



Received on 21 July, 2014; received in revised form, 30 October, 2014; accepted, 12 December, 2014; published 01 April, 2015

MULTIUNIT FLOATING DRUG DELIVERY SYSTEM A SIGNIFICANT TOOL FOR THE TREATMENT OF PEPTIC ULCER DISEASE

Pradeep Singh¹, Vikash Kumar Chaudhari^{*2}, Praveen Kumar Verma², Amit Kumar Singh² and Vijay Kumar Yadav²

Department of Pharmacy¹, Kalish Institute of Pharmacy & Management, Gorakhpur- 273209, Uttar Pradesh, India.

Department of Pharmacy², Kunwar Haribansh Singh College of Pharmacy, Jaunpur- 222001, Uttar Pradesh, India.

Keywords:

Single unit and multiunit floating microspheres, Gastroretentive drug delivery system, Floating drug delivery system

Correspondence to Author:

Vikash Kumar Chaudhari

Assistant Professor
Department of Pharmacy, Kunwar Haribansh Singh College of Pharmacy, Jaunpur- 222001, Uttar Pradesh, India.


E-mail: vikashk464@gmail.com

ABSTRACT: The gastroretentive drug delivery system has been utilized to obtain prolonged and uniform release of drug in stomach. Thus increase bioavailability and decrease the administration frequency. A peptic ulcer is a break in the lining of the stomach, esophagus or duodenum. Peptic ulcer may be due to H. Pylori bacteria, acid of the stomach cell or nonsteroidal anti-inflammatory drugs (NSAIDs). The gastroretentive drug delivery system may be single unit (floating tablet) or multiunit system (floating microspheres). The single unit floating system is more popular but has the disadvantage that its purpose would not be achieved if it fails to float or rapidly emptied from stomach. The multiunit floating system may be better because they reduce inter subject variability in absorption and also lower the probability of dose dumping. Thus, the purpose of preparing multiunit dosage form is to be developing suitable formulation and has all the advantage of a single unit dosage form and also devoid of disadvantage of single unit formulation.

INTRODUCTION: Historically, oral drug delivery systems are the most popular drug delivery system but these systems have some, limitation such as, patient incompliance due to frequent drug administration, undesirable side effect due to fluctuating plasma drug level, inability to maintain adequate drug concentration in plasma for therapeutic effect, larger dose than required dose¹.

This limitation can be overcome by modifying existing drug delivery systems (DDSs). An appropriately designed sustained release (SR) or controlled release DDS can be a major step toward solving the problem associated with conventional DDSs². Oral controlled release (CR) dosage forms (DFs) have been developed for the past three decades due to their considerable therapeutic advantages³.

However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine. This is due to the relatively short transit time of the DF in these anatomical segments. Thus,

QUICK RESPONSE CODE	DOI:
	10.13040/IJPSR.0975-8232.6(4).1351-62
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1351-62	

after only a short period of less than 2-3 h, the CR-DF has already left the upper gastrointestinal tract and the drug is released in nonabsorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability.

The medications that are included in the category of narrow absorption window are mostly associated with improve absorption at the jejunum and ileum due to their enhanced absorption properties, e.g. huge surface area⁴. It was suggested that preparing narrow absorption window drugs in a unique pharmaceutical DF with gastro retentive properties would enable an extended absorption phase of these drugs⁵.

Anatomy and Physiology of the Stomach:

The gastrointestinal tract is a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix and colon). Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml 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, inter-digestive motility pattern and digestive motility pattern (**Fig. 1**).

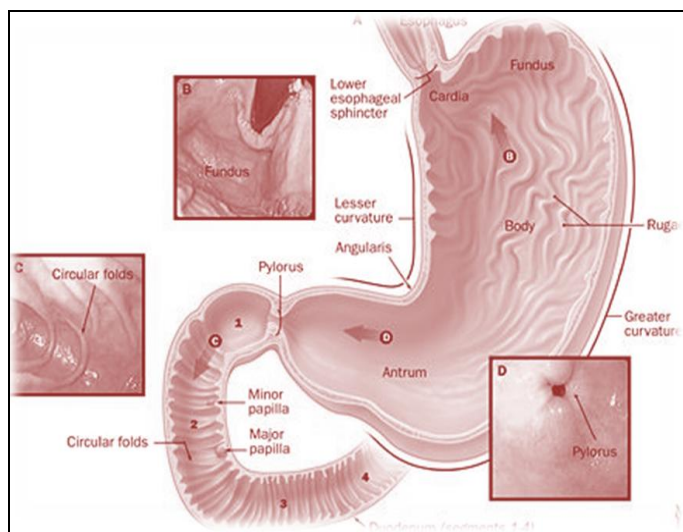


FIG. 1: ANATOMY AND PHYSIOLOGY OF THE STOMACH

The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter-digestive motility pattern is commonly called the 'migrating motor complex' (MMC) and is organized in cycles of activity and quiescence⁶. Anatomically, the stomach is divided into 3 regions: fundus, body, and antrum (pylorus).

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions⁷. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours⁸. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington⁹.

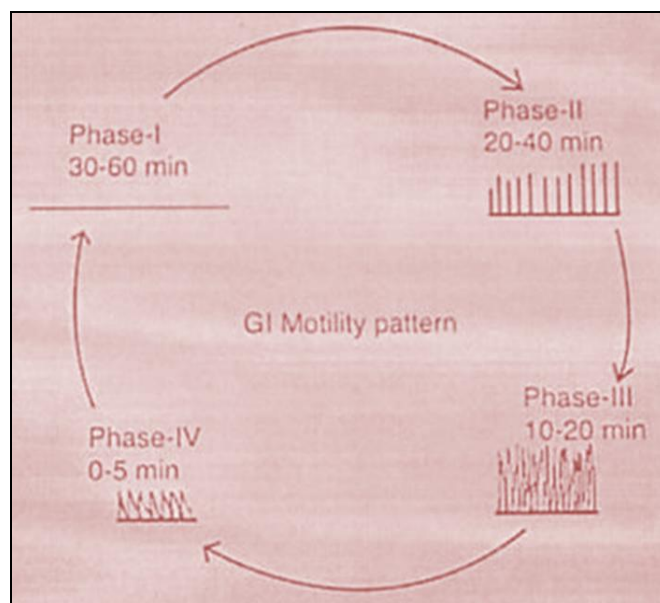


FIG. 2: GASTROINTESTINAL MOTILITY PATTERN

- Phase I** (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II** (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. 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 (**Fig. 2**).

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the

pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate¹⁰ (**Table 1**).

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 mmol of hydrogen ions per hour (**Table 2**).

TABLE 1: SALIENT FEATURES OF UPPER GASTROINTESTINAL TRACT

Section	Length (m)	Transition time (h)	pH	Microbial count	Absorbing surface area(m ²)	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, E, CM

P – Passive diffusion

A – Active transport

I – Ion-pair transport

CM – Carrier mediated transport

C – Aqueous channel transport

F – Facilitated transport

E – Entero or pinocytosis

TABLE 2: THE TRANSIT TIME (TT) OF DIFFERENT DOSAGE FORMS ACROSS THE SEGMENT OF GI TRACT¹¹

Dosage form	Transit time(h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellet	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0

Gastroretentive drug delivery systems:

Dosage forms that can be retained in the stomach for longer period of time are called gastroretentive drug delivery systems (GRDDS)¹². Gastroretentive floating drug delivery systems (GRFDDS) have a density lower (<1gm/dl) than that of gastric fluids (1.04gm/ml) and thus, remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time¹³. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system.

On the basis of configuration, the gastroretentive floating drug delivery systems may be single and multiunit. Single unit floating system is more popular but has the disadvantage that its purpose would not be achieved if it fails to float, or is rapidly emptied from the stomach since there is

high variability of GIT transit time¹⁴. On the other hand multiple units floating system may be better suited because they are claimed to reduce inter subject variability in absorption and also lower the probability of dose dumping¹⁵.

Multiunit Floating Systems:

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit dosage form and also is devoid of disadvantages of single-unit formulations. In pursuit of this endeavour many multiple-unit floatable dosage forms like microspheres, microbeads, and microcapsules etc. have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatine, starch, polymethacrylate, polyacrylamine, and

polyalkylcyanoacrylate. Spherical polymeric microspheres also referred to as “microballoons,” have been prepared.

Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In carbon dioxide-generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded Reports have been found on the development of both non-effervescent and effervescent multiple unit systems^{16,17}.

Advantages of Multiunit System:

Multiunit system provides constant and prolonged therapeutic effect, which will reduce the dosing frequency and thereby improve the patient compliance. They could be injected in to the body due to the spherical shape and smaller size¹⁸. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects. Many authors have reported that nanoparticles and microparticles have a tendency to accumulate in the inflamed areas of the body.

It was reported that multiunit system reduces the GI toxic effects, exhibit sustained action and of course increase patient and therapeutic compliance. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as nondisintegrating, polymeric matrix tablets^{19, 20}.

Potential Drug Candidates for GRFDDS:

1. Narrow absorption window in GI tract e.g. Riboflavin, Levodopa and Furosemide²¹.
2. Drug those are unstable in the intestinal or colonic environment e.g. Captopril, Metronidazole, Ranitidine HCl etc²¹.

3. Drug that disturb normal colonic bacteria, e.g. Antibiotic against *Helicobacter pylori*²¹.
4. Drug that act locally in the stomach, e.g. Antacid and Misoprostol.
5. Primarily absorb from stomach and upper part of GI tract e.g. calcium supplement, chlordiazopoxide etc²¹.
6. Drug that exhibit low solubility at high pH value e.g. diazepam, chlordiazepoxide, virapamil HCl etc²¹.

Unsuitable Drug Candidates for GRFDDS:

1. Drug that have very limited acid solubility e.g. Phenytion.
2. Drug that degrade in gastric environment e.g. Erythromycin.
3. Drug intended for selective release in the colon e.g. 5-Amino salicylic acid etc.²²

Approaches for Gastric Floating Drug Delivery Systems (GRFDDS):

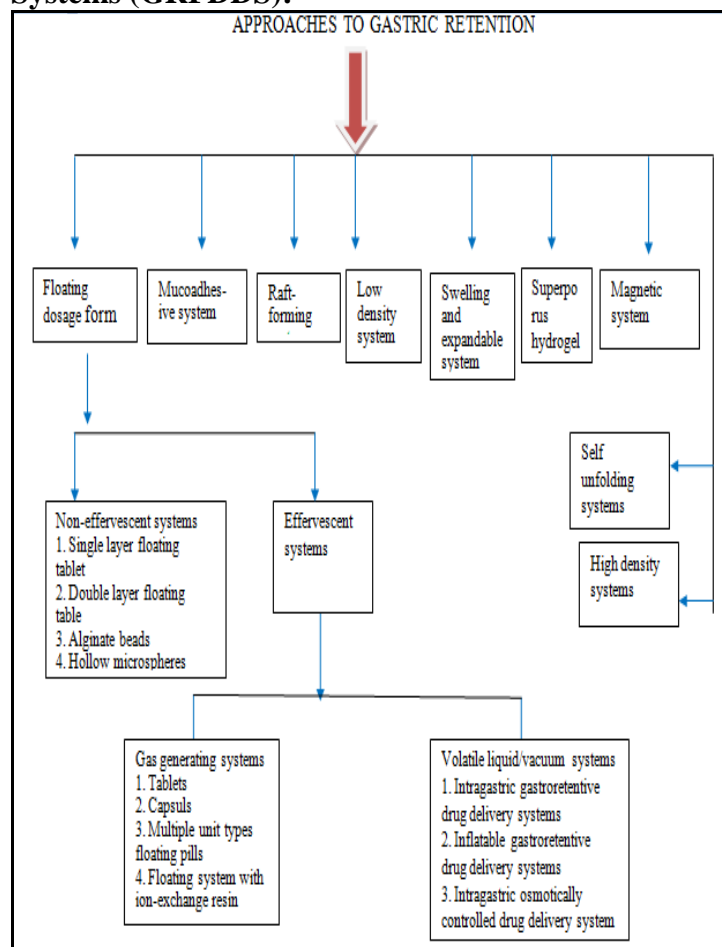


FIG. 3: APPROACHES TO GASTRIC RETENTION

Floating Drug Delivery System Are Of Two Types:

1. Effervescent systems
2. Non-effervescent systems

Effervescent Systems:

A. System containing volatile liquid:

The gastric retention time of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a volatile liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation 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 stomach²³.

B. Gas-generating Systems:

These systems utilize the reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the jellified hydrocolloid layer of the systems that decreasing the specific gravity of the system and thus it float over chime^{24, 25}. These buoyant systems utilize matrices prepared with swellable polymers (methocel, polysaccharides (chitosan), effervescent components (sodium bicarbonate), citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature²⁶. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose.

The ethylcellulose, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and

floating systems based on ion exchange resin technology, etc.²⁷ (Fig. 4 and 5).

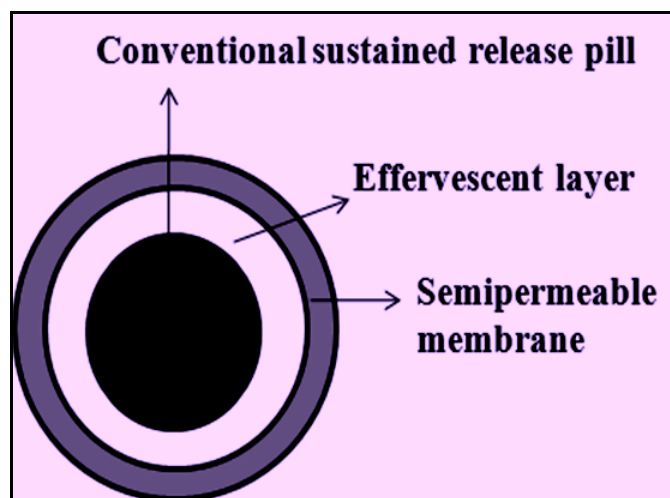


FIG. 4: EFFERVESCENT (GAS GENERATING) SYSTEMS

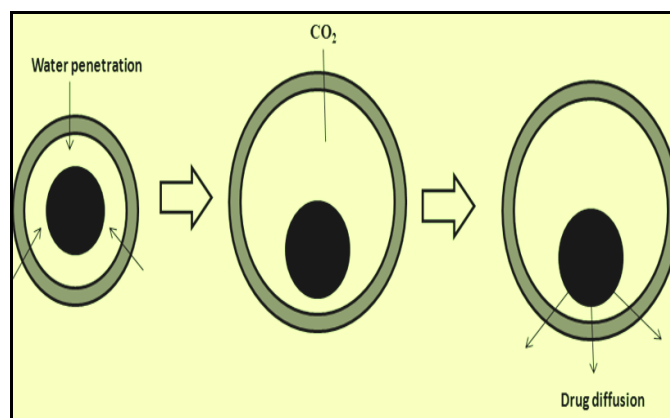


FIG. 5: DRUG RELEASE FROM EFFERVESCENT (GAS GENERATING) SYSTEMS

2. NON-EFFERVESCENT SYSTEMS

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment²⁸. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol²⁹.

A. Colloidal gel barrier systems:

Hydrodynamically balance system (HBS) 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, Na-CMC, Polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. 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 this dosage form³⁰.

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 absorption³¹.

C. Alginate beads:

It is a multiple-unit floating system based on cross-linked beads. They were made by using Ca²⁺ and low methoxylated pectin (anionic polysaccharide) or Ca²⁺ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs^{32,33}.

D. Hollow microspheres:

Microballoons/hollow microspheres loaded with drugs in their other polymer shelf were prepared by

simple solvent evaporation or solvent diffusion / evaporation methods³⁴ (Fig. 6) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours³². At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating (Fig. 6).

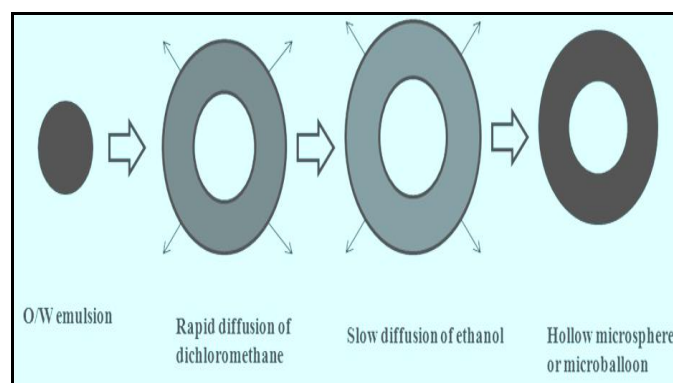


FIG. 6: FORMULATION OF FLOATING HOLLOW MICROSPHERE OR MICROBALLOON

Factor affecting Gastric Retention of Dosage Form:

The most important parameter that affect the gastric retention time of oral dosage form include; density, size and shape of dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index physical activity and disease state of individual (e.g. chronic disease, diabetes etc.)³⁵.

Density of Dosage Form:

Dosage form having a density lower than the gastric content can float on surface, while high density system sink to bottom of stomach³⁶. Density of 1.0gm/cm³ is required to exhibit floating property³⁷.

Shape and Size of the Dosage Form:

Dosage form having a diameter of more than 7.5mm show a better gastric residence time

compared with one having 9.9 mm³⁸. Ring shaped and tetrahedron shaped device have a better gastric residence time as compared with other shape³⁹.

Effect of Gender Posture and Age:

Generally female have slower gastric emptying rate than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individual in upright, ambulatory and supine state. In case of elderly person gastric emptying is slowed down⁴⁰.

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 form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drug absorption increase by allowing its stay at absorption site for long period. Increase in acidity and caloric value shows down gastric emptying time (get) which can improve the gastric retention of dosage form⁴¹.

Microspheres:

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core and solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 μ m. Microspheres having the following advantages-

1. Improves patient compliance by decreasing dosing frequency.
2. Enhances bioavailability.
3. Gastric retention time is increased due to buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach
5. Drug releases in controlled manner for prolonged period.

6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms because microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

Disadvantages of floating microspheres:

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. Tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

Mechanism of floating microspheres:

Swollen polymer lowers the density and confers buoyancy to the When floating microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the microsphere and consequent drug release.

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 microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy^{42, 43} (**Fig. 7**).

$$F = F \text{ buoyancy} - F \text{ gravity} = (D_f - D_s) gv \quad (1)$$

Where, F= total vertical force, D_f = fluid density, D_s = object density, v = volume and g = acceleration due to gravity

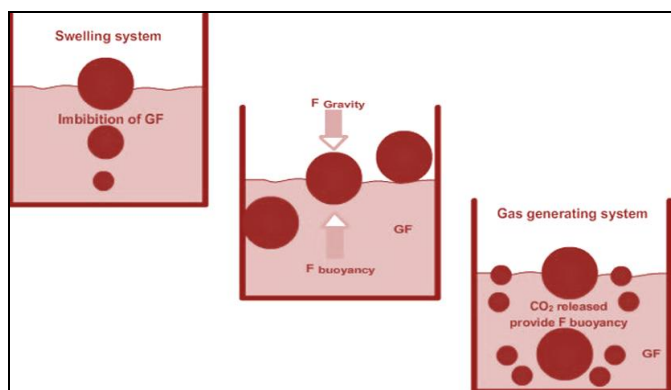


FIG. 7: MECHANISM OF FLOATING SYSTEMS, GF= GASTRIC FLUID

Methods of Microspheres Preparation:

Following are various methods of microspheres preparation;

A). Single Emulsion Technique:

The floating microspheres of natural polymers like proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium then it dispersed in non-aqueous medium like oil with the help of cross linking agent^{44, 45} (Fig. 8).

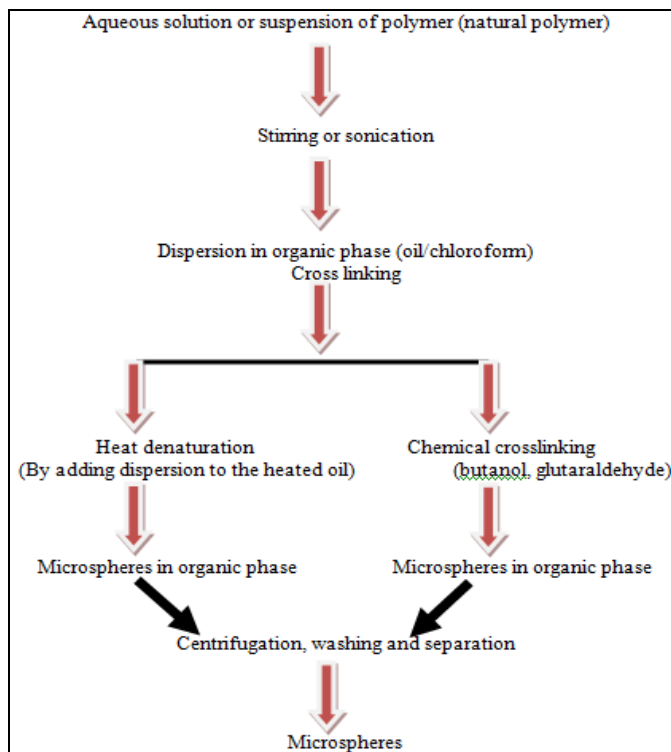


FIG. 8: SINGLE EMULSION TECHNIQUE

B). Double Emulsion Technique:

Double emulsion method of microspheres preparation involves the formation of the multiple

emulsions or the double emulsion such as w/o/w. This method can be used with the natural as well as synthetic polymer^{44, 45} (Fig. 9).

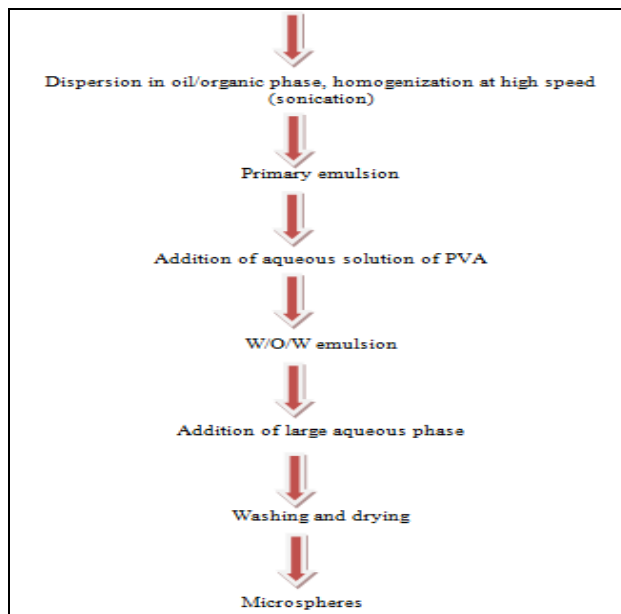


FIG. 9: DOUBLE EMULSION TECHNIQUE

C). Phase separation coacervation technique:

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer^{44, 45} (Fig. 10).

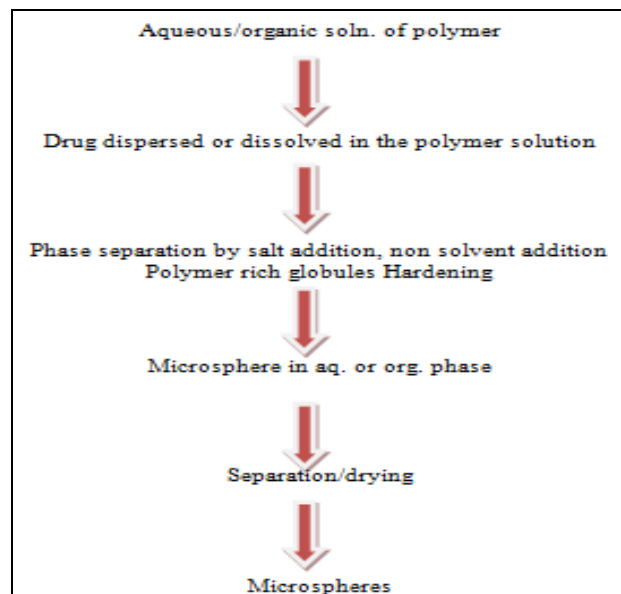


FIG. 10: PHASE SEPARATION COACERVATION TECHNIQUE

D). Spray Drying and Spray Congealing:

These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm . Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively^{44, 45} (Fig. 11).

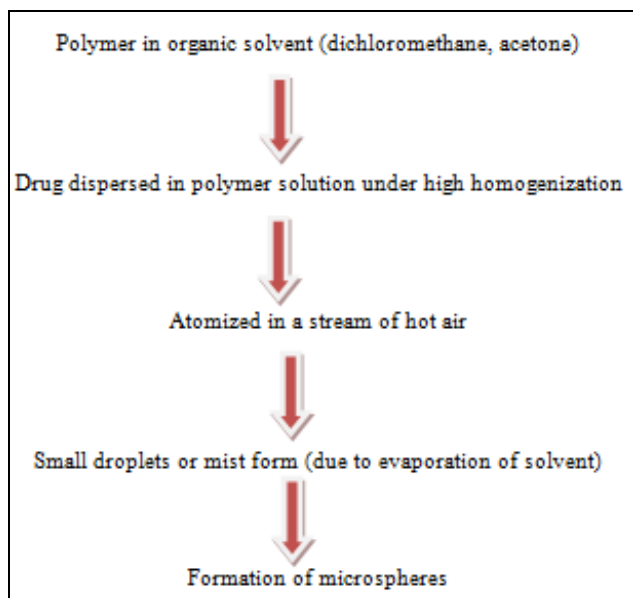


FIG. 11: SPRAY DRYING

E). Emulsion solvent evaporation:

This method involves removal of the organic phase by evaporation of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by evaporation with water. In order for the microsphere to form, the organic solvent must first diffuse into external phase and then evaporate at the water air Interface^{44, 45}. As solvent evaporation occurs, the microspheres harden and free flowing microspheres can be obtained after suitable filtration and drying. This process decreases the hardening time for the microspheres. The rate of solvent removal by evaporation method depends on the temperature of water, ratio of emulsion volume

to the water and the solubility profile of the polymer⁴⁶.

F). Ionic gelation:

Gonzalez-Rodriguez ML et al. reported alginate/chitosan particulate systems for Diclofenac sodium release by ionic gelation (Ca^{2+} and Al^{3+}). 25% w/v of the drug was added to 1.2% w/v aqueous solution of sodium alginate. The solution was stirred till a complete solution was formed. This solution was added drop wise to a solution containing Ca^{2+} or Al^{3+} and chitosan solution in acetic acid which results into formation of microspheres⁴⁷.

G). Hot melt encapsulation method:

Lin WJ and Kang WW compared the performance of Indomethacin microparticles and their release properties after coating with chitosan and gelatin, respectively. Here the poly (epsilon-caprolactone) (PCL) microparticles were prepared by the hot-melt encapsulation method. This method is having a disadvantage that thermo-labile substances cannot be used⁴⁸.

Evaluation parameter of floating microspheres:**1. Particle size determination:**

The particle size of the microspheres was determined with an optical microscope under regular polarised light, and mean particle size was calculated by measuring 100 microspheres with the help of a calibrated oculometer⁴⁹.

2. Tapped density:

Tapping method was used to calculate tapped density. The volume of a weighed quantity of the microspheres was determined, after 100 taps, using a tapped density apparatus.

$$DT = MT/VT \quad (2)$$

Where DT = tapped density, MT is mass of microspheres and VT = volume of microspheres after tapping.

3. Carr's (Compressibility) index:

This parameter was calculated from bulk density (the ratio of weighed quantity of microspheres to its volume),

$$\text{Compressibility index} = (DT - DP)/DT \times 100 \quad (3)$$

4. Angle of repose:

The angle of repose, $\tan\theta$, of the microspheres, which measures resistance to particle flow, was determined by the fixed funnel method⁴¹ and calculated as

$$\tan \theta = S/D \quad (4)$$

Where S = surface area of the free standing height of the microspheres heap and
D = diameter of the heap.

5. Scanning electron microscopy:

Scanning electron microscopy (SEM) studies were performed to determine the porous/hollow nature of the microspheres. Surface morphology of microspheres was also noted.

6. Drug loading:

The drug content of the floating microspheres was carried out by dissolving the microspheres in a small amount of suitable solvent in a separating funnel and extracting the drugs into 0.1N HCl by evaporating the solvent. Determination of drug loading was carried out suitable analytical technique.

7. In-vitro floatability:

In-vitro floatability studies on floating microspheres were carried out using USP XXIV dissolution apparatus II⁵⁰. The microspheres were placed in 0.1M hydrochloric acid containing 0.02 % v/v Tween 80 with the paddle rotating at 100 rpm for 12 h. The purpose of adding Tween 80 is to mimic the effect of natural surfactants in the stomach. The floating and the settled portions of the microspheres were filtered separately, dried and weighed. Buoyancy (floatability) was calculated as

$$\text{Buoyancy (\%)} = Q_f / (Q_f + Q_s) \times 100 \quad (5)$$

Where Q_f and Q_s are the weights of the floating and the settled microspheres, respectively.

8. In-vitro drug release studies:

Drug release studies were carried out in a six-basket USP XXIV dissolution apparatus type I rotating at 100 rpm in 0.1M hydrochloric acid as dissolution medium (900 ml) maintained at 37 ± 0.5 °C. At specific time intervals, up to 12 h, aliquots were withdrawn and analysed by suitable

analytical technique spectrophotometrically after suitable dilution. The withdrawn volume was replaced with an equal volume of fresh 0.1N hydrochloric acid to maintain sink conditions. All experiments were performed in triplicate. The drug release data were fitted to Zero order (cumulative % drug release versus time), First order (log cumulative % drug retained versus time) and Higuchi models (cumulative % drug released versus square root of time) to assess the kinetics of drug release and determine the release mechanism of the drug from the floating microspheres.

CONCLUSION: Single unit control release dosage form is not suitable for a variety of important drugs that have a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine. This is due to the relatively short transit time i.e. 2-3 hr. Thus after 2-3 hr the Control release dosage form left the upper gastrointestinal tract and the drug is released in nonabsorbing part of the gastrointestinal tract. Multiunit floating drug delivery system is a suitable system for the treatment of peptic ulcer because it removes the probability of dosage dumping and non floatability of single unit system. It also increases the bioavailability, patient compliance and decrease the frequency of administration.

ACKNOWLEDGEMENTS: The authors wish to express thanks to Dr. Anand K. Singh Head of Chemistry Department, Mariyahu PG College Mariyahu, Jaunpur UP. I would like to thank IIT (New Delhi), Central Drug Research Institute (Lucknow) for providing facility for sample analysis. The authors also wish to express their thanks to Dr. S. K. Jain Reader Institute of Pharmacy, Bundelkhand University, Jhansi, UP India for encouragement and for providing the necessary facilities and excellent support.

REFERENCES:

1. Baumgratner S, Kristl J, Vrecer F, Vodoprivec P: Optimisation of floating matrix tablet and evaluation of their gastric residence time. *Int J Pharm* 2000; 195:2; 125-35.
2. Khan GM: Control release oral dosage form: Some recent advances in matrix type drug delivery system 2001; 1:4:350.
3. Hoffman A: Pharmacodynamic aspect of sustain release preparation. *Adv Drug Del Rev* 1998; 33; 185-99.
4. Hwang SJ, Park K: Gastric retentive drug-delivery system. *Crit Rev the Drug Carriersys* 1998; 15: 243-84.

5. Hoffman A, Stepensky D: Pharmacodynamic aspect of mode of drug administration for optimization of drug therapy. *Crit Rev Ther Drug Carrier Sys* 1998; 16:571-639.
6. Deshpande AA, Rhodes CT, Shah NH: Controlled release drug delivery system for prolonged gastric residence: an overview. *Drug Dev Ind Pharm* 1996; 22, 531-539.
7. Desai S: A Novel Floating Controlled Release Drug Delivery System Based on a Dried Gel Matrix Network. Jamaica, NY: St John's University 1984.
8. Vantrappen GR, Peeters TL, Janssens J: The secretory component of interdigestive migratory motor complex in man. *Scand J Gastroenterol* 1979; 14:663-667.
9. Wilson CG, Washington N: The stomach: its role in oral drug delivery. In: Rubinstein MH, *Physiological Pharmacological: Biological Barriers to Drug Absorption*. Chichester, UK: Ellis Horwood 1998; 47-70.
10. Desai S, Bolton S: A floating controlled release drug delivery system: *In-vitro* and *In-vivo* evaluation. *Pharm Res* 1993; 10:1321-1325.
11. JAIN NK: Progress in controlled and novel drug delivery system. CBS publishers and Distributers, First edition 2004: 76.
12. Streubel A, Siemann J, Bodmeier R: Gastroretentive drug delivery system. *Expert Opin Drug Deliv* 2006; 63:235-239.
13. Singh BN, Kim KH: Floating drug delivery system: An approach to oral drug delivery system via Garg and Gupta. *J. Control Release* 2000; 63: 235-239.
14. Whitehead, Felljt, Collett JH, Sharma HL, Smith AM: Floating dosage form: An *In-vivo* study demonstrating prolonged gastric retention. *J Control Release* 1998; 55:3-12.
15. Rouge N., Leroux JC, Cole ET, Doelker E, Buri P: Prevention of sticking tendency of floating minitables into hard gelatin capsules. *Eur. J. Pharm. Biopharm* 1997; 43: 165-17.
16. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM: Microspheres as floating drug delivery system to increase the gastric residence of drugs. *Drug Meta Rev* 2001; 33:149-160.
17. Ichikawa M, Watanabe S, Miyake Y: A new multiple unit oral floating dosage system. I: Preparation and *In-vitro* evaluation of floating and sustained-release kinetics. *J Pharm Sci* 1991; 80:1062-1066.
18. United States Patent 6217911, Sustained release non-steroidal, Anti-inflammatory and lidocaine PLGA microspheres.
19. Alexander Florence: Novel Oral Drug Formulations: Their Potential in Modulating Adverse Effects. *Drug Safety* 1994; 10 (3): 233-266.
20. Sjoegren J, Prescott, LF, Nimmoe WS: Rate Control in Drug Therapy, Churchill Livingstone. Edinburgh 1985; 38-47.
21. Vyas SP, Khar RK: Gastroretentive systems. In: *Controlled drug Delivery*. Vallabh Prakashan, Second Edition, 2006; 197-217.
22. Nayak Amit kumar, Maji Ruma, Das Biswarup: Gastroretentive drug delivery systems: a review. *Asian Journal of Pharmaceutical and Clinical Research* 2010; 3:1-4.
23. Byas SP, Khar RK: *Controlled Drug Delivery Concepts and Advances*. CBS Publication, First Edition 2002; 96-217.
24. Chawla C, Gupta P, Koradia V, Bansal AK: Gastroretention: A Means to Address Regional Variability in intestinal drug Absorption. *Pharmaceutical technology* 2003; 27(2):50-68.
25. Sangekar S: Evaluation of effect of food and specific gravity of the tablets on gastric retention time. *Int J Pharm* 1987; 35:3:34-53.
26. Harrigan RM 1977: Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 4055178.
27. Garg S, Sharma S: Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003; 160-66.
28. Hilton AK, Deasy PB: *In-vitro* and *In-vivo* evaluation of amoxicillin trihydrate. *Int J Pharm* 1992; 86: 79-88.
29. Garg R, Gupta GD: Progress in controlled gastroretentive delivery systems. *Trop. J Pharm Res* 2008; 7(3): 1055-66.
30. Jain NK: Progress in Controlled and Novel Drug Delivery Systems. CBS Publishers and Distributors First Edition 2004; 84-85.
31. Thanoo BC, Sunny MC, Jayakrishnan A: Oral sustained release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluids. *J Pharm Pharmacol* 1993; 45:21-24.
32. Garg R, Gupta GD: Progress in controlled gastroretentive delivery systems. *Trop. J Pharm Res* 2008; 7(3): 1055-66.
33. Whiteland L, Fell JT, Collett JH: Development of gastroretentive dosage form. *Eur J Pharm Sci* 1996; 4: 182.
34. Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y: Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J Pharm Sci* 1992; 81: 135-140.
35. Streubel A, Siepman J, Bodmeier R: Drug delivery to the upper small intestine window using Gastroretentive technologies. *Curr Opin Pharmacol* 2006; 6: 501-508.
36. Dubernet C, Rieg F, Faivre V, Pirot F: Systems a liberation gastrique prolongee In: *Falson Nouvelles formes medicaments. Medicals Internationals. Editions TEC and DOC Cachan* 2004; 119-133.
37. Arrora S, Ali J, Khar RK, Baboota S: Floating drug delivery systems: A review. *AAPS Pharm Sci Tech* 2005; 6(3):372-390.
38. Garg S, Sharma S: Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2002; 160-66.
39. Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr ML: Effects of gender, posture and age on gastric Residence time of an indigestible solid: Pharmaceutical considerations. *Pharm Res* 1988; 10: 639-44.
40. Khosla R, Feely LC, Davis SS: Gastrointestinal transit of non-disintegrating tablets in fed subjects. *Int J Pharm* 1989; 53: 107-17
41. Soppimath KS, Kulkarni AR, Aminabhavi TM: Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: preparation and release characteristics. *Drug Dev. Ind Pharm* 2001; 27(6): 507-515
42. Jose GR, Omidian H, Shah K: Progress in Gastroretentive Drug Delivery Systems. *Pharm Tech* 2003; 152-154.
43. Vyas SP, Khar RK: Targeted and Controlled Drug Delivery Novel Carrier System. CBS Publishers and Distributors, First Edition 2004; 417-457.
44. Alagusundaram M, Madhusudana CC, Umashankari.K, Attuluri VB, Lavanya C, Ramkanth S: Microspheres as a Novel Drug Delivery Ssystem-A Review. *International Journal of Chemical Technology and Research* 2009; 1(3): 525-534.
45. Odonnell PB, Mc Ginity JW: Preparation of Microsphere by Solvent Evaporation Technique. *Adv Drug Deliv Rev* 1997; 28: 25-42.

46. Mathew TS, Devi SG, Prasanth VV, Vinod B: NSAID as Microspheres. The International Journal of Pharmacology 2008; 6(1): 101-105.
47. Sinha VR, Agarwal MK, Kumaria R: Influence of formulation and excipients variables on the pellet properties prepared by extrusion spherization. Curr. Drug Delivery 2005; 2: 1-8.
48. Martin A: Micromeritics. Physical Pharmacy, Lea Feiger, Philadelphia Fourth Edition 1993; 431-432.
49. Sinha VR, Agarwal MK, Kumaria R: Influence of formulation and excipients variables on the pellet properties prepared by extrusion spherization. Curr Drug Delivery 2005; 2: 1-8.

How to cite this article:

Singh P, Chaudhari VK, Verma PK, Singh AK and Yadav VK: Multiunit floating drug delivery system a significant tool for the treatment of peptic ulcer disease. Int J Pharm Sci Res 2015; 6(4): 1351-62.doi: 10.13040/IJPSR.0975-8232.6(4).1351-52.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)