IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FLOATING DRUG DELIVERY SYSTEM-An Advanced Technique in Drug Delivery

Km Nidhi *[1], Dr. Sanjar Alam, Shikha Sharma, Ms. Tabassum.

***Address for correspondence:**

Corresponding Author: Km Nidhi, Assistant Professor Pharmaceutics, Department of Pharmacy, J.K Institute of Pharmacy, Bulandshaher (AKTU Lucknow) Uttar Pradesh, India.

ABSTRACT: Gastro retentive drug delivery system are prepared with the intention to retain drug in the gastric region for a prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract (GIT) thus leading its optimal bioavailability. Gastro-retentive drug delivery systems are the system in which drug can be hold in the stomach. These drug delivery Systems is one of the most common gastro-retentive dosage forms used to achieve increased GRT and reduces fluctuation in plasma drug concentration. The main objective of writing this review on floating drug delivery systems was to accomplish the recent literature floating mechanism to achieve gastric retention time. Gastro-intestinal dosage forms provides many advantages like- Improved drug absorption, because of increased gastric residence time and more time spent by the dosage form at its absorption site. This review consist the detailed study of floating drug delivery system, approaches such as Single unit dosage forms, Multiple unit dosage forms and Raft-forming systems, consist advantages and disadvantages of floating drug delivery system, also consist gastric residence time of an oral dosage form contains factors affecting efficacy and various applications of the system like- sustained drug delivery, enhanced bioavailability, enhanced absorption, Reduced fluctuations of drug concentration, Site-specific dosage forms, and decreased undesirable activity at the colon.

KEYWORDS: Floating drug delivery systems, Approaches, Advantages, Factors affecting Efficacy, Applications.

INTRODUCTION

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. These systems are floats over the gastric contents; the drug is released slowly at the desired rate, this result in increased GRT and reduces fluctuation in plasma drug concentration (Patel et al., 2012).

A minimum amount of floating force (F) is also necessary to maintain the dosage form stably buoyant on the surface of the meal, in addition to a minimum stomach content required to allow successful realization of the buoyancy retention principle. Granules, powders, capsules, tablets, laminated films, and hollow microspheres have all been used to create buoyant systems.

(A.V. Mayavanshi et al., 2008).

APPROACHES TO DESIGN FLOATING DOSAGE FORMS

The following methods have been employed for the formulation of floating dosage forms of single and multiple- unit systems.

1. **Single Unit Floating Dosage Systems: -** Single unit dosage forms are the simplest to develop but suffers from the risk of losing their effects too early due to their all or none emptying from the stomach and, thus they may results in high variability in bioavailability and local irritation because of vast amount of drug delivered at a specific site of the gastrointestinal tract (Bharkatiya et al., 2014).

- Effervescent Systems (Gas-generating systems).
- Non-effervescent Systems.

2. **Multiple Unit floating dosage systems: -** Multiple unit dosage forms may be an appealing alternative since they have been shown to reduce inter and intra-subject variability‟s in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in different forms and using principles such as air compartment multiple unit systems, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS (Gajanan et al., 2014).

- Non-effervescent Systems
- Effervescent Systems (Gasgenerating systems)
- Hollow Microspheres

3. **Raft-Forming Systems: -** Raft-forming systems focus on the delivery of antacids and delivery of the drug in case of gastrointestinal infections and disorders. The process involved in the raft formation involves the development of viscous cohesive gel in contact with gastric content, 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 CO2. Usually, the system contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the liberation of CO2 results in making the

system less dense and floats over the gastric fluids an antacid raft forming floating system. The system contains a gel-forming agent, e.g., calcium carbonate, alginic bicarbonate, a sweetener, and mannitol. These ingredients were granulated, and citric acid was added to the granules. The formulation creates effervescence andaerates the raft formed, making it float acid, sodium bicarbonate and acid neutralizer, which form a foaming sodium alginate gel (raft) when interacting with gastric fluids. The raft thus formed floats on the gastric fluids and obstructs the reflux of the gastric acid into the esophagus by acting as a boundary between the stomach and esophagus. A patent allocated to Reckitt and Colman Products Ltd. describes a raft forming formulation for the treatment of Helicobacter pylori (H. Pylori) infections in the GIT (Chowdary et al., 2014).

ADVANTAGES OF FDDS

Floating dosage systems form critical technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:-

- Improved drug absorption, because of increased gastric residence time and more time spent by the dosage form at its absorption site.
- Drug delivery is controlled.
- Drugs are delivered for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at a controlled rate.
- Treatment of gastrointestinal disorders like gastro-esophageal reflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.

DISADVANTAGES OF FDDS

- Floating systems are not suitable for those drugs that have solubility or stability problems in gastric fluids drugs, e.g., Nifedipine, which is adequately absorbed in the GI tract and undergoes significant first-pass metabolism, are unsuitable candidates for FDDS since the gradual gastric emptying reduces the system bioavailability. Also, there are limitations to the suitability of FDDS for drugs that are irritant to gastric mucosa.
- Gastric retention is affected by numerous factors, for example, pH, gastric motility, and presence of food. These factors are never consistent, and hence the buoyancy cannot be anticipated.
- Drugs that induce irritation and lesion to gastric mucosa are not appropriate to bed signed as floating drug delivery systems (Dixit N., 2011, Arunachalam A., et al., 2011 and Kumar N., et al., 2012).

Suitable Drug Candidates for FDDS: Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. In general, appropriate candidates for FDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa.
- Drugs that primarily absorbed from the stomach and upper part of GIT, e.g.: Calcium supplements, chlordiazepoxide, and cinnarizine.
- Medications that demonstration locally in the stomach, e.g., Misoprostol and Antacids.
- Drugs that deteriorate in the colon, for e.g., Metronidazole and Ranitidine HCl.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate (Chowdary et al., 2014).

Drugs Unsuitable for FDDS: Drugs which are unsuitable for FDDS are as follows,

- Drugs which are less soluble in acid, e.g., phenytoin.
- Drugs which are unstable in the gastric environment, e.g., erythromycin.
- Drugs intended for selective release in the colon, e.g., 5-aminosalicylic acid and corticosteroids (Chandana et al., 2014).

FACTORS AFFECTING EFFICACY OF FDDF'S

The gastric residence time of an oral dosage form depends on several factors.

1. **Particle size:** The particle size ought to be in the range of 1 to 2 mm to go through the pyloric valve into the small intestine.
2. **Density:** The density of a dosage formal so influences the gastric emptying rate. A buoyant dosage form was having a density less than 1 that of the gastric fluids floats. Since it is far away from the pyloric sphincter, it can be held in the stomach for a prolonged period.
3. **Size:** Dosage forms with a diameter of more than 7.5 mm are accounted to have an extended GRT when compared with those with a diameter of 9.9 mm.
4. **The shape of dosage form:** Those with a tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5-kilopounds per square inch are accounted to have better GRT = 90% to 100% retention at 24 hours when compared with other shapes.
5. **Fed or unfed state:** Under fasting conditions, the GI motility is designated by periods of strong motor activity or the MMC that occur every1.5 to 2 hours. The MMC drags the undigested material from the stomach and, if the timing of administration of the formulation coexists with that of the MMC, the GRT of the unit can be relied upon to be very short. However, in the fed state, MMC is delayed, and GRT is considerably longer.
6. **Nature of meal:** Feeding of indigestible polymers or fatty acids salts can change the motility pattern of the stomach, thus decreasing the gastric emptying rate and prolonging drug release.
7. **Temperature of the meal:** High or low temperature of the ingested fluid reduce the gastric emptying time.
8. **Caloric content of meal:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats content.

9. **The frequency of feed:** The GRT can be increased by over 400 minutes when successive meals are given compared with a single meal.
10. **Gender:** Mean ambulatory GRT in males (3.4 ± 0.6 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.
11. **Age:** Older aged and those above 70, have a significantly longer GRT.
12. **Posture:** Gastric retention is affected by the position of the patient.
13. **Concomitant drug administration:** Drugs that are gastric emptying include poorly soluble antacids (Aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and Tricyclic antidepressants (Imipramine, Amitriptyline). Metoclopramide, domperidone, and cisapride (antiemetics) stimulate gastric emptying.
14. **Biological factors:** Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes, and hypothyroidism retard gastric emptying, Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate (Binoy & Jayachandran, 2012)

APPLICATIONS OF FDDS

- **Enhanced Bioavailability:** The bioavailability of riboflavin Control Release Gastro-retention delivery formulation (CR GRDF) appreciably increased in comparison to the administration of non-GRDF CR polymeric formulations. There are various processes, related to absorption and transit of the drug in the gastrointestinal tract that act along with to influence the magnitude of drug absorption.
- **Sustained drug delivery:** Oral CR formulations experienced several problems such as gastric residence time in the GIT. These problems can be controlled with the hydro dynamically balanced systems (HBS) which remains in the stomach for prolong period and have a bulk density of less than one which leads them to float on the gastric contents. These systems are moderately larger and going from the pyloric opening usually is not possible.
- **Site-specific drug delivery systems:** These systems are particularly favorable for drugs that are primarily absorbed from the stomach or the proximal part of the small intestinal tract. The controlled, gradual delivery of drug to the stomach gives adequate local therapeutic levels and restricts the systemic exposure to the drug. This will decreases the side effects that are caused by the drug in the blood circulation. Also, the prolonged gastric availability from a site-directed delivery system may also reduce the dosing frequency, e.g., Furosemide and Riboflavin.
- **Absorption enhancement:** Drugs which are having poor bioavailability because of site-specific absorption from the upper part of the GIT are probable candidates to be formulated as floating drug delivery systems, thereby amplifying absorption.
- **Reduced undesirable activity at the colon:** The amount of drug that reaches to colon can be reduced by maintaining the drug in HBS system at the stomach and hence the actions of drug which

are not required in the colon may be prevented. This Pharmacodynamic feature provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

- **Reduced fluctuations of drug concentration:** Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized, and concentration dependent adverse effects that are linked with peak concentrations can be controlled. This attribute is of special importance for drugs with a narrow therapeutic index (Chowdary et al., 2014).

EVALUATION PARAMETERS OF FDDS

The following evaluation parameters are includes like- The angle of repose, bulk density and tapped density, Compressibility Index Hardness Friability, DSC, and FTIR etc (Singh BN et al., 2000).

The angle of repose: The angle of repose of blend was measured by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was maintained in such a way that the tip of the funnel simply touched the apex of the blend. Then the powder blend was allowed to pass through the funnel freely on to the surface. So as the diameter of the powder cone was determined and then the angle of repose was calculated using the equation as shown below (Chaudhary A et al., 2013).

$$\theta = \tan^{-1}\frac{h}{r}$$

Where h and r are the height and radius of the powder cone.

Bulk Density and tapped density: Both densities were to be determined. A quantity of 2 g of the blend from each formula, previously shaken to break any agglomerates formed, was fed into a 10 ml measuring cylinder. The initial volume was noted, and the cylinder was permitted to fall under its particular weight on to a surface from the height of 2.5 cm at second intervals. Tapping proceeded until no further change in volume was observed. BD and TB were determined using the following equations (Senthil A et al., 2011 and Sarfaraz Md et al., 2012):

$$BD = \frac{Weight\ of\ powder\ blend}{Untapped\ volume\ of\ packing}$$

$$TD = \frac{Weight\ of\ powder\ blend}{Tapped\ volume\ of\ packing}$$

Compressibility Index: One of the useful measures that can be observed from the bulk density and tapped density determinations, it is the compressibility index of powder which is expressed in terms of percentage. The formula for Carr's Index is as below: (Carr R. L, 1965).

C = 100x (1 – Bulk Density / Tapped Density)

Hardness: Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression) was measured using a Monsanto type tester. The test was executed on three tablets from each formulation and the average reading was noted (Srinath KR, 2011).

Friability: Friability of the tablets was calculated using a Roche friabilator. Ten preweighed tablets were placed in the friabilator, operated for 4 min at 25 rpm. The tablets were taken out, de-dusted and weighed again. The percentage friability of tablets was determined as per the following formula: (Chaurasia G, 2016)

$$\% F = \text{Initial Weight} - \text{Final Weight}/\text{Initial Weight} \times 100$$

Fourier Transform Infrared (FT-IR) Spectroscopy: In IR spectroscopy, firstly the background was scanned and then the crystal window was closed. Samples were finely ground with infra-red grade KBr then pressed into pellet and IR spectra were taken in transmission over the range of 4000- 500 cm -1 at ambient temperature. The sample was pressed and scanned. In the spectra, that has appeared on the screen, the baseline was corrected. The drug was identified by infrared spectroscopy and characteristics peak obtained compared with standard spectra of pure drug reported in the official monograph (Peltonen L et al., 2002)

Differential Scanning Calorimeter (DSC) analysis: DSC is useful in the investigation of thermal properties of the formulation, providing both qualitative and quantitative information about the physicochemical state of a drug with polymers. DSC measurements were carried out on DSC Q10 V9.9, US. The instrument was calibrated using Indium as standard. Samples were kept in sealed aluminum pans and heated from 30ºC to 300ºC at a rate of 10ºC/min under a nitrogen atmosphere (60 ml/min), with the empty pan as the reference. The drug was further confirmed by DSC analysis (Liu LS et al., 1997).

Floating & swelling behavior:

1. **In vitro buoyancy studies:**

- **Floating lag time (FLT):** It is determined to assess the time taken by the dosage form to float on the top of the dissolution medium after it is placed in the medium.
- **Total floating time (TFT):** The time for which the dosage form continuously floats on the dissolution media is termed as floating time.
- **Swelling index:** The swelling properties of tablets were determined by putting the weighed tablet matrices (w1) in the dissolution apparatus in 900 ml of acidifying 0.1 N HCl at 37 ± 0.5°C. The tablets were removed intermittently from the dissolution medium and, after removing free water, the swollen weight (w2) was measured. Swelling Index was determined according to the equation:

2. **In-vitro release of drug:**

- **Dissolution study:** In vitro dissolution study of model drug was performed in USP Dissolution apparatus type II, in 900 ml acidify 0.1 N HCl (pH 1.2), maintained at 37± 0.5ºC at a speed of 50

rpm. Samples of 10 ml were withdrawn, and replenished with fresh medium at pre-determined intervals for 8 h and analyzed using UV spectrophotometer at 265 nm (Angilicam et al., 2015).

Table 1: Marketed formulations of Floating Drug Delivery system.

S.NO	PRODUCT	INGREDIENT	REFERENCE
1	Liquid gavison	Alginic acid and sodium bicarbonate	Washington N, et al., 1986
2	Madopar	Levodopa and benserzide	Erni W et al., 1987
3	Almagate flatcoat	Antacid	Fabregas JL et al., 1994
4	Valrelease	Diazepam	Sheth PR et al., 1984
5	Topalkan	Aluminum magnesium antacid	Degtiareva H., 1994

Table 2: List of Drugs Formulated as Floating Drug Delivery System.

S.NO	FORMULATION	DRUG	REFERENCE
1	Capsules	Furosemide84 Propranlol112 hlordiazepoxide HCl64 Misoprostal86 Diazepam111	Menon A et al., 1994 Khattar D et al., 1990 Sheth PR. 1984 Oth M et al., 1992 Gustafson JH al., 1981
2	Tablets	Diltiazem106 Theophylline23 Sotalol77 Florouracil107 Prednisolone109 Acetylsalicylic acid52 Nimodipine59 Chlorpheniramine maleate4 Pentoxyfillin40 Captopril44 Piretanide108 Furosemide31 Amoxycillin trihydrate71	Gu TH et al., 1992 Yang L, 1996 Cheuh HR. 1995 Watanbe K et al., 1993 Inouye K et al., 1988 Sheth PR. 1979 Wu W et al., 2000 Deshpande AA et al., 1997 Baumgartner S et al., 2000

			Nur AO. 2000 Rouge N et al., 1998 Ozdemir N et al., 2000 Hilton AK. 1992
3	Granules	Prednisolone115 Indomathacin71 Diclofenac sodium88	Inouye K et al., 1989 Hilton AK. 1992 Malcolm SL., 1987
4	Microspheres	Tranilast55 Iboprufen80 Verapamil27 Ketoprofen49 Terfenadine114	Kawashima Y et al., 1991 Kawashima Y et al., 1992 Soppimath KS et al., 2001 El-Kamel AH et al., 2001 Jayanthi G et al., 1995

CONCLUSION: Floating drug delivery system of any drug were prepared with an objective to prolong its residence time in the stomach and upper intestine, to improve its absorption and bioavailability of drug and to prolong the drug release. In recent time, it is very difficult to design effective dose formulation for gastro retentive tract disorders. Preparing floating dosage forms is a problem for any developer. In this study we have write a review paper on floating drug delivery system to conclude that a floating drug delivery system is a ease mode for the treatment of gastro-retentive disorders because it shows local action in the stomach for a long duration of time. This shows that the dosing frequency is decreases and toxicity reduced. After this they show longer GI residence time of the dose formulation and also increase absorption of the drug. So, we can say that this floating drug delivery system reduces all problems regarding conventional dosage form.

ACKNOWLEDGMENT: Authors are highly thankful to Dr. Sanjar Alam, Principal, R V Northland Institute, Dadri, Greater Noida, G B Nagar, India for providing support during my literature survey.

Conflict of interest: The Author clarifies that there is no conflict of interest.

REFERENCES

1. Patel A.K and Patel V.M. A review- Gastro- retentive drug delivery systems and its rationale in peptic ulcer treatment. Journal of Pharmaceutical Science and Bio scientific Research, 2012; 2(4): 179-188.
2. Mayavanshi A.V. and Gajjar S.S. 2008. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research J. Pharm. and Tech.
3. Bharkatiya M, Kitawat S and Ojha A. Floating Drug Delivery Systems- A review, Journal of Drug Delivery & Therapeutics, 2014; 4(2): 130-134.
4. Gajanan R.K., Kadam V.S., Jadhav S.B., Bharkad V.B., Shinde S.G and Zamerruddin M. A review of Gastro-retention Drug Delivery System. World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(3):490-507.
5. Chowdary K.P.R. and Chowdary K.L.C. Recent Research Floating Drug Delivery Systems- A review, Journal of Global Trends in Pharmaceutical Sciences, 2014; 5(1): 1361-1373.
6. Dixit N.. 2011. Floating Drug Delivery System. *Journal of Current Pharmaceutical Research.* 7, 6-20.
7. Arunachalam A., Karthikeyan M., 2011. Floating drug delivery systems: A review. *Int. J. Res. Pharm. Sci*. 2, 76-83.
8. Kumar N., Niranjan S.K, Irchhaiya R, Vishkarma K., Akhtar Ali. 2012. A Novel floating drug delivry system. *International Research Journal of Pharmacy*. 3.
9. Chandana S.B., Vishnu P., Babu K.N., Rao, U.K., Sai S. and Sarvani T.A; 2014. Brief review of floating drug delivery Systems. South Pacific Journal of Pharma and Biosciences, Vol., 2(2), pp. 137-153.
10. Binoy B and Jayachandran N.C.V. Floating Drug Delivery Systems- A new approach in the gastric retention- a review, Journal of Drug Delivery Research, 2012; 1(3): 18-31.
11. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000; 63:235Y259.
12. Chaudhary A, Garud N, Garud A. Formulation and *in-vitro* characterization of floating drug delivery system of Nateglinide. Am J PharmTech Res. 2013; 3(2): 477-486
13. Senthil A, Raja BD, Sureshkumar P, Thakkar HR, Sivakumar T. Chitosan Loaded Mucoadhesive Microspheres Of Glipizide For Treatment Of Type 2 Diabetes Mellitus In Vitro And In Vivo Evaluation: Research Article. Scholars Research Library. 2011; (3):366-379.
14. Sarfaraz Md, Venubabu.P, Doddayya Hiremath and Prakash SG. Mucoadhesive Dosage Form of Glibenclamide. Design and Characterisation: Research Article. Ijpbs. Apr-Jun 2012; (2):162-172.
15. Carr R. L. Evaluating flow properties of solids. *Chem. Eng.* 1965; 72:69–72. [Google Scholar]

16. Srinath KR, "Formulation and Evaluation of Effervescent tablets of Paracetamol", International Journal of Pharmaceutical Research & Development, 2011; 3(3):76- 104.
17. Chaurasia G: A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. Int J Pharm Sci Res 2016; 7(6): 2313-20.
18. Peltonen L, Koistinen P, Karjalainen M, *et al*. The effect of cosolvents on the formulation of nanoparticles from low molecular weight polylactide. AAPS PharmSciTech. 2002, 3: 1-7.
19. Liu LS, Liu SQ, Ng SY, Froix M, Heller J. Controlled release of interleukin 2 for tumour immunotherapy using alginate/chitosan porous microspheres. J Control Release. 43, 1997, 65-74.
20. Angilicam Avinash*, Karimunnisa Sk, Sumathi P. Lipospheres: A Comprehensive Overview. International Journal of Current Trends in Pharmaceutical Research. 2015, 3(3): 909–915.
21. Washington N, Washington C, Wilson CG, Davis SS. What is liquid Graviscon? A comparison of four international formulations. Int J Pharm. 1986; 34:105Y109.
22. Erni W, Held K. The hydrodynamically balanced system: a novel principle of controlled drug release. Eur Neurol. 1987; 27:215Y275.
23. Fabregas JL, Claramunt J, Cucala J, Pous R, Siles A. In vitro testing of an antacid formulation with prolonged gastric residence time (Almagate flot coat). Drug Dev Ind Pharm. 1994; 20:1199Y1212.
24. Sheth PR, Tossounian J. The hydrodynamically balanced systems (HBS): a novel drug delivery system for oral use. Drug Dev Ind Pharm. 1984; 10:313Y339.
25. Degtiareva H, Bogdanov A, Kahtib Z, etal. . The use of third generation antacid preparations for the treatment of patients with nonulcerous dyspeosia and peptic ulcer complicated by reflux esophagus [in Chinese]. Liakrs' ka sprava. 1994; 5-6:119Y122.
26. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994; 83:239Y245.
27. Khattar D, Ahuja A, Khar RK. Hydrodynamically balanced systems as sustained release dosage form for Propranalol hydrochloride. Pharmazie. 1990; 45:356Y358.
28. Sheth PR, Tossounian J. The hydrodynamically balanced systems (HBS): a novel drug delivery system for oral use. Drug Dev Ind Pharm. 1984; 10:313Y339.
29. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: a stomach directed drug delivery system for misoprostal. Pharm Res. 1992; 9:298Y302.
30. Gustafson JH, Weissman L, Weinfeld RE, Holazo AA, Khoo KC, Kalpan SA. Clinical bioavailability evaluation of a controlled release formulation of diazepam. J Pharmacokinet Biopharm. 1981; 9:679Y691.

31. Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou JM. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets [in Chinese] Chung Kao Yao Li Hsuesh Pao. 1992; 13:527Y531.
32. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery: effects of CO2 gas forming agents. Int J Pharm. 2002; 239:81Y91.
33. Cheuh HR, Zia H, Rhodes CT. Optimization of Sotalol floating and bioadhesive extended release tablet formulation. Drug Dev Ind Pharm. 1995; 21:1725Y1747.
34. Watanbe K, Machida Y, Takayama M, Iwta M, Nagai T. Preparation and evaluation of intragastric floating tablets having pH independent buoyancy and sustained release property. ArchPract Pharm Yakuzaigaku. 1993; 53:1Y7.
35. Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release tablets based on chitosan. Drug Des Deliv. 1988; 2: 165Y175.
36. Sheth PR, Tossounian JL. Novel sustained release tablet formulations. 4 167 558. September 11, 1979.
37. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao. 1997; 32:786Y790.
38. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 14:815Y819.
39. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195:125Y135.
40. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm. 2000; 26:965Y969.
41. Rouge N, Cole ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating minutesitablets containing piretanide and atenolol as model drugs. Pharm Dev Technol. 1998; 3:73Y84.
42. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluation of bilayer tablet formulation. Drug Dev Ind Pharm. 2000; 26:857Y866.
43. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxycillin trihydrate. Int J Pharm. 1992; 86:79Y88.
44. Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release tablets based on chitosan. Drug Des Deliv. 1989;4: 55Y67.
45. Malcolm SL, Allen JG, Bird H, etal. . Single dose pharmacokinetics of Madopar HBS in volunteers. Eur Neurol. 1987; 27:28SY35S.

46. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (in vivo). J Control Release. 1991; 16:279Y290.
47. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Hollow microspheres for use as floating controlled drug delivery system in stomach. J Pharm Sci. 1992; 81:135Y140.
48. 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; 33:149Y160.
49. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral drug delivery system. Int J Pharm. 2001; 220:13Y21.
50. Jayanthi G, Jayaswal SB, Srivastava AK. Formulation and evaluation of terfenadine microballoons for oral controlled release. Pharmazie. 1995; 50:769Y770.