ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2011; 2(6):1561-1568

REVIEW ARTICLE

A Review On: Recent Advancement of Stomach Specific Floating Drug Delivery System

Shukla Shruti*, Patidar Ashish, Agrawal Shikha, Choukse Raju

Swami Vivekanad College of Pharmacy, Indore, M.P, India

Received 25 Aug 2011; Revised 22 Oct 2011; Accepted 28 Oct 2011

ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed.

Key words: Floating Drug Delivery System, Floating Systems, Effervescent Systems, Non-Effervescent Systems.

1. Introduction

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance. Oral drug delivery remains the most user friendly form of drug delivery, having the highest degree of patient compliance, and still the preferred route of drug administration. As such, drugs for chronic conditions are often administered orally for ease of long-term use. Drugs that are easily absorbed from the gastrointestinal tract and having short biological half-life are eliminated quickly from the blood circulation. An incomplete release of the drug and shorter residence time of the dosage form in the upper gastro intestinal tract, a prominent site for the absorption of the many drugs, will lead to lower bioavailability .Therefore, prolonged gastric retention is important in achieving control over the gastro retention time because this helps to retain the controlled release system in the stomach for a longer and predicted time.

Drugs that require to be designed as gastro retentive systems are those acting locally in stomach, primarily absorbed from the stomach, poorly soluble in alkaline pH, absorbed rapidly from the gastrointestinal tract, and that degrades in the colon .Small size tablets leave the stomach during the digestive phase while large size tablets are emptied during the house keeping waves . Floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the non floating units, which lie in the antrum region and are propelled by the peristaltic waves.

***Corresponding Author:** Shruti shukla**, Email:** shruti17new@gmail.com

IJPBA, Nov - Dec, 2011, Vol. 2, Issue, 6

Various approaches have been worked out to improve absorption of an oral dosage form in stomach. High density systems whose action is based on their dipping to the bottom of the stomach. Systems attaching to the mucus membrane are bioadhesive systems are retained in the stomach due to their ability to stick to and stay on the surface of the mucus membrane of the stomach .Intra gastric floating systems are based on the phenomenon of drug floating in the gastric contents. There are three possible techniques to rendered drug floating. Gas contains floating systems: generation of co_2 via chemical reaction between sodium bicarbonate and hydrochloric acid of gastric juice. The gas kept in the stomach ensures its floatation. Thus prolongs the period of drug occurring in the stomach. Systems with low density core not subject to rapid chemical and physical changes, providing for the drug floatation. The core is coated with a gel or other polymeric shells from which drug are gradually released.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT).Dosage form with a prolonged GRT ,i.e. gastro retentive dosage form (GRDFs), will provide us with new and important therapeutic options .To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems[2].

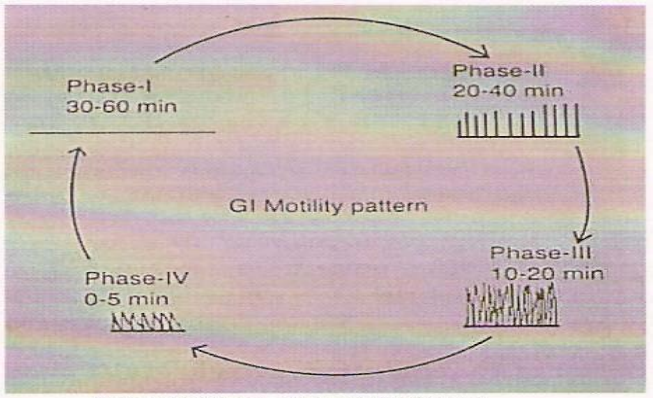
The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. The retentive characteristics of the dosage form are not significant for the drugs that

1) Are insoluble in intestinal fluids
2) Act locally
3) Exhibit site-specific absorption

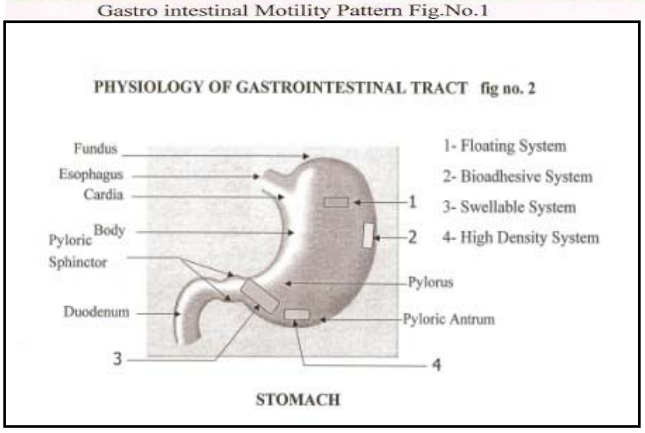
2. Physiology of the Stomach:

The gastrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organised in cycles of activity and quiescence [4].



Gastro intestinal Motility Pattern Fig.No.1



Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the

GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions.

The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food [5].

The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal [6].

Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids≤7mm can empty from the fed stomach in humans.

3. Salient Features of Upper Gastrointestinal Tract:

Section	Length (m)	Transit time(h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I,

P – Passive diffusion; C – Aqueous channel transport; A – Active transport; F – Facilitated transport;
I – Ion-pair transport; E – Entero-or pinocytosis ; CM – Carrier mediated transport

4. Different Features of Stomach

Gastric pH: Fasted healthy subject 1.1 ± 0.15
Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 ml

Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mol of hydrogen ions per hour.

Effect of food on Gastric secretion: About 3 liters of secretions are added to the food. Gastro intestinal transit time.

5. Requirements for Gastric Retention:

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

6. Drugs that could take advantage of gastric retention include:

Furosemide, cyclosporine, allopurinol ciprofloxacin and metformin. Drugs whose solubility is high in the stomach then intestine (e.g. chlordiazepoxide and cinnarizine) the drugs prone for degradation in the intestinal pH (e.g. captopril), and the drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention.

7. Based on the mechanism of buoyancy FDDS can be classified into

A. Single Unit Floating Dosage Systems
   a) Effervescent Systems (Gas-generating Systems)
   b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems
   a) Non-effervescent Systems
   b)Effervescent Systems (Gas-generating Systems)
   c) Hollow Microspheres

C. Raft Forming Systems

8. Floating Systems:

Floating systems, first described by Davis in 1968,have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolong period.

A. Effervescent Systems:

a. Volatile liquid containing systems:

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 PVA, 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[14].

b. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme [1,17,40]. How the dosage form float is shown in the following figure.

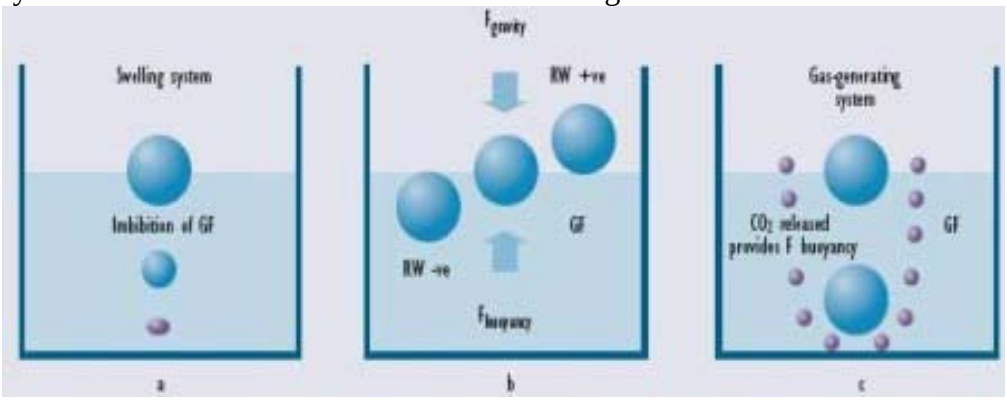


Figure 3: The Mechanism of Floating Systems [19]

B. Non-effervescent systems:

a. Colloidalgel barrier systems

Hydrodymamically balance system (HBS^{TM}) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g.HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms [16].

b. Microporous Compartment System:

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

3. Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating fource over 12 hours [14,16].

4. Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ehanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro [16].

Factors Affecting Gastric Retention

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kiloponds per square inch (KSI) are reported to have better GIT @ 90 to 100 % retention at 24 hours compared with other shapes [1].

Fed or Unfed State

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 longer.[12,12]

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 release.[18]

Caloric Content

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

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 MMC [16].

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 surface.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.[20]

Posture [19].

GRT can very between supine and upright ambulatory states of the patients

Concomitant drug administration

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Advantages of Gastroretentive Drug Delivery System

Gastro retentive drug delivery systems have numerous advantages listed below:

- 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.
- 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.
- The principle of HBS can be used for any particular medicament or class of medicament.
- 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.
- 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.
- 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.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
- 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 intestine.
- Certain types of drugs can benefit from using 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; and
- Drugs those degrade in the colon.

DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3) Other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.
4) Not suitable for drugs that have solubility or stability problem in GIT.
5) Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
6) Not suitable for drugs that have solubility or stability problem in GIT.
7) Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.

MARKETED PRODUCTS OF GRDDS

Some of the marketed formulations are listed as follows: (Kormeyer, R.W., 1983)

Marketed Products of GRDDS

Brand name	Delivery system	Drug (dose)	Company name
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche,
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flot coat®	Floating dosage form	Al – Mg antacid	----------
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS

Weight variation:

Uniformity of Weight according to Indian pharmacopoeia, 20 tablets were selected at random, weight together and individually for the determination of weight of tablets. The mean and standard deviations were calculated.

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric Compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

Thickness:

Thickness and diameter of ten tablets were measured using vernier calipers.

Friability

Friability The friability test was carried out in Roch Friabilator. Ten tablets were weighted (Wo) initially and put in a rotating drum. Then the tablets were subjected to 100 falls of 6 in. height. After completion of rotation, the tablets were again weighted (W).

% Weight loss or friability (f) = $(1 - w/w_0) \times 100$

Disintegration time

In vitro disintegration time was determined using disintegration test apparatus. For this, a tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured.

Buoyancy time

A tablet was introduces in to beaker containing 100ml of 0.1N HCL. The time taken by the tablet to come up to the surface and floated was taken as the buoyancy time. An average of three

determinations from of batch was taken for the floating forms.

Floating time and dissolution:

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37^0C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit-1 HCl as the dissolution medium at 37^0C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

Drug release:

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Content uniformity

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of solvent, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically in UV.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

ACKNOWLEDGMENT

We are thankful to swami Vivekanand College of pharmacy, Indore for providing me knowledge about project work. We are also thankful to Dr. shikha agrawal who generously shared her wisdom and expertise with me & has provided me an excellent guidance and general interest.

REFERENCES

1. Baumgartner, S., Kristl, J., Vrecer, F., Vodopivec, P., Bojan, Z., 2008. Optimisation of floating matrix tablets and evaluation of their gastric residence time, European Journal of Pharmaceutics and Biopharmaceutics. 69, 708–717.
2. Fukuda, M., Nicholas A. P., James, W. M., 2003. Floating hot-melt extruded tablets for gastroretentive controlled drug release system, European Journal of Pharmaceutical Sciences 18, 37–45.
3. Sauzet, C., Brunob, M.C., Nicolasc, M., Kister, J., Piccerelle, P., Prinderrea, P. 2009. An innovative floating gastro retentive dosage system: Formulation and in vitro evaluation; International Journal of Pharmaceutics. 378, 23-29.
4. Sandra, S.B., Tamara, A., Renata, V. C., Hendrik, M., Karsten, M. (2008). New insights on poly (vinyl acetate)-based coated floating tablets: Characterisation of hydration and CO2 generation by benchtop MRI and its relation to drug release and floating strength. European Journal of Pharmaceutics and Biopharmaceutics. 69,708-717.
5. Sangekar, S., Vadino, W.A., Chaudry, I., Parr, A., Beihn, R., and Digenis, G.,1987.Evaluation of the effect of food and specific gravity of tablets on gastric retention time, International Journal Pharmaceutics. 35,187-191.
6. Singh, B.N., Kim, H.K. 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled Release, 63,235–259
7. Chavanpatil, M.D., Jain, P., Chaudhari, S., Shear, R., Vavia, P.R. 2006. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin International Journal of Pharmaceutics. 316, 86–92
8. M. Rosa JimCnez-Castellanos , Zia, H., Rhodes, T.C. 1994. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application, International Journal of Pharmaceutics. 105,65-70.
9. Sungthongjeen, S., Paeratakul, O., Limmatvapirat, S., Puttipipatkhachorn, S. 2006 Preparation and in vitro evaluation of a multiple-unit floating drug delivery system based on gas formation technique, International Journal of Pharmaceutics. 324, 136–143.
10. Shoufeng, L., Senshang, L., Daggy, D.P., Mirchandani, H.L., Chien, Y.W. 2003. Effect of HPMC and Carbopol on the release and floating properties of Gastric

Floating Drug Delivery System using factorial design, International Journal of Pharmaceutics. 253, 13–22.

11. Nakamichi, K., Yasuura, H., Fukui, H., Oka, M., Izumi, S. 2008. Evaluation of a floating dosage form of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate prepared using a twin-screw extruder,International Journal of Pharmaceutics. 218, 103–112.
12. Ali, J., Arora, S., Ahuja,A., Babbar,K.A., Sharma,K.R., Khar,K.R., Baboota,S., European Journal of Pharmaceutics and Biopharmaceutics ,Formulation and development of hydrodynamically balanced system for metformin In vitro and in vivo evaluation, 67 (2007) ,196–201.
13. Karim, F., Roeri, C.S., Saphier, D. 1996. Role of 5 –Hydroxytryptamine(5SHT3) Antagonists in the Prevention of Emesis Caused by Anticancer Therapy, Biochemical Pharmacology. 52,685-692.
14. King, G.R., Xiong, Z., Ellinwood, E.H. 1999. Blockade of accumbens 5-HT receptor down-regulation by ondansetron administered during continuous cocaine administration European Journal of Pharmacology. 364, 79–87.
15. Tullberg, S., Ondansetron. 2007. University of Southampton.
16. Shah S.H., Patel J.K., Patel N.V. International Journal of PharmTech Research Coden(Usa): Ijprif Issn : 0974-4304vol.1, No.3, Pp 623-633 , July-Sept 2009.
17. Klausner, E.A., Lavy, E., Michael, F., Hoffman, A. 2003. Expandable gastroretentive dosage forms, Journal of Controlled Release. 90, 143–162.
18. Lachman Leon, Liberman H.A. and Kanig J.L. “The Theory and Practice of Industrial Pharmacy” (3rd Edn.), Varghese publishing House Bombay, 443-453.171.
19. Tripathi, K.D., In: Essentials of medical pharmacology, 2008 6th edition. JAYPEE Brothers Medical Publishers Ltd. New Delhi. 214.
20. Robinson, J., Lee, R., In Controlled drug delivery. 1987. 2nd edition, 418.
21. Florey, K., 1987. Analytical profile of drug substances, Academicpree, Florida, l-9, 87.
22. Chien, Y.W., Novel drug delivery system, Marcel Dekker, 2nd Edi. Rev. Expand., 50, 139-196.
23. Cremer, K., Drug delivery: gastro-remaining dosage forms, The Pharm. Journal 1997, 259, 108.
24. Garg, S., Shringi, S., Gastroretentive drug delivery systems, Business briefing, Pharmatech, 5th edition, Available on: http://www.touchbriefings.com, 160-166.