Asian Journal of Pharmacy and Life Science ISSN 2231 – 4423
Vol. 1 (3), July-Sept, 2011

Floating Drug Delivery Systems: A Review

Shiv Shankar Hardenia[1], Ankit Jain[1], Ritesh Patel[1], Anu kaushal[2]
1. College of pharmacy IPS Academy, Indore, India
2. ASBASJSM College of Pharmacy, Bela, Ropar, Punjab, India.

ABSTRACT

Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract).[1]

Keywords: *floating drug delivery, oral drug delivery, and gastric emptying time.*

Corresponding Author's Email: - shivsharma280485@gmail.com, Ph. +918871234208

Received: 15/09/2011 Accepted: 29/09/2011

INTRODUCTION

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[2] Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastricresidence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system[3], lowdensity system[4-6], raft systems incorporating alginate gels[7-9], bioadhesive or mucoadhesive systems[10], high density systems[11-13], superporous hydrogels[14] and magnetic systems[15-17].

Stomach specific floating drug delivery

Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density,while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in

the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulkdensity is lower than that of the gastric contents. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropylmethylcellulose (HPMC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy [18].

Mechanism of floating systems

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Fig. 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durabilityof floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations19.

F = F buoyancy - F gravity = (Df - Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.

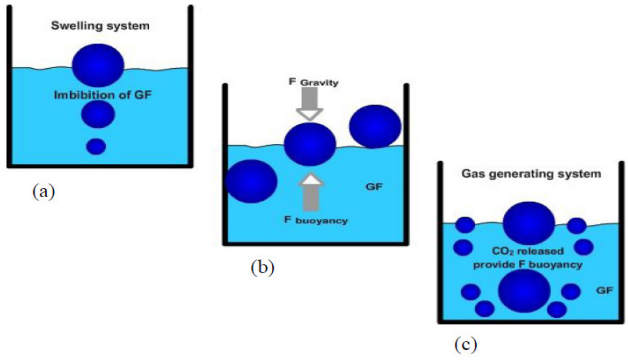

Figure 1. Mechanism of floating systems, GF= Gastric fluid

Approaches to design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.[20]

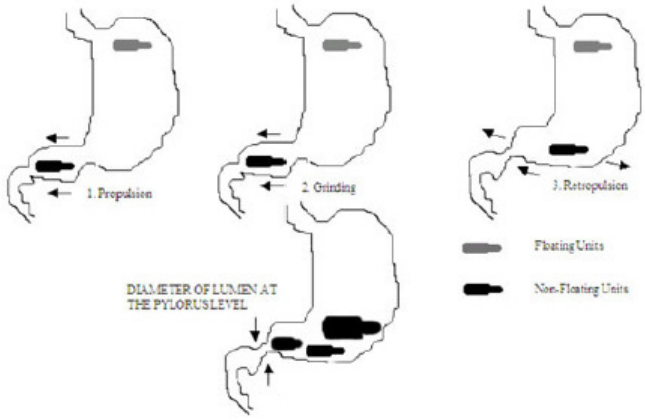

Figure 2. Intragastric residence positions of floating and nonfloating units

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

A. Single unit floating dosage systems

a) Effervescent Systems (Gas-generating Systems)

These buoyant systems utilised matrices prepared with swellable polymers like HPMC,

polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. 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 coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach [21]. Excipients used most commonly in theseSome of the polymers used are hydroxypropyl cellulose, hydroxypropylmethylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose.[22]

Talwar *et al* [23] prepared a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked PVP initially and the gelforming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug.

b) Non-effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier[24], microporous compartment system [25], alginate beads [26], and hollow microspheres[27].

Fluid- filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. [28]

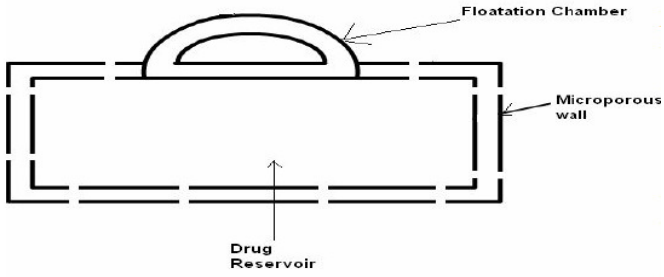

Figure 3. Gas filled floatation chamber

Nur and Zhang [29] prepared floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

B. Multiple unit floating dosage forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the

advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations.[22] Reports have been found on thedevelopment of both non-effervescent and effervescent multiple unit systems [30]. Much research has been focussed and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate.

a) Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported [31]. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

b) Effervescent Systems (Gas-generating Systems):

Ikura *et al*[32] reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h.

Ichikawa *et al*[33] developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in Fig. 3). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

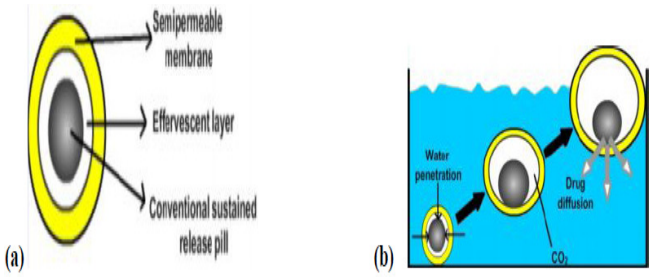

Figure 4. a) Different layers i) Semi-permeable membrane, ii) Effervescent Layer iii) Core pill layer b) Mechanism of floatation via CO_2 generation.

c) Hollow Microspheres

Hollow microspheres are considered as one of the most promising buoyant systems , as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® S and cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio.

Kawashima *et al*[34] described hollow microspheres (microballoons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method. A solution of drug and enteric

acrylic polymer (Eudragit® S) in a mixture of ethanol and dichloromethane is added to the aqueous phase containing polyvinyl alcohol (0.75% w/v) and stirred continuously to obtain o/w emulsion. The microspheres obtained are filtered, water washed and dried. The diffusion and evaporation profiles of ethanol and dichloromethane, suggested a rapid diffusion of ethanol from the droplets into the aqueous phase, which might reduce the polymer solubility in the droplet because of insoluble property of Eudragit® S in dichloromethane. Hence, the polymer precipitation occurs instantly at the droplet surface, forming a film-like shell enclosing dichloromethane and drug. The microspheres showed good flow and packing properties, and a floating time of more than 12 h on acidic medium containing surfactant.

C. Raft forming systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids[7]Jorgen *et al* [8,9] described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

Drugs used in the formulations of stomach specific floating dosage forms

Floating microspheres – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen [35], Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast[36]and Terfinadine[37]

Floating granules - Diclofenac sodium, Indomethacin and Prednisolone

Films – Cinnarizine[38], Albendazole

Floating tablets and Pills - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate[39], Para-aminobenzoic acid, Piretanide[40], Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol[41], pentoxyfilline and Diltiazem HCl.

Polymers and other ingredients

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs.

Hydrocolloids (20%-75%)

They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan,agar, casein, bentonite, veegum, HPMC(K4M, K100M and K15M),Gellan gum(Gelrite®), Sodium CMC, MC, HPC.

Inert fatty materials (5%-75%)

Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Effervescent agents:

Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine

Carbonate, CG (Citroglycine). · Release rate accelerants(5%-60%): eg lactose, mannitol

Release rate retardants (5%-60%):

Dicalcium phosphate, talc, magnesium stearate Buoyancy increasing agents(upto80%): eg. Ethyl cellulose

Low density material:

Polypropylene foam powder (Accurel MP 1000®).

Evaluation parameters of stomach specific FDDS

However, it has to be pointed out that good *in vitro* floating behaviour alone is not sufficient proof for efficient gastric retention *in vivo*. The effects of the simultaneous presence of food and of the complex

motility of the stomach are difficult to estimate. Obviously, only *in vivo* studies can provide definite proof that prolonged gastric residence is obtained.

1) Measurement of buoyancy capabilities of the FDDS[42]

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media, deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

2) 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^{0}C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit^{-1} HCl as the dissolution medium at 370C. 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[43].

Recently Gohel *et al*[54] proposed a more relevant *in vitro* dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit^{-1} HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution

Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stickto the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level (f2=57). The proposed test may show good *in vitro-in vivo* correlation since an attempt is made to mimic the *in vivo* conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3) 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.

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weighttotal beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM) [45].

5) X-Ray/Gamma Scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day [46]. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner [47]. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract[48].

6) Pharmacokinetic studies:

Pharmacokinetic studies are the integral part of the *in vivo* studies and several works has been on that.

Sawicki[59] studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0-infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

Recent advances in stomach specific floating dosage forms

Strübing *et al*[50] investigated the mechanism of floatingand drug release behaviour of poly (vinyl acetate)-based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm2 were investigated regarding drug release in 0.1 mole.lit-1 HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, benchtop MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Jang *et al* [51] has prepared a gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis

Rajnikanth and Mishra[52] have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti-H. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of H. pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. pylori

REFERENCES

1. Shah S.H, Patel J.K and Patel N.V., Stomach specific drug delivery systems: A review International Journal of PharmTech ResearchVol.1, No.3. 2009; 623-633.
2. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985; 19:77-83.
3. Deshpande A.A., Shah N.H., Rhodes C.T., Malick W., Development of a novel controlledrelease system for gastric retention, Pharm. Res. 1997; 14:815-819.
4. Kawashinia Y, Niwa T. Takcuchi H. Hino T, Itoh Y. Hallow microspheres for use as afloating controlled drug delivery system in the stomach. J.Pharm. Sci.1992; 81(2): 135-140**.**
5. Ichikawa M., .Watemblc S., Miyake V.A. Multiple unit oral floating dosage systems I: Preparation and in-vivo evaluation of' floating and sustained release characteristics. J.Pharm. Sci. l99l; 80:l062-1066.
6. Sato Y, Kawaafaima Y., Takenchi H. Invitro and *in vivo* evaluation of riboflavin containing microoballoons for floating controlled delivery system in healthy humans. Int. J.Pharm. 2004; 275:75-82.
7. Washington N., Investigation into the barrier action of an alginate gastric reflux suppressant, Liquid Gaviscon, Drug Investig. 1987; 2:23-30.
8. Foldager J., Toftkjor H., Antacid composition.US Patent 5068109, 1991.
9. Fabrcgas J.L, Cucala C.G., Pous J., Sites R.A. *In vitro* testing of an antacid formulation withprolonged gastric residence time. Drug Dev. Ind. Pharm. 1994; 20:1199-1212.
10. Ponchel G., Irache J.M. Specific and nonspecific bioadhesive particulate system for Oraldelivery to the gastrointestinal tract. Adv.Drug.Del.Rev.1998; 34:191-219.
11. Redniek. A.B, Tucker S.J. Sustained release bolus for animal husbandry US Patent 3,507,952, 1970.
12. Bechgaard H., Ladefoged K. Distribution of pellets in the gastrointestinal tract: The influence on transit time exerted by density or diameter of pellets. J.Pharm. Pharmacol. 1978; 30:690-692.
13. Davis S.S, Stockwell S.F, Taylor M.J, Hardy J.G, Whelley D.R, The effect on density on thegastric emptying of Single and multiple-unit dosage form. Pharm.Res.1986; 3:208-213.
14. Hwang S.J., Park H.. Gastric retentive drugdelivery systems.Cri.Rev.Ther.DrugCarr.Syst.1998; 15:234-284.
15. Ito R., Mchida Y., Sannan T., Nagai T..Magnetic granules: a novel system for specific drug delivery to oesophageal mucosa in oral administration. Int. J. Pharm. 1990; 61:109-117.
16. Fujimori J. Machida Y., Nagai T. Preparation of magnetically-responsive tablet and confirmation of its gastric residence in beagle dogs. STP Pharm.Sci. l994; 4:425-430.
17. Griming R., Berntgen M. Estimation of the gastric residence time magnetic dosage forms using the Heidlberg capsule. Pharmazie. 1996; 51:328-331.
18. Reddy L.H, Murthy R.H, Floating dosage systems in drug delivery, Crit.Rev. Ther. Drug Carr. Syst. 2002; 19(6): 553-585.
19. Garg S. and Sharma S. Gastroretentive Drug Delivery System, Business Briefing: Pharmatech. 2003;160-166.
20. Yang L, Fassihi R. Zero order release kinetics from self correcting floatable configuration drug delivery system. J Pharm Sci. 1996; 85:170-173.
21. Rubinstein A., Friend D.R, Specific delivery to the gastrointestinal tract, in: Domb A.J(Ed.), Polymeric Site-Specific Pharmacotherapy, Wiley, Chichester, 1994; 282-283.
22. Arora S.,Ali J.Floating drug delivery systems: A review AAPS PharmSciTech 2005; 6 (3) Article 47: 1-19.
23. Talwar N., .Sen H., Staniforth J.N, Orally administered controlled drug delivery system providing temporal and spatial control. US patent 6261601, 2001.
24. Sheth P.R. and Tossounian J.L. U.S. Patent no.4140755, 1979.
25. Roy H.M, U.S. Patent no. 4055178, 1977.
26. Whitehead L.., .Fell J., Sharma H.L. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. J.cont. Rel. 1998,55:3-12.

27. Sato Y., Kawashima Y. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Eur. J. Pharm. Sci. 2003, 55:297-304.
28. Joseph NJ, Laxmi S, Jayakrishnan A. A floating type oral dosage from for piroxicam based on hollow microspheres: in vitro and in vivo evaluation in rabbits. J Control Release. 2002; 79:71-79.
29. Nur A.O, Zhang J.S. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev. Ind. Pharm. 2000; 26:965- 969.
30. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug delivery system to increase the gastric residence of drugs. Drug Metab Rev. 2001;33:149-160.
31. Tardi P., Troy H., European patent no. EP 1432402. 2002.
32. Ikura, Hiroshi, Suzuki, Yoshiki United States Patent 4777033.1988.
33. Ichikawa M., Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I: Prepration and *in vitro* evaluation of floating and sustained-release kinetics. J. Pharm.Sci. 1991; 80:1062-1066.
34. Sato Y., Kawashima Y., Takeuchi H. and Yamamoto H., *In vivo* evaluation of riboflavincontaining microballoons for floating controlled drug delivery system in healthy human volunteers, J. Cont. Rel. 2003; 93: 39-47.
35. El-Kamel A.H., Sokar M.S, Algamal S.S, Naggar V.F. Preparation and evaluation ofketoprofen floating oral drug delivery system. Int. J. Pharm. 2001; 220:13-21.
36. Kawashima Y., Niwa T., Takeuchi H., Hino T., ItoY. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (*in vivo*). J. Cont. Rel. 1991; 16:279-290.
37. Jayanthi G., Jayaswal S.B., Srivastava A.K. Formulation and evaluation of terfenadine microballoons for oral controlled release. Pharmazie. 1995; 50:769-770.
38. Gu T.H. *et al*. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets. Chung Kao Yao Li Hsuesh Pao. 1992; 13:527-531.
39. Ichikawa M., Watanabe S., Miyake Y. A new multiple-unit oral floating dosage system. II: *Invivo* evaluation of floating and sustainedrelease characteristics with para amino benzoic acid and isosorbide dinitrate as model drugs. J. Pharm. Sci. 1991; 80:1153-1156.
40. Rouge N., Cole E.T., Doelker E., Buri P. Buoyancy and drug release patterns of floatingmini tablets containing piretanide and atenolol as model drugs. Pharm. Dev. Technol. 1998; 3:73-84.
41. Cheuh H.R., Zia H., Rhodes C.T. Optimization of Sotalol floating and bioadhesive extended release tablet formulation. Drug Dev. Ind. Pharm. 1995; 21:1725-1747.
42. http://www.drugdeliverytech.com/ME2/dirmod.asp?sid=4306B1E9C3CC4E07A4D64E23FBDB232Candnm=Back+Issuesandtype=Publishingandmod=Publications%3A%3AArticleandmid=8F3A7027421841978F18BE895F87F791andtier=4andid=CC1CDA11871540EFAFAB50839AFFD292.
43. Karande A.D., Yeole P.G. Comparative Assessment of Different Dissolution Apparatus for Floating Drug Delivery Systems. Dissolutiontech, (2006); 13(1):20-23.
44. Gohel M.C., Mehta P.R.., Dissolutiontech. 2004; 11(4):22-25.
45. Agnihotri S.A., Jawalkar S.S. and Aminabhavi T.M., Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release, Eur. J. Pharm. Biopharm. 2006; 63:249–261.
46. Fell J., Digenis C.G. Imaging and behaviour of solid oral dosage forms *in vivo*. Int.J.Pharm.1984; 22(1):1-15.
47. Harries D., .Sharma H.L. GI transit of potential bioadhesive formulations in man: A scintigraphic study. J.Cont.Rel. 1990;12(1):45-53.
48. Timmermans J.,Gansbeke V.B., .Moes A.J.. Assessing by gamma scintigraphy the *in vivo* buoyancy of dosage forms having known size and floating force profiles as a function of time. Vol I. Proceedings of the 5th International

Conference on Pharmacy Technology. Paris, France: APGI, 1989:42-51.

49. Sawicki W. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. Eur. J. Pharm. Biopharm. 2002; 53:29-35.
50. Strübing S., Abbouda T., Renata C. Metza H. 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 J.Pharm.and Biopharm. 2008;69:708-717.
51. Janga S., Lee J., Park S. Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis. Int.J.Pharm. 2008;356:88-94.
52. Rajinikanth P. and Mishra B. Floating in situ gelling system for stomach site-specificdelivery of clarithromycin to eradicate H.pylori, J.Cont.Rel. 2008; 25: 33-41.