Asian Pac. J. Health Sci., 2014; 1(2): 80-89 ISSN: 2349-0659

GASTRORETENTIVE DRUG DELIVERY SYSTEM - A MINI REVIEW

Devkant Sharma[1*], Anjali Sharma[2]

[1]Smt. Tarawati Institute of Biomedical and Allied Sciences, Roorkee, Uttarakhand, India
[2]Roorkee College of Pharmacy, Roorkee, Uttarakhand, India

ABSTRACT

Oral delivery of drugs is by far the most preferable route of drug delivery. This route has high patient acceptability, primarily due to ease of administration. Effective oral drug delivery depend upon the factors such as gastric emptying process, gastrointestinal transit time of the dosage form ,drug release from the dosage form, and site of absorption of drug. In the recent years, scientific and technological advancement have been made in the research and development of gastroretentive drug delivery system. Henceforth a wide spectrum of dosage form have been developed for the drugs which have narrow absorption window, unstable at intestinal pH , soluble in acidic pH and have site of action specific to stomach.The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. These includes floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits , demerits and applications of gastroretentive drug delivery systems.

Keywords: gastroretentive drug delivery system ; floating system; swelling; expanding system; bio/mucoadhesive system; high density system.

Introduction

Despite of considerable advancements in the drug delivery, oral delivery of drugs is the most preferred route because of its ease of administration[1] and low cost of therapy and high level of patient compliance. Oral controlled release drug delivery system have drawn considerable attention as these systems provide drug release at a predetermined, predictable and controlled rate. However some drugs show poor bioavailability because of incomplete absorption or degradation in the git [2].Therefore to overcome such problems gastroretentive drug delivery systems are designed to prolong the gastric retention time of the drugs which are:

- Locally active in the stomach.
- Unstable in the intestinal environment.
- Have narrow absorption window in the git.
- Have low solubility at the high pH regions.[3]

**Correspondence*
Devkant Sharma
Smt. Tarawati Institute of Biomedical and Allied Sciences, Roorkee, U.K., India.
E Mail: devkant2088@gmail.com

Various approaches have been proposed to increase the gastric residence of the drug delivery that includes floating drug delivery system (FDDS), mucoadhesion or bioadhesion system, high density system, expansion system, magnetic system, superporous huydrogel, raft forming system and floating ion exchange resins.[4]

Potential candidates for gastroretentive drug delivery system

1. Drugs that are primarily absorbed in the stomach eg Amoxicillin.
2. Drugs that are poorly soluble in alkaline pH eg Furosemide , Diazepam.
3. Drugs that have narrow absorption window eg Levodopa, Methotrexate.
4. Drugs that degrade in the colon eg. Ranitidine , Metformin HCL.
5. Drugs that disturb normal colonic microbes eg Antibiotics against Helicobacter pylori.
6. Drugs rapidly absorbed from the gi tract eg Tetracycline.
7. Drugs acting locally in the stomach[5].

Advantages of gastroretentive drug delivery system

1. It increases patient compliance by reducing dosing frequency
2. Buoyancy increases gastric residence time
3. Better therapeutic effect of short half life drugs
4. Site specific drug delivery to stomach can be achieved
5. In this drug is released in a controlled manner
6. Gastric irritation can be avoided by designing sustained release.
7. No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.[6]

Limitations of gastroretentive drug delivery system

1. Aspirin and NSAID'S can cause gastric lesions and slow release of such drug in the stomach is unwanted.
2. Drugs such as isosorbide dinitrate which are equally absorbed throughout the GIT will not be benefit from incorporation into a gastric retention system.
3. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of the technique
4. Physical integrity of the system is very important and primary requirement for the success of the system.
5. High variability in gastric emptying time due to variations in emptying process , unpredictable bioavailbility.[6][7]

Anatomy of the stomach

The gastro intestinal tract can be divided into three main regions

- Stomach
- Small intestine- duodenum, jejunum, and ileum
- Large intestine

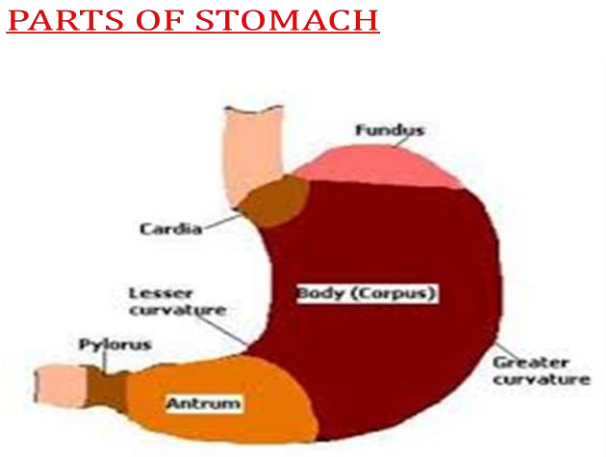

Figure 1: Shows parts of Stomach

The git is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layer called oblique muscle and it is situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided into fundus, body and pylorus[8]. The stomach is a J shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily , grind it and releases slowly in to the duodenum.

Physiology of the stomach

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown upinto folds called rugae. There are 4 major types of secretory epithelial cells that covers the stomach and extends into gastric pits and glands.

1. mucous cells- secrete alkaline mucus
2. parietal cells – secrete HCL
3. chief cells- secrete pepsin
4. G cells- secrete hormone gastrin[9].

Gastric motility and gastric empty rate

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state. The bioavailbility of the orally adminsterd drug depend upon the state of feeding. In the fasted state , it is characterized by an interdigestive series of electric event called inter digestive myoelectric cycle or migrating motar complex.

It is divided into 4 phases[10]

- phase I (basal phase) it lasts from 40-60 min with rare contractions
- phase II (preburust phase) last from 40-60min with intermittent potential and contractions.
- Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the undigestive food is swept from stomach to intestine. These are known as house keeper waves.
- Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles.

After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility pattern, these contractions reduces the size of the food particles to less than 1mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.[11]

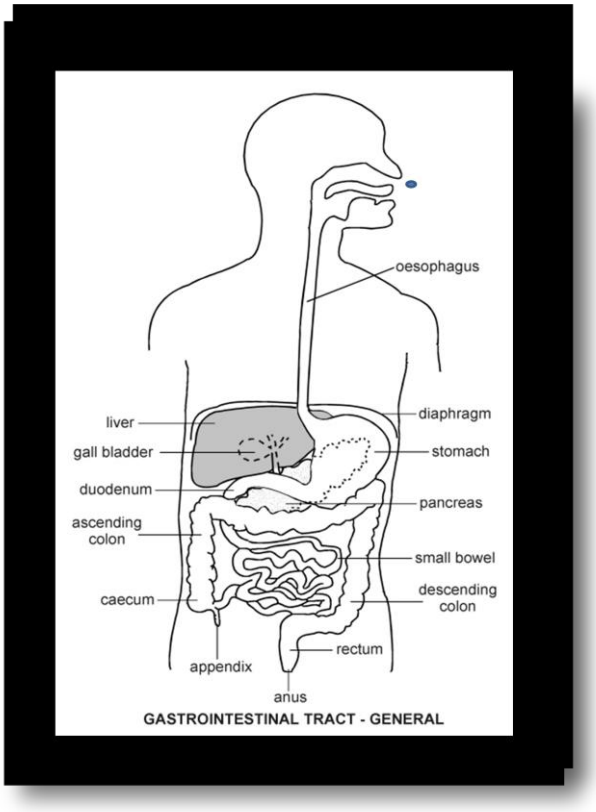

Figure 2 :Shows general Gastrointestinal tract

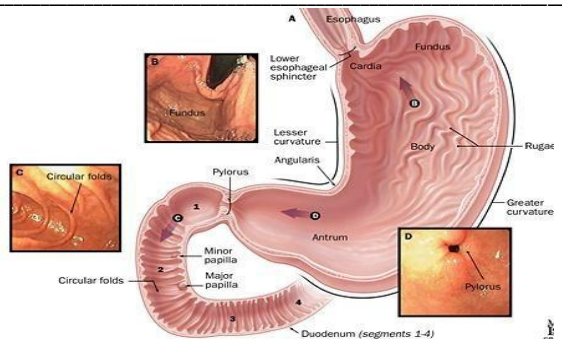

Figure 3: Shows Physiology of stomach

Factors affecting gastric retention

Density- the density of the dosage form should be less than that of the gastric contents (1.004g/ml)

Size- dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.

Shape of the dosage form- the tetra hedron resided in the stomach for longer period than other devices of similar size.
Single or multiple unit formulation- multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units. , allow co-adminstration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form[12].

Fed or unfed state- under fasting conditions, the gi motility is characterized by periods of strong motar activity that occurs every 1.5-2 hrs. the MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC ,the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.

Nature of meal- feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state,thus decreasing gastric emptying rate and prolonging drug release.[13]

Caloric content-GRT can be increased by 4-10 with a meal that is high in protein and fat [14].

Frequency of feed- The GRT can be increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

Gender- mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched femalecounterparts(4.6hrs) regardless of height, weight and body surface.

Age- people with age more than 70 have a significant longer GRT[15].

Concomitant drug administration- anticholinergics like atropine and propetheline, opiates like codeine can prolong GRT[2][15].

Gastroretentive dosage form

Gastroretentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment.[16]

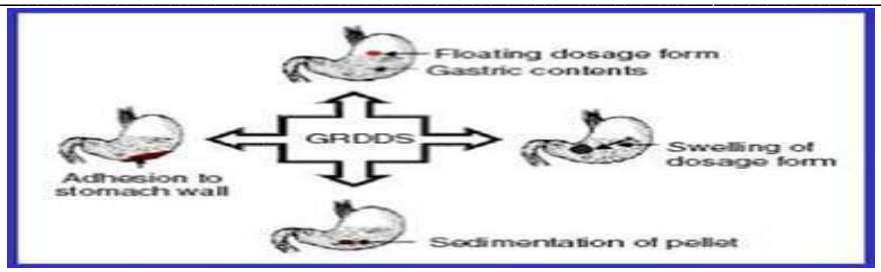

Figure 4:Shows Cycle for Gastroretentive dosage forms

Classification of GRDF

- High density system
- Floating system
- Expandable system
- Superporous hydrogels
- Mucoadhesive bioadhesive system
- Magnetic system

High density system

This approach involves formulation of dosage forms with density that must must exceed density of normal stomach content(1.004g/ml). these formulations are prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlled membrane [17].

These systems have some drawbacks like they are technically difficult to manufacture with a large amount of drug because the dry material of which it is made interacts within the gastric fluid to release its drug contents. One other problem is that no such system is available in the market.

Floating or low density system

By virtue of their low densities, FDDS remain afloat above the gastric contents for prolonged periods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GRRDS is also evident from the large number of floating dosage forms being commercialized and marketed world-wide.[18]

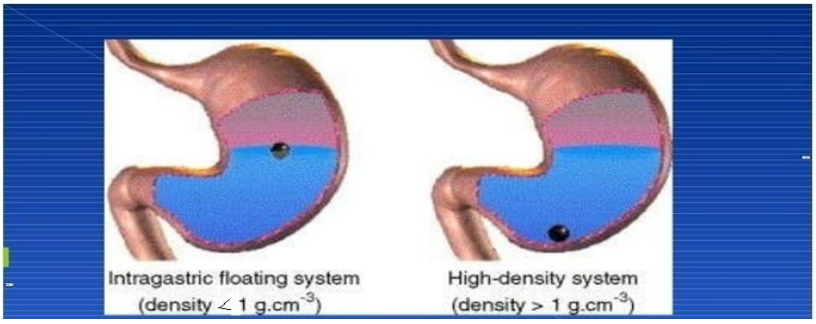

Figure 5:Shows schematic localization of floating dosage forms in stomach

List of drugs explored for various floating system
Microspheres tablets/ pills: Aspirin, Griseofulvin, Acetyl salicyclic acid, Ibuprofen, Ampicillin, Captopril, Sotalol, Isosrbide dinitrate, Terfanadine.
Films: Cinnarizine,Peritanide, Quinidine,Prednisolone, P-aminobenzoic acid, Prednisolone.
Classification of floating system

- Non effervescent systems
- Effervescent system

Granules: Diclofenac sodium, Cinnarizine, Indomethacin,Fluorouracil,Diltiazem,Isosorbidedinitrate, Isosorbide mononitrate.
Powders: Riboflavin, Sotalol, Theophylline
Capsules: Verapamil HCL, Diazepam, Misoprostol,Furosemide, L –dopa,Nicardipine[19].

Effervescent FDDS

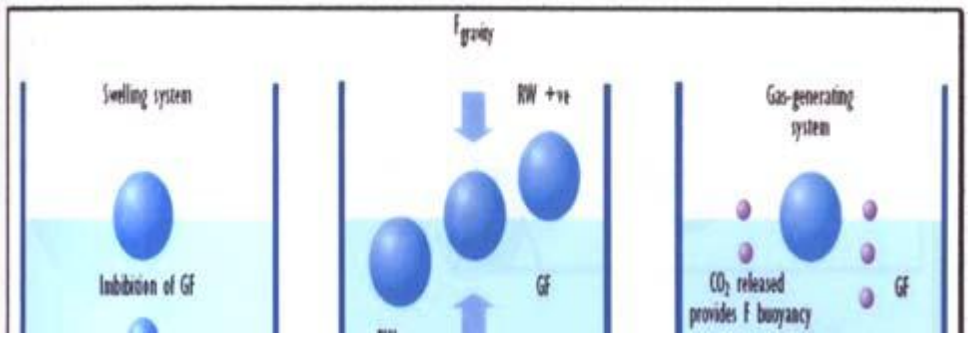

Figure 6:Shows working of effervescent FDDS

Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach[20].

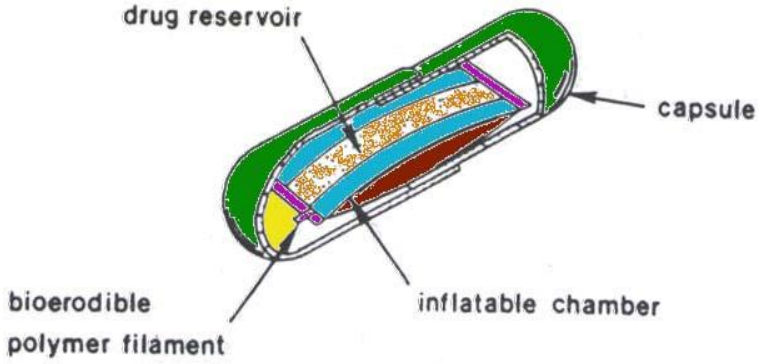

Figure 7:Inflatable Gastrointestinal Delivery System

Gas-generating Systems: These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric content.

Non-Effervescent FDDS: The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan.[21].

Mucoadhesive systems

mucoadhesive drug delivery systems contain, a mucoadhesive polymers that adheres to the gastric mucosal surface and prolong its gastric retention in the git. The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful exicipients in the GRRDS. These polymers can be natural such as

sodium alginate, gelatin , guar gum etc semisynthetic polymers such as HPMC, carbopol,sodium carboxy methyl cellulose[22].The adhesion of polymers with mucous membrane may be mediated by hydration, bonding,or receptor mediated. In hydration mediated adhesion , the hydrophilic polymer become sticky and mucoadhesive upon hydration. Bonding mediated involves mechanical or chemical bonding.chemical bonds may involve ionic or covalent bonds or vander waal forces between the polymer molecule and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers can be cationic or anionic or neutral[23].

Swelling system

These are the dosage forms , which after swallowing swells to such an extent that their exit from the pylorus is prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. The formulations are designed for gastric retention and controlled delivery of drugs in the gastric cavity, such formulations remain in the gastric cavities for several hours even in the fed state. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release [24]. On coming in contact with gastric fluid the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross links prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form. An optimum cross-linking, which maintains a balance between the swelling and the dissolution, should be maintained. Agyilirah developed a polymeric coating system that formed an outer membrane on the conventional tablets. In the dissolution media the membrane detached from the core and sweeled to form a balloon that kept the unit floating . the size of the units increased by three to six folds, thus the floating ability as well as the increased dimension offered the system gastroretentive property[25].

Superporous hydrogels

Superporous hydrogels are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states[26] during which the premature evacuation of the dosage form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size within a minutes, due to rapid intake of waterby capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by co- formulation of a hydrophilic particulate material, Ac-Di-Sol[27].

Magnetic system

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet , gastric residence time of the dosage form can be enhanced for a prolonged period of time[28].

***Invitro* method of evaluation**

Fourier transform infrared analysis

Fourier transform infrared spectroscopy is mostly used to identify organic, polymeric, functional group, and some inorganic materials as well. FT-IR measurement of pure drug, polymer and drug loaded formulations are obtained by using this technique[29]. The pellets are prepared on kbr press under hydraulic pressure of 150kg/cm^2 and the spectra are scanned over the wave number range of 3600-400cm^{-1} at ambient temperature[30].

Differential scanning calorimetry

DSC are performed to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DSC instrument equipped with an inter cooler zinc standards are used to calibrate the DSC temperature and enthalpy scale[31]. The sample preparations are sealed in aluminium pan and heated at a constant rate of 10°C/min over a temp range 25°C-65°C[32].

Particle size analysis and surface characterization (for floating microspheres and beads)

The particle size and size distribution of beads or microspheres are determined in the dry state using optical microscopy method. The external and cross sectional morphology is done by scanning electron microscope[33-34].

Floatation studies

The *invitro* buoyancy is characterized by floating lag time and total floating time[35]. The FLT and TFT are measured by placing the tablets in a 250 ml beaker containing 200ml of 0.1N HCL. The time required by the to rise to the surface and float is known as floating lag time and the time period upto which the tablet remained buoyant is called toatal floating time[36][37].

Swelling studies

Swelling of tablet excipients particles involves the absorption of a liquid resulting in increase in weight and volume . liquid uptake by the particles may be due to saturation of the capillary spaces within the particles or hydration of macromolecules[36]. The liquid enters the particles through pores and bind to large molecules, breaking the hydrogen bond and resulting in the swelling of particles. Tablet is weighed and placed in a beaker containing 200 ml of 0.1N HCL. after each interval the tablet is removed from the beaker, soaked by using filter paper and weighed again[38].

Swelling index (SI) = $(W_t\text{-}W_O)/W_O \times 100$

W_t – weight of the tablet at time t

W_O – initial weight of the tablet

Determination of drug content

Percentage drug content provides how much amount of drug is present in the formulation. It should not exceed the limit acquired by the monograph.drug content is determined by using HPLC, HPTLC methods, microtitrimetric methods, and also by using spectroscopy techniques[39]. To determine drug content 10 tablets are triturated in the mortarand .10 mg of powdered tablet dissolved in 10 ml of 0.1N HCL and after that drug sample is analysed under u.v spectro photometer[30][39].

Dissolution studies

The dissolution test are generally performed for calculating the amount of drug release using USP dissolution apparatus.[40]. The test is performed using 900ml of 0.1 N HCL, at 37ºC and 100 rpm[41]. A sample of 10 ml is withdrawn hourly and analysed under u.v and absorbance is measured. The sample is replaced by the dissolution media [42] Cumulative percentage is calculated using equation obtaine from standard curve[43-44].

***In vivo* methods**

X-ray / gamma scintigraphy

It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form in the git. The inclusion of a radio opaque material into solid dosage form enables it to be visualized by the X-ray[45]. The inclusion of a gamma emitting radionuclide in the formulation allows indirect external observation using gamma camera, the gamma rays emitted by radionuclide is focused on the camera which helps to monitor the location of the dosage form[46].

Gastroscopy

It comprises of peroral endoscopy used with a fibereoptic and video system. It is used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS [45][47].

Future potentials

- The floating drug delivery concept can be used in development of anti reflux formulations
- Buoyant delivery system is beneficial in the treatment of gastric and duodenal ulcers.
- Developing a controlled release of drugs which is used to treat Parkinson disease.
- To explore the eradication of helicobacter pylori by using narrow spectrum antibiotic.

Conclusion

Under certain circumstances, the prolongation of gastric residence time of a delivery system is desirable for achieving a better therapeutic benefit of the drug substance. For instance the drugs that show absorption in the proximal part of the gastrointestinal tract and the drugs which are degraded or less soluble in alkaline pH may be benefitted by prolonging the gastric residence time.Prolnged gastric retention of therapeutic moiety offers many advantages like improved bioavailability , reduction of drug wastage and possible reduction of dose size.

A controlled drug delivery system with prolonged gastric retention may have great practical importance for the drugs which have narrow absorption window in the upper small intestine. Ciprofloxacin, levodopa , sotalol HCL , furosemide are examples of such drugs. Drugs like chlorpheniramine maleate which is locally used in the treatment of Helicobacter Pylori requires

longer residence time in the stomach which can be achieved by designing gastroretentive dosage forms. Drug absorption through git is a complex procedure and is subjected to many variables. It is widely acknowledged that extent of drug absorption is related to contact time of drug with intestinal mucosa . small intestine transit time is important parameter for drugs which are incompletely absorbed. Over the last two decades , various gastroretentive dosage forms have been designed to increase the gastric retention time. Nevertheless, there are opportunity and potential for the development of effective GRDDS with a improving bioavailability of the drugs that have absorption window in the proximal and mid git.

References

1. Basak SC, Rao NK, Manavalan R, Rao RP. Development and invitro evaluation of an oral floating matrix tablet formulation of ciprofloxacin. *IJPS*, 2004;66(3):313-316.
2. Streubel A,Siepmann, Bodmeir J. Drug delivery to the upper intestine window using gastroretentive technologies. *Curr Opin Pharmacol*, 2006:6:501-508
3. Chen YC, Ho H, Lee TY, Sheu MT. Physical characterizations and sustained release profiling of gastroretentive drug delivery system with improved floating and swelling capabilities. *International Journal Of Pharmaceutics*, 2013;44:162-169.
4. Prajapati DV, Jani GK, Khutliwala TA, Zala BS. Raft forming system- An upcoming approach of gastroretentive drug delivery system. *Journal of Controlled Release*, 2013; 168:151-165.
5. Subhramananyam CVS , Setty JT. Laboratory manual of physical pharmaceutics. Vallabh prakashan 2002; pg no 212.
6. Khan R. Gastroretentive Drug Delivery Sytem – A Review. *Int J Pharm Bio Sci*, 2013;4(2):630-646.
7. Vinod KR, Vasa S, Anbuazagahan S. Approaches for gastroretentive drug delivery, *IJABPT*, 2008;589-601.
8. Pawar V.K, Shaswat K, Garg G, Awasthi R. Gastroretentive dosage form: A review with special emphasis on floating drug delivery systems, *Informa Healthcare* 2011;18(2):97-110
9. Dixit N. Floating drug delivery system. *Journal of Current Pharmaceutical Research*, 2011;7(1):6-20.
10. Vyas SP, Khar RK. Controlled drug delivery: concept and advances. Vallabh prakashan Delhi,2002;1:123-231.
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 Sciences*, 2003;18:37-45.
12. Robinson J, Lee R. Controlled Drug Delivery, 2nd edition , 1987: pg 418.
13. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms. *Journal of Controlled Release*, 2006; 111:1-18.
14. Arora S, Javed A, Ahuja A, Khar RK, Baboota S. Floating drug delivery system : a review. *AAPS Pharm Sci Tech*, 2000;6(3):372-390.
15. Patel GM, Patel HR, Patel M. Floating drug delivery system an innovative approaches to prolong gastric retention. Pharmainfo.net 2007.
16. Garg AK, Kapoor G, Sachdeva RK. Formulation and evaluation of nizatidine floating tablets. *American Journal of pharmatech Research*, 2012;2(5):504-515.
17. Singh B and Kim KH. Floating drug delivery system : an approach to oral controlled drug delivery system via gastric retention. *Journal of Controlled Release*, 2000;63:235-259.
18. Waterman KC. A critical review of gastric retentive controlled drug delivery. *Pharmaceutical Development and Technology*, 2007;12: 1-10.
19. Kotreka U and Adeyeye MC. Gastroretentive floating drug delivery system a review. *Therapeutic Drug Carrier System*, 2011;28(1):47-99.
20. Mayavanshi AV and Gajjar SS. Floating drug delivery system to increase gastric retention of drugs. *RJPT*, 2008;1(4):345-348.
21. Jamil F, Sunil K, Sharma S, Vishvakarma P, Singh L. Review on stomach specific drug delivery :development and evaluation. *IJRPBS*, 2011;2(4):1427-1433.
22. Talukder R, Fassihi R. Gastroretentive delivery systems. *Drug development and industrial pharmacy*,2004;30(10):1019-1028.
23. Krogel I and Bodmeier R. floating or pulsatile drug delivery system based on coated effervescent cores. *International Journal of Pharmaceutics*, 1999;187:175-184.
24. Groning R, Heun C. Oral dosage forms with controlled gastrointestinal transit drug delivery, 1984;10(4):527-539.
25. Agyilirah GA, Green M, Ducret R. Evaluation of gastric retention properties of cross linked polymer- coated tablet versus those of non

disintegrating tablets. *Int J Pharma*.1991;75:241-247

26. 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.

27. Nayak AK, Maji R, Das B. Gastroretentive drug delivery system a review. *Asian Journal of Pharm Clin Res*.2010;3(1):2-10

28. Satinder Kakar, Deepa Batra, Ramandeep Singh, Ujjwal Nautiyal. Magnetic microspheres as magical novel drug delivery system: A review. *Journal of Acute Disease* 2013:1-12

29. Girish S, Sonar , Devendra K, Jain, Dhananjay M. Preparation and invitro evaluation of bilayer floating bioadhesive tablets of Rosiglitazone Maleate. *Asian Journal of Pharmaceutical Sciences*.2007;2(4):161-169.

30. Sruthy PN and Anoop KR. Formulation and evaluation of olmesartan medoxomil floating tablets. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2013;5(3):691-696.

31. Pawar HA, Gharat PR, Dhavale RV, Joshi PR, Rakshit PP, Development and evaluation of gastroretentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. *ISRN*, 2013;10(11):1-9.

32. Khan AZ, Tripathi R, Mishra B. Floating elementary osmotic pump tablet for controlled d delivery of diethylcarbamazine citrate: a water-soluble drug. *AAPS Pharm Sci Tech*, 2011;12(4):1312-1323.

33. Subhramananyam CVS , Setty JT. Laboratory manual of physical pharmaceutics. Vallabh prakashan 2002;pg no 212.

34. Tanwar YS, Naruka PS, Ojha GR. Development and evaluation of floating microspheresof verapamil HCL. *BJPS*,2007;43(4):529-534.

35. Kharkhile VG, Karmarkar RR, Sontakke MA, Badgujar SD, Nemade LS. Formulation and evaluation of floating tablets of furosemide. *International Journal of Pharma. Research and Development*, 2012;(12):1-9.

36. Chinthala SK, Kota SR, Hadassah M, Metilda, Sridevi S. Formulation and evaluation of gastroretentive floating tablets of gabapentin using effervescent technology. *Int J Pharm Biomed Res*, 2012;3(4):202-208.

37. Pamu S, Banu N, Sunitha M. Formulation and evaluation of olmesartan medoxomil floating tablets. *International Journal of Pharmacy and Industrial Research*, 2013;3(4):329-334.

38. Vedha BN, Brahma RA, Samyuktha RB. Floating drug delivery of Nevarapine as a gastroretentive system. *Journal of Yung Pharmacist*, 2010;2(4)350-355.

39. Boldhane SP and Kuchekar BS. Development and optimization of metoprolol succinate gastroretentive drug delivery system. Acta Pharm, 2010;60:415-425.

40. Khan F, Razzak S. Formulation and invitro evaluation of theophylline loaded floating tablets using HPMC K4M. *J Pharm Sci*, 2008;7(1):65-70.

41. Biswas M, Gupta RN, Parhi R, Sethi KK, Sahoo SK. Formulation and invitro evaluation of gastroretentive floating drug delivery system of ritonavir. *Turk J Pharm Sci*, 2013;10(1):69-86.

42. Tanwar YS, Jamini M, Srivastava. Formulation and invivo evaluation of floating tablets of losartan potassium. *Mahidol University Journal of Pharmaceutical Sciences*, 2013;40(2):17-24.

43. Pawar HA, Gharat PR, Dhavale RV, Joshi PR, Rakshit PP, Development and evaluation of gastroretentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. *ISRN*, 2013;10(11):1-9.

44. Solanki ND, Shah S, Patel J, Upadhyay P. Formulation and evaluation of once bilayer floating tablets of antihypertensive drug involving dissolution enhancement technique. Der Pharmacia Sinica, 2013; 4(5):54-66.

45. Bhowmik D, Chiranjib B, Jayakar B. Floating drug delivery system- a review. Der Pharmacia. Lettre,2009;1(2):199-218.

46. Chander S, Shireesh K, Nagendra B. Preparation and evaluation of gastroretentive floating tablets of ketoconazole. *IJPRD*,2010;2(9):175-176.

47. Chandel A, Chauhan K. Gastroretentive approaches. *ICPJ* 2012;1:110-118.