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FLOATING MATRIX TABLETS – A COMPLETE STUDY

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ABSTACT

Floating drug delivery system (FDDS) is a safe and efficient technology for drug delivery which has a bulk density lower than gastric fluids thus, remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. The drug is released slowly and almost completely at a desired rate from the system after which the residual system becomes liable to be emptied from the stomach. This results in an increase in the gastro retentive time, bioavailability and a better control of fluctuations in the plasma drug concentrations. It may of two types i.e., effervescent type & non-effervescent type. Effervescent systems include use of gas generating agents, to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. The non effervescent floating drug delivery systems are based on mechanism of swelling of polymer in gastric fluid. Floating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms.

KEYWORDS: Gastric emptying, Intragastric, Ingastric.

INTRODUCTION

"Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either direct compression or molding methods".

Advantages of tablets

Some of the potential advantages of the tablets include the following such as, they are a unit doses form and offer the greatest dose precision and the least content variability, their cost is lowest of all oral dosage forms, they are the lightest and most compact of all oral dosage

forms, they are in general the easiest and cheapest to package and ship of all oral dosage forms, they may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid, they lend themselves to certain special release profile products, such as enteric or delayed-release products, they are better suited to large scale production than other unit oral forms and they have the best-combined properties of chemical and mechanical and microbiologic stability of all the oral forms.[6]

Disadvantages of tablets.

Some of the disadvantages of tablets include the following such as, some drugs resist compression into dense compacts owing to their amorphous nature or flocculent low density character, drugs with poor wetting, slow dissolution properties, intermediate to large dosages or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability and bitter tasting drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression or the tablets may require coating.[6]

Types of tablets

There are many types of tablets are available in the market such as, sugar-coated tablets, film-coated tablets, enteric-coated tablets, multiple-coated tablets, layered tablets, press-coated tablets, controlled release tablets, buccal or sublingual tablets, tablets for solution, molded tablets or tablet triturates and fast dissolving/disintegrating tablets.[7]

Methods of manufacturing

Generally tablets are manufactured by wet granulation, dry granulation and direct compression method.

Wet granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules are then compressed to form tablets.

Dry granulation

In this technique, there is no use of liquids. The process involves the formation of slug. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

Direct compression

In this process, the tablets are compressed directly from powder blends of active ingredients and suitable excipients (including fillers, disintegrates and lubricants), which will flow uniformly in the die cavity and form the firm compact.[6]

ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

The oral route is the most promising and convenient route of drug administration. Conventional immediate release system achieves as well as maintains the drug concentration within the therapeutically effective range, but one has to take such formulations several times a day. This results in significant fluctuations in plasma drug levels and also the frequency of administration leads to patient non-compliance. Recently, several technical advancements in the pharmaceutical field have led to the development of many novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits.

Objectives

- It should, on a single administration, release the active ingredient over an extended period of time.
- It should deliver the active entity in the required concentration at the site of action, minimizing or eliminating the side effects. The limitations of conventional immediate release systems are overcome by these novel sustained release systems.

Advantages

- Reduced dosing frequency.
- Better patient convenience and compliance.
- Reduced gastrointestinal side effects and any other toxic effects.
- Less fluctuations in plasma drug level.
- Reduction in the total dose.
- Improved bioavailability.

This also helps to provide better acceptability for drug molecules (new or existing) with potential therapeutic advantages. The development process of sustained release system includes several physiological difficulties such as inability to restrain and localize sustained drug delivery system within the desired regions of the gastrointestinal tract and variability in the nature of the gastric emptying process. The sustained release systems are also not suited for certain drugs that have a narrow absorption window.[8] Gastro retentive dosage form is a novel drug delivery system which has emerged and gathered momentum in the research to overcome the above mentioned limitations of conventional sustained release systems.

GASTRO RETENTIVE DOSAGE FORM

Recent scientific literature reveals that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. These are the most feasible approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal tract which can control the gastric residence time and they are collectively called gastro retentive dosage forms. Delivery of drugs at a specific region in gastrointestinal tract, the so called absorption window has necessitated the development of gastro retentive dosage forms. The attempts to develop gastro retentive drug delivery systems may be largely divided into two classes, those that rely on the natural physiology of the gastrointestinal tract and those that are designed to overcome it. Approaches such as size or floatation, which rely on delayed emptying from the stomach, depend on the normal physiological duration of the fed state of 4-8 hours. The main approaches that have been examined for gastro retentive dosage forms are, low density systems that cause buoyancy (Floating drug delivery system), high density which retains the dosage form in the stomach, raft forming systems, concomitant administration of drugs or excipients which slow the motility of the gastro intestinal tract, bioadhesion to gastric mucosa, swelling to a large size which prevent passage of dosage form through the pyloric sphincter.[9]

Floating Drug Delivery Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids thus, remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly and almost completely at a desired rate from the system. After the release of the drug, the residual system becomes liable to be emptied from the stomach. This results in an

increase in the gastro retentive time, bioavailability and a better control of fluctuations in the plasma drug concentrations. Thus floating drug delivery system is a safe and efficient technology for drug delivery.

Need for Floating Drug Delivery System

- Drugs that act locally in the stomach e.g., Antacids, proton pump inhibitors for ulcers.
- Drugs particularly useful for the treatment of peptic ulcers caused by *Helicobacter pylori* e.g., Tetracycline, Amoxicillin.
- Drugs that are absorbed primarily in the stomach.

e.g., Albuterol.

- Drugs that are less soluble or are degraded in the alkaline intestinal pH.

e.g., Bromocriptine.

- Drugs that have a narrow window for absorption e.g., Riboflavin, Levodopa, p-amino benzoic acid.
- Drugs that are absorbed mainly from the proximal part of small intestine e.g., Diltiazem, Furosemide.
- Drugs that degrade in the colon e.g., Captopril, Metoprolol.

Advantages of Floating Drug Delivery System

- **IMPROVEMENT OF BIOAVAILABILITY**

Furosemide has poor bioavailability due to its restricted absorption only from the upper gastrointestinal tract. This was improved by formulating its floating dosage form. The floating system containing Furosemide exhibit 42.9% bioavailability as compared to 33.4% shown by commercial tablet and 27.5% shown byenteric coated tablets.[10]

- **REDUCTION IN PLASMA LEVEL FLUCTUATIONS**

The reduced plasma level fluctuations results from delayed gastric emptying, for example, the bioavailability of Madopar as conventional tablet was found to be 60-70% whereas a hydro dynamically balanced system is 100% bioavailable. The difference in the bioavailability of standard and hydrodynamically balanced systems was due to the incomplete absorption. The study also reported that hydrodynamically balanced systems had reduced Fluctuations in plasma drug levels.[11]

- **REDUCTION IN THE VARIABILITY IN TRANSIT PERFORMANCE**

Floating dosage forms with sustained release characteristics are useful in reducing the variability in transit performance, for example formulating Tacrine as hydro dynamically balanced systems reduced its gastrointestinal side effects in Alzheimer's patients.[12, 13]

- **DOSE REDUCTIONS**

The recommended adult oral dose of Ranitidine is 150 mg twice daily or 300 mg once daily. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hrs only. If 300 mg is administered as single dose then, it leads to plasma fluctuations. On formulating Ranitidine as floating drug delivery system, the dose has been reduced and a sustained action was also observed.[14, 15]

- **ENHANCEMENT OF THERAPEUTIC EFFICACY**

Floating systems are particularly useful for acid soluble drugs that are poorly soluble or unstable in the alkaline intestinal fluids. Bromocriptine used in the treatment of Parkinson's disease have low absorption potential that can be improved by formulating it as hydrodynamically balanced systems and thus its therapeutic efficacy was found to be enhanced.[16]

- **ERADICATION OF *HELICOBACTER PYLORI***

Helicobacter pylori are responsible for chronic gastritis and peptic ulcers. Its eradication from patients requires high concentrations of drug to be maintained within gastric mucosa which could be achieved mainly by floating drug delivery system.[17, 18]

Limitations

- The floating drug delivery systems based on effervescent technique cannot be efficient in patients with achlorhydria.
- Bioadhesion technique may be less effective in the acidic environment and high turnover of mucus.
- Retention of high density systems in the pylorus part under the migrating waves of the stomach is questionable.
- This is not suited for drugs that are unstable in the strong acidic environment.
- These systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed uniformly throughout the gastrointestinal tract.

Classification of Floating Drug Delivery Systems

Floating drug delivery systems can be classified majorly under two types,

- Effervescent systems.
- Non effervescent systems.

EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature. These effervescent systems are further classified into two types.

A. Gas generating systems

B. Volatile liquid/Vacuum systems

A) *GAS GENERATING SYSTEMS*

(i) *Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System*

Hydro dynamically balanced systems (HBS) are formulated by intimately mixing the carbon dioxide generating agents and the drug within the matrix tablet. These systems swell as well as entrap the gas generated in the hydrogel, leading the system to have a bulk density lower than gastric fluids and therefore remain floating in the stomach for a prolonged period.

The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the gastric residence time and a better control over fluctuation in plasma drug concentration.

(ii) *Multiple Unit type floating pills.*

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer.

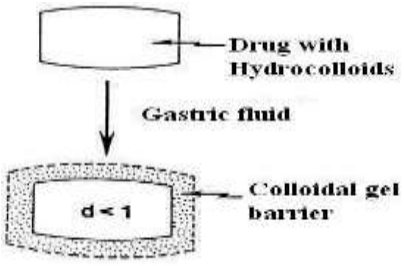

Fig1. Intra gastric floating tablets.

When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of carbon dioxide within the system.

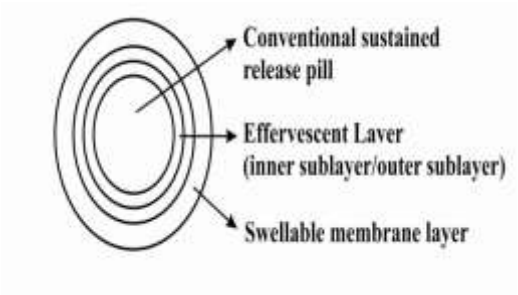

Fig 2. Multiple-unit oral floating dosage system.

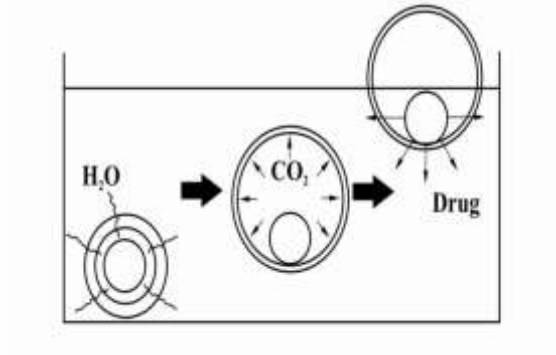

Fig 3. Stages of floating mechanism.

B. *VOLATILE LIQUID/VACUUM CONTAINING SYSTEMS*

(i) Intra-gastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

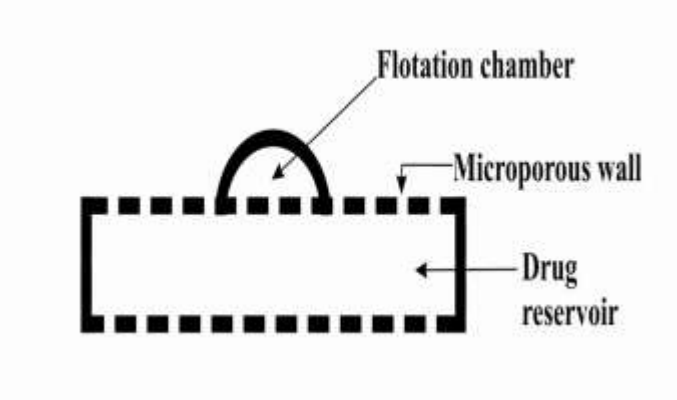

Fig 4. Intragastric floating drug delivery device.

(ii) Inflatable gastro intestinal delivery systems

The inflatable gastro intestinal delivery systems have an inflatable chamber, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the inflatable chamber automatically inflates, make the whole system float and retain the drug reservoir into the gastric fluid for a prolonged period.

(iii) Intragastric osmotically controlled drug delivery system

Intragastric osmotically controlled drug delivery system comprises of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

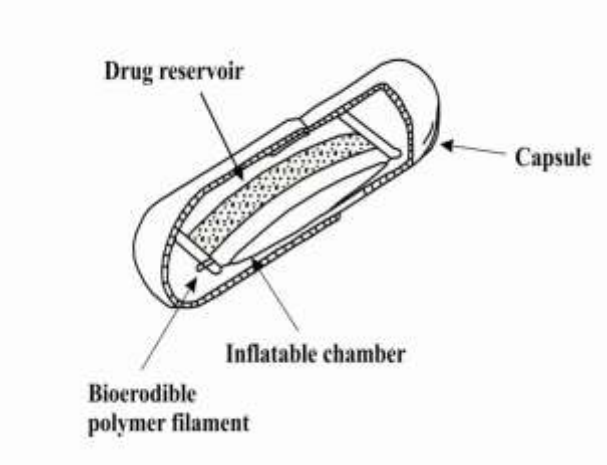

Fig 5. Gastro-inflatable drug delivery device.

The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the gastrointestinal fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotic salt, as a result an osmotic pressure is created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume.

NON EFFERVESCENT SYSTEMS

The non effervescent floating drug delivery systems are based on mechanism of swelling of polymer in gastric fluid.

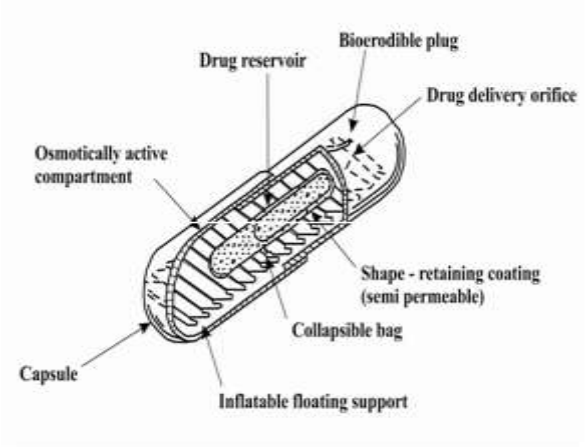

Fig 6. Intragastric osmotic drug delivery system.

The most commonly used excipients in non effervescent floating drug delivery systems are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol.

(I) SINGLE LAYER FLOATING TABLETS

Single layer floating tablets are formulated by intimate mixing of drug with the gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

(II) BILAYER FLOATING TABLETS

A bilayer tablet contain two layers an immediate release layer which releases the initial dose from system and a sustained release layer which absorbs gastric fluid forming an impermeable colloidal gel barrier on its surface maintaining a bulk density of less than unity. Such a device remains buoyant in the stomach.

(III) ALGINATE BEADS

Multi unit floating dosage forms are developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate

leading to the formation of porous system, which can maintain a floating force for over 12 hours. As compared with solid beads, which gives a short residence time of 1 hour, these floating beads give a prolonged residence time of more than 5.5 hours.

(IV) HOLLOW MICROSPHERES

Hollow microspheres (microballons), loaded with drug in their outer polymer shells are another technique prepared by a novel emulsion solvent diffusion method. In this system the microballons formed floats continuously on the surface of acidic dissolution media containing surfactant for more than 12 hours.

Dynamics in GI Tract

The gastrointestinal tract is always in the state of continuous motility. There are two modes of motility pattern, the digestive mode and the interdigestive mode involved in the digestion of food.[19]

The interdigestive gastrointestinal motility is characterized by a cyclic pattern that originates in the foregut and propagates to the terminal ileum and consists of four distinct phases.

- Phase I (Basal phase) is a period of no contraction and it lasts from 40 to 60 minutes.
- Phase II (Preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (Burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

A complete cycle of these four phases has an average duration of 90 – 120 minutes. Certain disease states such as bacterial overgrowth, mental stress and diurnal variations, or their combinations, can influence the duration of each individual phase as well as the total cycle.[20,21] Phase III as a house keeping role and serves to clear all undigested materials from the stomach to the small intestine. Any sustained release gastrointestinal drug delivery system designed to stay during the fasted state should be capable of resisting the house keeping action of phase III if one intend to prolong the gastrointestinal retention time. The

bioadhesive properties added to the gastrointestinal drug delivery system must be capable of adhering to the mucosal membrane strongly enough to withstand the shear forces produced in this phase.

Gastrointestinal Transit

The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a sustained release gastro retentive drug delivery system. The patterns of gastrointestinal transit depend on whether the person is in a fasted or fed state. In addition the physical state of the drug delivery system, either a solid or a liquid, also influences the transit time through the gastrointestinal tract.

Factors Controlling Gastric Retention Time of a Dosage Form

The gastric retention time of dosage form is controlled by several factors, which affect their efficacy as a gastro retentive system, they are,

- **DENSITY**

Gastro retentive time is a function of dosage form buoyancy that in turn depends on the density difference of dosage form in the environment.

- **SIZE OF DOSAGE FORM**

Dosage form units with a diameter of more than 9.5 mm are reported to have an increased gastro retentive time.

- **SHAPE OF DOSAGE FORM**

Tetrahedron and ring shaped device with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better gastro retentive time, 90% to 100% retention at 24 hours compared with other shapes.

- **SINGLE OR MULTIPLE UNIT FORMULATION**

Multiple unit formulation show a more predictable release profile as impairing of performance due to failure of a little fraction of such units give insignificant influence compared to single unit systems. They allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **FED OR UNFED STATE**

Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or the migrating myoelectric complex (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 then the formulation shall also be swept to the small intestine reducing gastric transit time considerably.

- **NATURE OF MEAL**

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

- **CALORIC CONTENT**

Gastro retentive time can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

- **FREQUENCY OF FEED**

The gastro retentive time can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

- **AGE**

Elderly people, especially those over 70, have a significantly longer gastro retentive time.

- **POSTURE**

Gastro retentive time can vary between supine and upright ambulatory states of the patient.

- **CONCOMITANT DRUG ADMINISTRATION**

Anti-cholinergic like Atropine, opiates like Codeine and prokinetic agents like Metoclopramide increase the gastro retentive time when concomitantly administered with the dosage forms.

CONCLUSION

Floating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. The dosage form had a good balance over disintegration time and mechanical strength.

REFERENCES

1. Millar-Craig M *et al*. Circadian variation of blood pressure. *Lancet,* 1978; 1: 795–797.
2. Mancia G *et al*. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res*, 1983; 53: 96–104.
3. Beevers G *et al*. The pathophysiology of hypertension. *BMJ,* 2001; 322: 912–916.
4. Kearney PM *et al*. Global burden of hypertension: analysis of worldwide data. *Lancet,* 2005; 365: 217–223.

5. Pickering T *et al*. Recommendations for blood pressure measurement in humans and experimental animals.Part 1: blood pressure measurement in humans. *Hypertension,* 2005; 45: 142–161.
6. Lachman L., Liberman H.A., kanig J.L. The Theory and Practice of Industrial Pharmacy, Lea and Fibiger, Philadelphia, 1989; 293-345.
7. Aulton M.E. Pharmaceutics, The Science of Dosage Form Design, 2nd (ed), Churchil Livingstone, 2002; 199-206.
8. Chien, Y. W., 2003, "Oral drug delivery" in Novel drug delivery systems, 2nd ed., Revised and Expanded, Informa health care USA Inc., New York., 50: 139-196.
9. Banker, G.S, and Rhodes C.T., 1996, "Modern Pharmaceutics", 3rd ed., Marcel Dekker, New York, 678-721.
10. Menon, A., Ritschel, W.A., and Sakr, A., 1994, "Development and evaluation of a monolithic floating dosage form for Furosemide", J. Pharm. Sci., 83: 239–245.
11. Malcolm, S.L., Allen, J.G., Bird, H., Quinn, N.P., Marion, M.H., Marsden, C.D., and O'Leary C.G., 1987, "Single-dose pharmacokinetics of Madopar HBS in patients and effect of food and antacid on the absorption of Madopar HBS in volunteers", Eur. Neurol., 21: 28–35.
12. Singh, B.N., and Kim, K.H., 2000, "Floating drug delivery systems: an approach to oral controlled drug delivery systems via gastric retention", J. Cont. Rel, 63: 235-259.
13. Ichikawa, M., Watanabe, S., and Miyake, Y., 1989, "Granule remaining in stomach", U.S patent 4844905. July, pp.4.
14. Dave, B.S., Amin, A.F., and Patel, M., 2002, "Gastroretentive drug delivery system of ranitidine HCl formulation and in vitro evaluation", AAPS Pharm. Sci. Tec., 5: 1-10.
15. Mastiholimath, V.S., Dandagi, P.M., Gadad, A.P., Mathews, R., and Kulkarni, A.R., 2008, "In vitro and in vivo evaluation of ranitidine hydrochloride ethyl cellulose floating microparticles", J. microencapsulation, 1-8.
16. Kopitar, Z., Vrhovac, B., Povsic, L., Plavsic, F., Francetic, I., and Urbancic, J.S., 1991, "The effect of food and metoclopramide and side effects of bromocriptine", Eur. J. Drug Metab. Pharmacokinet, 16: 177–181, 216.
17. Yang, L., Eshraghi, E., and Fassihi, R., 1999, "A new drug delivery system for the treatment of Helicobacter pylori associated gastric ulcers: in vivo evaluation", J. Controlled Release, 57: 215- 222.

18. Rajnikanth, P.S., Balasubramnium, J., and Mishra, B., 2007. "Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of H. pylori", Int. J. Pharm., 335: 114-122, 2007. 3.061
19. Quigly, E.M.M., Phillips, S.F., and Dent, J, 1984, "Distinctive patterns of interdigestive motility at the canine ilio-colonic junction", Gastroenterology, 87: 836.
20. Kellow, J.E., Borody, T.J., Philips, S.F., Tucker, R.L., and Hadda, A.C., 1986, "Human interdigestive motility: Variations in patters from esophagus to colon" Gastroenterology, 91: 386.
21. Mc Rae, S., Younger, K., Thompson, D.G., and Wingate, D.L., 1982, "Sustained mental stress alters human jejuna motor activity", Gut., 23: 404.