



AN OVERVIEW ON LIMITATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

Ganesh N. S., Suraj Mahadev Ambale*, Ramesh B., Kiran B. Deshpande

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya Dist., Karnataka – 571422, India.

*Corresponding author's E-mail: suraj_198853@yahoo.com

Accepted on: 14-03-2011; Finalized on: 05-06-2011.

ABSTRACT

Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. Floating drug delivery systems (FDDS) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs, thereby improving bioavailability, reduced drug waste and improved solubility for drugs that are less soluble at a higher pH environment. In order to understand the various physiological barriers to achieve gastric retention, a thorough understanding of the important factors controlling gastric retention is essential.

Keywords: Floating drug delivery systems (FDDS); gastric emptying; gastric retention; physiological barriers.

INTRODUCTION

The oral route remains the most considered one for administration of drugs. Several reasons can be pointed out to support this fact, namely ease of administration and full control of administration by the patient, together with a high degree of flexibility on dosing¹. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for the prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastroretentive delivery systems. For example floating, swelling, mucoadhesive, and high-density systems have been developed to increase gastric retention time of the dosage forms. These systems have more flexibility in dosage design than conventional dosage form².

However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the Drug Delivery System (DDS) within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels.

Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed⁴. This review deals with the physiological problems, limitations, approaches for various gastroretentive systems, including clinically available products, and recent advances.

ADVANTAGES

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
3. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
5. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.
6. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
7. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
8. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption



due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine⁵.

BASIC PHYSIOLOGY, PROBLEMS

Gastric emptying

It is well recognized that the stomach may be used as a 'depot' for controlled-release (CR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying

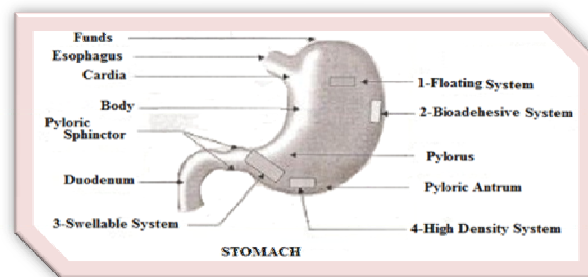


Figure 1: Physiology of upper gastrointestinal tract¹³

The oral route is the first-pass effect, which leads to reduced systemic bioavailability of a large number of drugs. Overall, the relatively brief GI transit time of most drug products, which is approximately 8–12 h, impedes the formulation of a once daily dosage form for most drugs. These problems can be exacerbated by alterations in gastric emptying that occur due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore, desirable to have a CR formulation's that exhibits an extended GI residence and a drug release profile independent of patient related variables³.

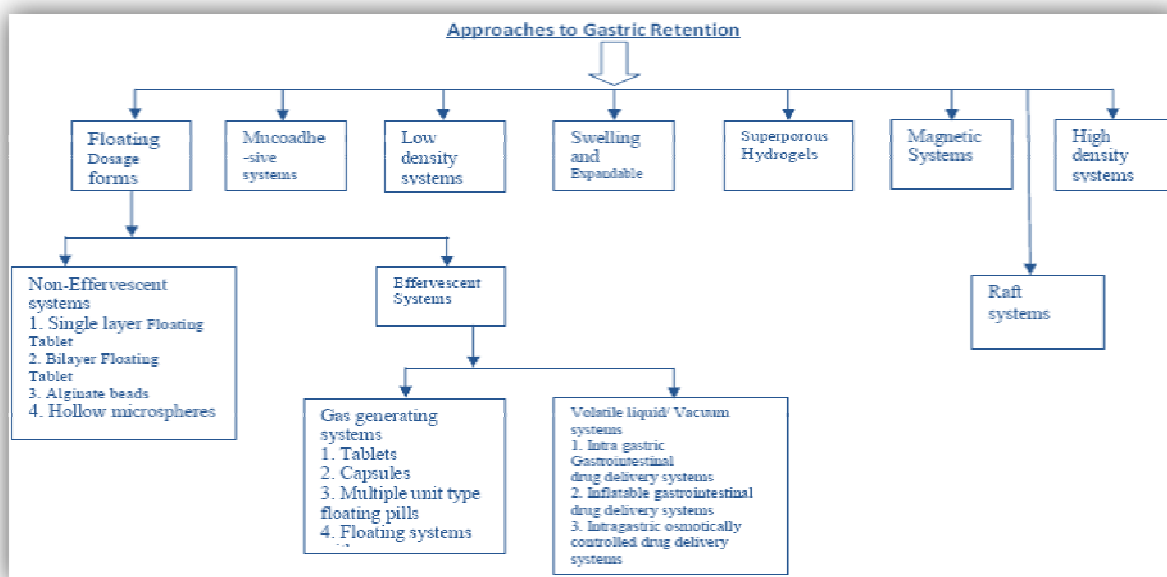


Figure 2: Schematic representation of various gastroretentive formulations⁸

CURRENT APPROACHES TO GRDDS

1. Floating drug delivery systems (FDDS)

Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period¹⁰. Floating systems can be classified as effervescent and non-effervescent systems.

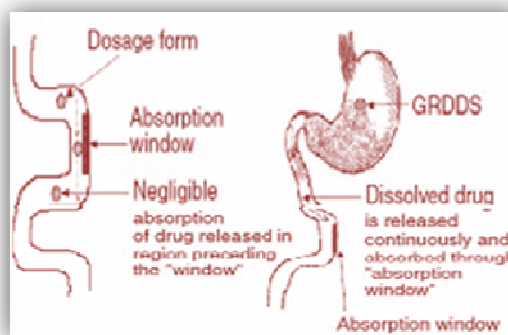


Figure 3: Drug absorption in the case of (a) Conventional dosage forms (b) Gastroretentive drug delivery systems¹⁹

i) Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed¹⁰.

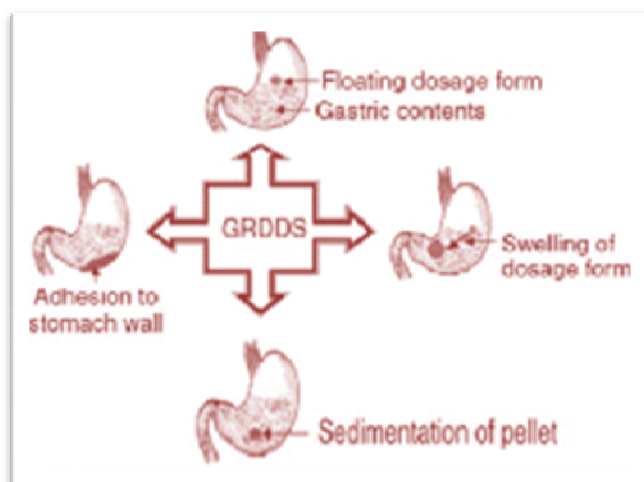


Figure 4: Classification of Gastroretentive Drug Delivery Systems¹⁹

ii) Noneffervescent systems

Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose [HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules¹¹. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release¹²⁻¹³. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form.

2. Bio Mucoadhesive systems

Bio mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability¹⁴. A bio mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bio-adhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and non-absorbable, form non-covalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug and offer no hindrance to drug release, have a specific site of attachment, and be economical. The binding of polymers to the mucin–epithelial surface can be subdivided into three broad categories¹⁵

- a. Hydration-mediated adhesion
- b. Bonding-mediated adhesion

a. Hydration-mediated adhesion

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

b. Bonding-mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

4. Swelling/ Expanding Systems

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as *plug type systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours

even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells.

These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration³⁵.

5. High-density systems

Gastric contents have a density close to water (~1.004 g/cm³). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall²⁸⁻²⁹. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3 g/cm³ seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm³

6. Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe₂O₃). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h¹⁷. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance¹⁸⁻¹⁹.

7. Raft systems

Raft systems incorporate alginate gels these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating²⁰.

Drugs used in the formulations of floating dosage forms

Local treatment of the GI wall or targeting the intestine mucosa is aimed. GRDF is the formulation of choice when the drug is mainly absorbed in the upper GI tract, and a reduction of plasma level fluctuations is required to minimize concentration-dependant adverse drug reactions. When a drug is mainly absorbed in the upper part of the GI tract and the unabsorbed fraction, which arrives to the colon, may cause serious local side effects, the GRDF is an excellent solution to reduce the appearance of such drugs in the colon. A good example for such compounds are given below²¹.

- **Floating microspheres** – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam,

Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast and Terfenadine.

- **Floating granules** - Diclofenac sodium, Indomethacin and Prednisolone.
- **Films** – Cinnarizine, Albendazole.
- **Floating tablets and Pills** - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl.
- **Floating Capsules** - Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol²².

Criteria for selection of Drugs

Certain types of drugs only benefit for gastro retentive devices. These include:

- Drugs acting locally in the stomach.
- Drugs those are primarily absorbed in the stomach.
- Drugs those are poorly soluble at an alkaline pH.
- Drugs with a narrow window of absorption.
- Drugs absorbed rapidly from the GI tract.
- Drugs those degrade in the colon⁵.

Table 1: Commercially available preparations⁴

Product	Active Ingredient
Madopar	Levodopa and Benserazide
Valrelease	Diazepam
Topalkan	Alu. Mag. Antacid
Almagate flatcoat	Antacid
Liquid gavison	Alginate acid and sodium bicarbonate

Polymers and other ingredients

Following types of ingredients can be incorporated into HBS (hydrodynamically balanced system) dosage form in addition to the drugs:

- Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, Chitosan, Agar, Casein, Bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite), Sodium CMC, MC, HPC.
- Inert fatty materials(5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.



- Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine). Release rate accelerants (5%-60%): eg lactose, mannitol. Release rate retardants (5%-60%): eg. Dicalcium phosphate, talc, magnesium stearate. Buoyancy increasing agents (upto80%): eg. Ethyl cellulose. Low density material: Polypropylene foam powder²².

FACTORS AFFECTING GASTRIC RETENTION

1) Density

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach². Therefore density of the dosage form should be less than the gastric contents (1.004gm/ml)²⁰. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period²⁸.

2) Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GIT retention 90 to 100 % retention at 24 hours compared with other shapes²⁰.

When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed²⁸.

3) Fed or Unfed State

The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the Migrating Myoelectric Complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer²⁰.

4) Nature of the meal

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release²⁰.

5) Caloric Content

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats²⁰.

6) Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC²⁰. Food intake and its nature Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms².

7) Gender

Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface²⁰.

8) Age

Elderly people, especially those over 70 years have a significantly longer GRT²⁰.

9) Posture

GRT can vary between supine and upright ambulatory states of the patients²⁰. A comparison was made to study the affect of fed and non-fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention²⁸.

LIMITATIONS

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery buoy to float therein and to work efficiently. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall. Alternatively, the dosage form may be administered with a glass full of water (200–250 ml). Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs



such as Nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability⁶. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

Recent advances in Gastroretentive Drug Delivery System.

Gangadharappa HV, et al., formulated and evaluated Atenolol floating tablets based on gas formation technique was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form. The floating dosage forms which exhibit prolonged residence in the stomach. They showed a satisfactory dissolution profile, floating lag time and floating characteristics. The tablets remained floating for up to 24 h²³. Patel JK, et al., studied the effects of formulation and processing parameters on a floating matrix controlled drug delivery system consisting of a poly (styrene-divinyl benzene) copolymer low density powder, a matrix-forming polymer(s), drug, and diluents (optional). The tablets were prepared by the direct compression technique which shows that the Hydroxypropyl Methyl Cellulose (HPMC K100M), which is often used in hydrophilic matrix drug delivery systems, can be used to modify the release rates in hydrophilic matrix tablets prepared by direct compression. A 15% (w/w) low density copolymer (based on the mass of the tablet) was sufficient to achieve proper *in vitro* floating behavior for at least 8 h²⁴. Puneeth KP, et al., studied the floating tablets of Rosiglitazone maleate which was developed using gas forming agents, like sodium bicarbonate, tartaric acid and polymers like Hydroxypropyl Methyl Cellulose (HPMC K15M) and xanthan gum. The prepared tablets evaluated in terms of their precompression parameters, physical characteristics, *in-vitro* release, buoyancy and buoyancy lag time. The *in vitro* drug release profiles obtained for formulation containing xanthan gum showed controlled drug release for 12h²⁶. Rishad RJ, et al., described the design and development of self-correcting monolithic gastroretentive system of Baclofen. Tablets were prepared by direct compression method. It was observed that for the development of controlled-release dosage form of Baclofen, polymer like Polyethylene Oxide (PEO) which imparts hydrophilic environment leads to more uniform drug release²⁷. Kishan V, et al., systematically studied different polymers in different concentrations to prepare Norfloxacin floating tablets. Floating matrix tablets of Norfloxacin were developed to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by the wet granulation technique, using polymers such as Hydroxypropyl Methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum. Optimized formulations and with HPMC floated with a lag time of less than 1 minute and continued to float for 24 h¹¹.

CONCLUSION

The FDDS proves advantageous for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum, and jejunum when compared to the conventional dosage form. Some of the unresolved, critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states, the role of buoyancy in enhancing GRT of FDDS and the correlation between prolonged GRT and other characteristics. Finally, considering the biological and other factors mentioned above, it is suggested that future research work in the floating drug delivery systems should be aimed at discovering means to accurately control the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents.

REFERENCES

1. Joao F. Pinto, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon, International Journal of Pharmaceutics, 395, 2010, 44–52.
2. Nayak A K*, Maji R, Das B, Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research Vol.3 Issue 1, 2010
3. Brahma N. Singh, Kwon H. Kim*, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release, 63, 2000, 235–259
4. Akash Yadav*, Dr. D.K. Jain, Dr. Neelam Balekar, Floating controlled drug delivery systems or prolonged gastric retention: a review, The Pharma Research, Year: 2009, 01
5. Patidar H.C, A Comprehensive Review on Floating Tablets, Pharmainfo.net, 2009
6. N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136, 1996, 117–139.
7. Vedha Hari B.N.*, Samyuktha Rani B., Brahma Reddy. A., Punitha. S., Parimala Devi, Victor Rajamanickam, The recent developments on gastric floating drug delivery systems: an overview, International Journal of PharmTech Research, 2, 2010, 524-534
8. vinod k.r.*, Santhosh Vasa, Anbuazaghan S, David Banji, Padmasri A, Sandhya S, approaches for gastroretentive drug delivery systems, International Journal of Applied Biology and Pharmaceutical Technology, I, 2, 2010, 589
9. Chawla G., Gupta P., Koradia V. and Bansal A. K., Gastroretention : A Means to Address Regional Variability in Intestinal Drug Absorption, Pharmaceutical Technology, 2003, 50-68
10. chikawa M., Watanabe S., and 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. 80, 1991, 1062-1066.
11. Hilton A.K. and Deasy P.B., In Vitro and In Vivo Evaluation of an Oral Sustained-Release Floating Dosage Form of Amoxicillin Trihydrate, Int. J. Pharm. 86, 1, 1992, 79-88.
 12. Sheth P.R. and Tossounian J.L., Novel Sustained- Release Tablet Formulations," US Patent os, 755 1979.
 13. Sheth P.R. and Tossounian J.L., The Hydrodynamically Balanced System: A Novel Drug Delivery System for Oral Use, Drug Dev. Ind.Pharm. 10, 2, 1984, 313-339.
 14. Wilding I.R., Davis S.S. and O'Hagan D.T., Targeting of Drugs and Vaccines to the Gut, in Pharmac. Ther., C.J.Hawkey, Eds., 1994, 98-124.
 15. Park K. and Robinson J.R., Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 19, 1, 1984, 107-127.
 16. Caldwell L.J., Gardner C.R., and Cargill R.C., Drug Delivery Device Which Can Be Retained in the Stomach for a Controlled Period of Time, US Patent No. 4735804, 1988.
 17. Ito R., Machida Y., Sannan T., Nagai T., Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration, Int. J. Pharm. 61, 1-2, 1990, 109-117.
 18. Hwang S.J., Park H., Park K., Gastric retentive drug delivery systems, Crit. Rev. Ther. Drug Carr. Syst. 15, 3, 1998, 243-284.
 19. Anand S. Surana*, Rakhee K. Kotecha , An Overview on Various Approaches To Oral Controlled Drug Delivery System via Gastroretention, International Journal of Pharmaceutical Sciences Review and Research, 2, 2, 2010.
 20. Patel Geeta M, Patel Hitesh R, Dr. Madhabhai Patel, Floating Drug Delivery System: An Innovative Approach to Prolong Gastric Retention, Pharmainfo.net, 5, 6, 2007.
 21. *Encyclopedia of pharmaceutical technology* Third Edition volume 1
 22. Shah S.H. *, Patel J.K., Patel N.V. , Stomach specific floating drug delivery system: a review, International Journal of PharmTech Research, 1, 3, 2009, 623-633.
 23. Gangadharappa HV, Balamuralidhara V, Pramod Kumar TM. Formulation and *in vitro* Evaluation of Gastric Floating Tablets of Atenolol. Journal of Pharmacy Research, 3, 6, 1450-1455.
 24. Patela JK, Naihong Lib, Patela M, Ravala JA. Ranitidine hydrochloride floating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release. Asian Journal of Pharmaceutical Sciences 2, 4, 2007, 130-142.
 25. Puneeth KP, Kavitha K, Tamizh Mani T. Development and Evaluation of Rosiglitazone Maleate Floating Tablets. International Journal of Applied Pharmaceutics, 2, 2, 2010.
 26. Rishad RJ, Jivani, Chhagan NP, Nuruddin PJ. Design and Development of a Self Correcting Monolithic Gastroretentive Tablet of Baclofen. Sci Pharm, 77, 2009, 651–667.
 27. Kishan V, Ramesh B, Rongala ASN, Madhusudan RY. Development and evaluation of gastroretentive Norfloxacin floating tablets. Acta Pharm, 59, 2009, 211–221.

