Multidisciplinary

Gastro-retentive drug delivery systems: a brief review

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Received 3 Mar 2022; Accepted 8 Apr 2022; Published 19 Apr 2022

Abstract

In pharmaceutical companies, floating tablets are used for sustained drug delivery. It also enables the development of tablet formulation with different drug release profiles. These tablets remain buoyant in the stomach, thereby increasing the gastric residence time and hence the effect of the drug. These tablets have bulk density less than that of gastric fluid. Such drugs are released very slowly over the food material and taken up by esophagus. It can increase the GRT and controls the fluctuations in drug plasma concentration.

Keywords: GRDDS, gastric retention time, floating systems, gastro-retention, high density systems, low density systems

Introduction

Most commonly used approach for administration of drugs is through Oral Route. It helps to administer and prolongs the drug release [1, 2]. To comply with the aim of therapy, to succeed a steady-state drug level, for therapeutic effectiveness and non-toxicity, oral route is very much effective. "For the design of dosage form, optimization of the formulation is must to achieve the controlled release of drug for therapeutic effects. Some fluctuations in *in-vivo situation of drug have been observed. It happens when the drug availability is maximized. It maximizes the rate and extent of the drug absorption"* [3, 4]. "Administration of drugs by oral route is most preferred and most convenient for delivering drug to the systemic circulation. For improving the therapeutic effectiveness, oral drug delivery is most popular in pharmaceutical field like patient compliance, ease of dose administration and flexibility in formulation [5, 6, 7]. In systemic circulation, such drugs which have short half-lives and are easily absorbed in gastrointestinal tract (GIT), are eliminated quickly. For achieving optimum therapeutic activity, drug doses are given frequently [8, 9, 10]. By developing the oral sustained-controlled release formulations which slowly release drug into the gastrointestinal tract (GIT), drug concentrations are maintained in the therapeutic range for long duration of time. After the administration of drug by oral route, it gets retained into the stomach and release the drug in controlled manner. From here the drug goes to the absorption sites in the gastrointestinal tract (GIT)" [11, 12].

"The two adversities that harm the conventional drug delivery systems are unpredictable short gastric emptying time (GET) and short gastric retention time (GRT). They show incomplete drug release from the dosage form in the stomach or upper part of small intestine and affect the efficacy of administered dose. The gastric residence time of a drug can be prolonged by formulating a site-specific orally administered controlled release dosage form. Bioavailability can be improved if the gastric retention is prolonged" [13, 14]. "It will increase the drug release duration, reduce the drug wastage and solubility of drugs which are less soluble at high pH may improve. It provides local action on stomach. For the successful performance of oral drug delivery system, it is most important that the drugs have good rate of absorption along the gastrointestinal tract (GIT) and ensures the continuous absorption of drug" [15, 16]. "The transportation of large amounts of drug is not uniform across the intestinal epithelium in each segment of GIT and is restricted in a particular segment (window) only. For prolonged and predictable drug delivery, it is important to control the gastric residence time in the stomach. For higher bioavailability, retention of oral dosage form may cause the prolonged contact time of drug with the GI mucosa which will improve the therapeutic efficacy, drug administration time will reduce, dose size is also reduced and the patient compliance is improved. It may lead to the development of oral controlled release dosage form with gastro retentive properties" [17, 18].

Gastro retentive drug delivery systems

Gastro retentive drug delivery systems may be well-defined as the dosage forms which can remain in the gastric region (stomach) for many hours. It is helpful in delaying the gastric residence time of the drug. After the administration of drug by oral route, these dosage forms preserve in the abdominal for long time and slowly release the medication in stomach in controlled and prolonged way. "Gastro retentive drug delivery system is used to increase time in the gastric region and target the site-specific drug release for local and / or systemic effects in the GIT. Many gastro retentive drug delivery system has been designed and developed in past few decades, some are high sinking systems and remain in the bottom of the stomach, some are low density or floating systems, which causes buoyancy in the gastric fluid, then we have mucoadhesive systems that causes bio adhesion in the stomach, pyloric sphincter in stomach and also there are unfold able, extendible

or swellable systems, hydrogel and magnetic systems etc" [19, 20].

Physiology of GIT

Stomach is a part of the alimentary canal which is muscular, hollow and dilated. It is situated below the diaphragm. Functions of stomach are storing the food for short time, grind the food, and then slowly release the grinded food. For the production of enzymes, stomach is the most important site because its surface area is small and very minuscule absorption. It forms a barrier in the small intestine. Skeletal build of a person, posture of person and volume ingested may affect the position of the stomach. Stomach is classified in 3 parts namely: fundus, body and pylorus/antrum, as shown in Figure 1."Undigested material is reserved in proximal part made of fundus and body. For mixing motion, antrum or pylorus is the main site and it forms a gastric pump for the emptying by propelling actions" [21]. During fasting, the gastric emptying occurs. "In fasting state, inter digestive series of electrical events occurs. It moves through intestine and stomach for some hours. This is known as the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC)" [21, 22].

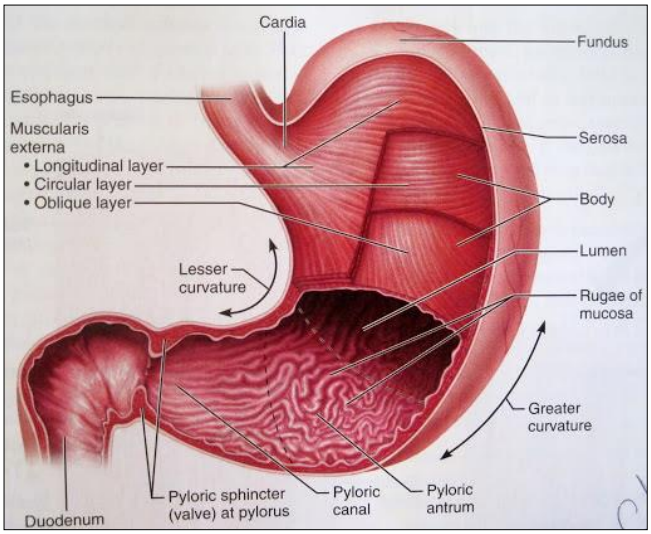

Fig 1: Anatomy of stomach

Gastric motility

Neural and hormonal signals are used to control the gastric motility. Nervous system controls the parasympathetic and sympathetic systems. To influence the gastric motility, a large number of hormones are involved, for example, "gastrin and cholecystokinin are used to relax the stomach and enhances the contractions of distal stomach" [23]. For inhibitory and stimulatory signals, gastric motility is used to integrate the smooth muscle cells. Liquid is passed through the pylorus but solid must contain a diameter of 1-2mm before passing pyloric. *In vivo* gastric volume of distribution of drug in dosage form is important.25-50 ml is the resting volume of stomach. "In drug delivery system, GI pH has pronounced effect on absorption of drugs. 1.2-2.0 and 2.0-6.0 are the pH values under the fasting and fed condition" [23, 24].

Gastric emptying rate

"In both fasting and fed state, gastric emptying occurs. It can be separated into two stages. In fasting stage, inter-digestive series of electrical events occur. It may pass through the gastrointestinal area every 2 to 3 h and it is known as migrating myoelectric cycle (MMC). It is further sub-divided into 4 phases: -

Phase I: (Basal phase) it may stand up to 40 to 60 min with rare contractions.

Phase II: (Preburst phase) which lasts for 40 to 60 mins. It is characterized by irregular action potential and contractions. As the frequency increases, the phase advances and the intensity also increase.

Phase III: (Burst phase) which lasts up to 4 to 6 min. The undigested material is swept out of the stomach into the small intestine. The waves of intense and regular contractions occur for short period. It is also known as house-keeper wave.

Phase IV: Lasts for 0 to 5 min and occurs between III and I phase. After the ingestion of meal, contractions pattern changes from fasted to feed state. This is called as digestive motility pattern. It consists of continuous contractions in Phase II. It results in decreasing the size of the food particles up to 1 mm and propelled in the pylorus in suspension form. The fed state onset of MMC is delayed which results in decelerating the gastric emptying rate" [25, 26, 27, 28].

Gastric retention approaches

For increasing the GRT, various systems have been established. The principle of gastric retention is used to classify these.

- **High density systems**

High density systems have approximately 3g/ml of rugae in stomach and are capable to withstand the peristaltic movements. "The main problem which is occur in these systems is the preparation of bulky dosage form and it should attain the necessary density which is 2.4-2.8 g/ml. Barium sulphate, zinc oxide, titanium oxide and iron powder are the diluents which are used to prepare the systems" [29].

- **Swelling and expanding systems**

"These systems are used for absorption of water and enlarge in size. These systems are known as plug type system and remain in pyloric sphincters. In fed state, these polymeric matrix dosage forms stay in the gastric cavity. Polymer selection should have the appropriate molecular weight and swelling properties and it should attain the controlled and sustained drug release. The polymer in these systems absorbs water and swells, when it is in contact with the gastric fluid. Due to the presence of hydrophilic polymer network, polymers which exhibit the cross linking show extensive swelling. Cross linkage stops the polymer dissolution and physical integrity of the dosage form is sustained. By rapid dissolution of polymer, low degree of cross-linking shows extensive swelling" [30, 31].

- **Incorporating delaying excipients**

It functions by feeding the digestible polymers or fatty acid salts into the formulation. It can change the motility pattern in the stomach, due to which in fed stage the gastric emptying rate is decreased and prolongation of the drug release occurs. By incorporation of delaying excipients like triethanolamine myristate, GRT of the dosage form is prolonged.

- **Modified systems**

"This system contains the non-disintegrating geometric shape/molded. It contains silastic elastomers or extruded from polyethylene blends and increases the GRT by change of size, shape and flexural modules of dosage form" [32, 33].

- **Mucoadhesive & bioadhesive systems**

For localization of dosage form within the lumen or enhancing the drug absorption in a specific site, mucoadhesive and bio adhesive systems are used. Bio adhesive polymers can stick to the epithelial surface in the stomach. Some commonly used bio adhesives are polycarbophil, carbopol, lectins, chitosan, CMC, gliadin, etc. Bioadhesion can be sub-divided into two categories:

a) Hydration mediated adhesion

A large amount of water is imbibed into certain hydrophilic polymers and become sticky and thereby show bio adhesive properties.

b) Bonding mediated adhesion

On mucus or epithelial cell surface, the adhesion of polymers occurs. It contains some bond forming mechanisms, like physical-mechanical bonding and chemical bonding or ionic bonding. Chemical bonds consist of dispersive interactions (Vander Waals interactions) and stronger specific interactions (hydrogen bonds). Hydrogen bonds are formed between hydrophilic functional groups [34, 35].

- **Floating systems**

"Floating systems have bulk density which is less than that of gastric fluids. It floats in the stomach without changing the gastric emptying rate for a prolonged period of time. The drug is released slowly by this floating system and pushes the system out when the drug is completely released. The floatation can be achieved by incorporation of floating chamber filled with vacuum, air or inert gas in stomach" [36, 37].

References

1. Streubel A, Siepmann J, Bodmeier R. Gastro retentive drug delivery system. Expert Opin Drug Delivery. 2006;3(2):217-33.
2. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compartment multiple-unit system for prolonged gastric residence Part-I Formulation study. International Journal of Pharmaceutics. 1998;174:47-54.
3. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Tropical Journal of Pharmaceutical Research. 2008;7(3):1055-66.
4. Chawla G, Gupta P, Koradia V, Bansal A. Gastro retention: A means to address regional variability in intestinal drug absorption. Pharmaceutical Technology, 2003, 50-58.
5. Hwang SJ, Park H, Park K. Gastric retentive drug delivery systems. Critical Reviews in Therapeutic Drug Carrier System. 1998;3(15):243-284.
6. Fell JT. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. Journal of Anatomy. 1996;189(3):517-519.
7. Streubel A, Siepmann J, Bodmeier R. Multiple unit gastroretentive drug delivery: anew preparation method for low density micro particles. Journal of Microencapsulation. 2003;20:329-47.
8. Dave B, Amin A, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in-vitro* evaluation. American Association of Pharmaceutical Scientists Pharm Sci Tech. 2004;5(2):77–82.
9. Nayak AK, Maji R, Das B. Gastro retentive drug delivery systems: A review. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):2-10.
10. Rouge N, Allemann E, Gex FM, Balant L, Cole ET, Buri P, *et al*. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharmaceutica Acta Helvetiae. 1998;73:81-7.
11. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. European Journal of Pharmaceutical Science. 2003;18:37-45.
12. Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. International Journal of Pharmaceutics. 2007;334:35-41.
13. Sharma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. International Journal of Pharmaceutics. 2006;313:150-58.
14. Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, *et al*. An *in vitro - in vivo* investigation of oral bio adhesive controlled release furosemide formulations. European Journal of Pharmaceutical Biopharmaceutics. 1997;44:39-52.
15. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastro retentive dosage forms. Journal of Controlled Release. 2003;90(2):143-62.
16. Deshpande AA, Shah N, Rhodes CT, Malik W. Development of a novel controlled-release system for gastric retention. Pharmaceutical Research. 1997;14(6):815-819.
17. Park K. Enzyme-digestible swelling as platforms for long term oral drug delivery: synthesis and characterization. Biomaterials. 1998;9:435.
18. Fujimori J, Machida Y, Nagai T. Preparation of a magnetically-responsive tablet and configure ration of its gastric residence in beagle dogs. STP Pharma Science. 1994;4:425-430.

19. Lokendrapal S, Rajesh KS, Deepak GU. Floating effervescent tablet: a review. International Journal of Pharma and Bio Sciences. 2011;5(11):1-6.
20. Debjit B, Chiranjib B, Margret C, Jayakar B, Sampath KP. Floating drug delivery system- Review. Der Pharmacia Lettre. 2009;1(2):199-218.
21. Vyas SP, Khar RK. Gastro retentive systems. In: Targeted and controlled drug delivery. 1st ed. New Delhi: CBS Publishers and Distributors, 2006, p197-217.
22. Desai S, Bolton SA. Floating controlled release drug delivery system: *in-vitro- in-vivo* evaluation. Pharmaceutical Research. 1993;10(9):1321-1325.
23. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Control Release. 2000;63:235-259.
24. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):1-18.
25. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A Review, American Association of Pharmaceutical Scientists. 2005;6(3):E372-390.
26. Vyas SP, Khar RK. Gastro retentive systems, In: Controlled drug delivery. 1st ed. New Delhi: Vallabh Prakashan, 2006, p197.
27. Moes AJ. Gastric retention system for oral drug delivery. Business Briefing. Pharmatech, 2003, 157.
28. Ito R, Machida Y, Sannan T, Nagai T. Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration. International Journal of Pharmaceutics. 1990;61(1-2):109-117.
29. Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time, 1998, US Patent No. 4735804.
30. Prasanna KJ. Modulation of gastro-intestinal transit time by floating drug delivery system. Indo American Journal of Pharmaceutical Research. 2012;2(10):1223-1232.
31. Arunachalam. Floating drug delivery systems: A review. International Journal of Research in Pharmaceutical Sciences. 2011;2(1):76-83.
32. Sheth PR, Tossounian J. The hydrodynamically balanced system (Hbs): A novel drug delivery system for oral use. Drug Development and Industrial Pharmacy. 1984;10:313.
33. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. International Journal of Pharm Tech Research. 2009;1(3):623-633.
34. Despande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharmaceutical Research. 1997;14(6):815-819.
35. Nayak AK, Maji R, Das. Gastro retentive drug delivery system a review. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):2-10.
36. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A Review. American Association of Pharmaceutical Scientists. 2005;6(3):E372-390.
37. Garg A, Mishra A. Sustained Release Dosage Forms: A Review. Annals of Pharma Research. 2021;9(09):542-550.
38. Garg Ayush, Mishra Amul. Sustained Release Dosage Forms: A Review. Journal of Pharmacy and Pharmaceutical Research. 2021;6(3):1-2.
39. Garg Ayush, Mishra Amul. Preparation and Evaluation of Bilayer Tablet for the Treatment of Hypertension. Natural Volatiles & Essential Oils. 2021;8(5):9098-9115.