lowering density agents (propylene powder)

Figure 6. Evaluation of Gastro Retentive Drug Delivery Systems

Table 1. Marketed Formulation of GRDDS

S.No	Brand Name	Drug	Remark	Manufacturer
1	Cfran OD	Ciprofloxacin	Floating tablet	Ranbaxy-India
2	Valrelease	Diazepam	Floating capsule	Hoffman-LaRoche
3	Xifaxan	Rifaximin	Bioadhesive tablet	Lupin-India
4	Cytotec	Misoprostol	Bilayer floating capsule	Pharmacia-USA
5	Conviron	Ferrous sulphate	Colloidal forming FDDS	Ranbaxy-India
6	Oflin OD	Ofloxacin	Gas-generating floating tablet	Ranbaxy-India
7	Madopar	Levodopa	Hydrodynamically balanced system	Roche products- USA
8	Liquid Gaviscon	Aluminium hydroxide	Raft forming system	Glaxosmithkline-India
9	Topalkan	AL-MG antacid	Floating liquid alginate	Pierre Fabre drug-France
10	Almagate float coat	AL-MG antacid	Floating liquid form	Pierre Fabre drug-France

Conclusion

Since the upper portion of the gastrointestinal tract is closed off to the absorption of the active ingredients, the gastro-retentive drug delivery system has the potential to improve absolute bioavailability and increase the absorption of active components with low bioavailability. The treatment of H. pylori infection is one of the main uses of GRDDS. The physiology and operation of the stomach, variables influencing the GRDDS, and types of gastro-retentive drug delivery systems are the primary areas of study.

References

Arora, S., Ali, J., Ahuja, A., Khar, R. K., & Baboota, S. (2005). Floating drug delivery systems: a review. *AAPS PharmSciTech*, *6*(3), E372–E390. https://doi.org/10.1208/pt060347

Bardonnet, P. L., Faivre, V., Pugh, W. J., Piffaretti, J. C., & Falson, F. (2006). Gastroretentive dosage forms: overview and special case of Helicobacter pylori. *Journal of controlled release : official journal of the Controlled Release Society*, *111*(1-2), 1–18. https://doi.org/10.1016/j.jconrel.2005.10.031

Faivre, V., Falson-Rieg, V., & Pirot, F. (2004). Aspects theories de la adhesion. Nonvelles formes medicamenteuses, Editions Medicales Internationales. *Editions TEC and DOC, Cachan, 2004,* 1-24.

Garg, R. G. D. G., & Gupta, G. D. (2008). Progress in controlled gastroretentive delivery systems. *Tropical journal of pharmaceutical research, 7*(3), 1055-1066. http://dx.doi.org/10.4314/tjpr.v7i3.14691

Garg, S., & Sharma, S. (2003). Gastro retentive Drug Delivery Systems. *Business Briefing pharmacy*, 160-164.

Gopal, S. V., Chaurasia, P. K., Pardhe, H. A., Santosh, S. S., & Sonar, N. S. (2020). Gastro retentive Drug Delivery System: A Systematic Review. *Asian Journal of Pharmacy and Technology, 10*(4), 278-284. https://doi.org/10.5958/2231-5713.2020.00046.X

Gouda, K. H., Kishore, V. S., Balaji, N., Kumar, V. V., & Raghuram, N. (2011). An Overview of Various Approaches for Gastro retentive Drug Delivery Systems. *Research Journal of Pharmaceutical Dosage Forms and Technology, 3*(4), 159-168. https://doi.org/10.2174/1872211312666180308150218

Gupta, R., Tripathi, P., Bhardwaj, P., & Maho, A. (2018). Recent advances in gastroretentive drug delivery systems and their application in the treatment of H. Pylori infections. *Journal of Analytical & Pharmaceutical Research, 7*(4), 404-410. https://doi.org/10.15406/JAPLR.2018.07.00258

Hilton, A. K., & Deasy, P. B. (1992). In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxicillin trihydrate.

International Journal of Pharmaceutics, 86(1), 79-88. https://doi.org/10.1016/0378-5173%2892%2990033-X

Huang, Y., Leobandung, W., Foss, A., & Peppas, N. A. (2000). Molecular aspects of muco-and bioadhesion:: Tethered structures and site-specific surfaces. *Journal of controlled release, 65*(1-2), 63-71. https://doi.org/10.1016/s0168-3659(99)00233-3

Khosla, R., Feely, L. C., & Davis, S. S. (1989). Gastrointestinal transit of non-disintegrating tablets in fed subjects. *International journal of pharmaceutics, 53*(2), 107-117. https://doi.org/10.1016/0378-5173(89)90234-2

Klausner, E. A., Lavy, E., Friedman, M., & Hoffman, A. (2003). Expandable gastroretentive dosage forms. *Journal of controlled release, 90*(2), 143-162. https://doi.org/10.1016/s0168-3659(03)00203-7

Kshirsagar, S. J., Wadekar, S. B., Bhalekar, M. R., Ughade, P. B., & Madgulkar, A. R. (2011). Gastroretentive drug delivery system of hydrochlorothiazide: formulation, optimization and in vivo evaluation. *Asian journal of pharmaceutical sciences, 6*(3-4), 166-174.

Lin, Y. H., Chang, C. H., Wu, Y. S., Hsu, Y. M., Chiou, S. F., & Chen, Y. J. (2009). Development of pH-responsive chitosan/heparin nanoparticles for stomach-specific anti-Helicobacter pylori therapy. *Biomaterials, 30*(19), 3332-3342. https://doi.org/10.1016/j.biomaterials.2009.02.036

Moes, A. J. (2003). Gastric retention systems for oral drug delivery. *Business Briefing: Pharmatech,* 157-59.

Mojaverian, P., Vlasses, P. H., Kellner, P. E., & Rocci, M. L. (1988). Effects of gender, posture, and age on the gastric residence time of an indigestible solid: pharmaceutical considerations. *Pharmaceutical research, 5*(10), 639-644. https://doi.org/10.1023/a:1015922903843

Schubert, M. L. (2016). Gastric acid secretion. *Current Opinion in Gastroenterology, 32*(6), 452-460. https://doi.org/10.1097/mog.0000000000000308

Sharma, S., & Pawar, A. (2006). Low-density multiparticulate system for pulsatile release of meloxicam. *International journal of pharmaceutics, 313*(1-2), 150-158. https://doi.org/10.1016/j.ijpharm.2006.02.001

Sneha, S. W., Trupti, V. K., Darekar, A. B., & Saudagar, R. B. (2015). A review: Floatable gastro retentive drug delivery system. *Asian Journal of Pharmaceutical Research, 5*(1), 51-60. http://dx.doi.org/10.5958/2231-5691.2015.00008.8

Tobias, A., & Sadiq, N. M. (2020). *Physiology, Gastrointestinal Nervous Control.* Stat Pearls.

Van der Lubben, I. M., Verhoef, J. C., Borchard, G., & Junginger, H. E. (2001). Chitosan for mucosal vaccination. *Advanced drug delivery reviews, 52*(2), 139-144. https://doi.org/10.1016/s0169-409x(01)00197-1

Vyas, S. P., & Khar, R. K. (2006). *Gastro retentive systems. Controlled drug Delivery.* Vallabh Prakashan, Delhi, India, 197-217.