Review Article

An Overview on Gastroretentive Buoyant Drug Delivery System

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ABSTRACT

Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain due to the limited gastric residence times. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours to improve the absorption of drugs by increasing the contact time. The floating or gastroretentive or hydrodynamically controlled drug delivery systems are useful in controlling the gastric retention. From the formulation and technological point of view, the floating drug delivery system is comparatively easy and logical approach. The present review addresses briefly about the advantages and various factors affecting the floating drug delivery systems. It also summarizes methods of in vitro and in vivo evaluation of various floating dosage forms, marketed preparations, recent trends and applications of these systems.

Keywords: Floating drug delivery system, single unit, multiple unit, evaluation and applications.

INTRODUCTION

Historically, the oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed**.** Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[1].

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract[2]. The type of drugs that can be used in gastroretentive devices are (a) drugs having narrow absorption window in the stomach (b) drugs that act locally in the stomach (c) drugs that are unstable in intestinal and colonic environment.

PHYSIOLOGY OF STOMACH

The stomach is divided into four major regions: fundus, body, antrum, and pylorus. Its functions are mainly:

Reservoir function: achieved through the flexible volume of the stomach.

Emptying function: achieved through low sustained pressure produced by the stomach body

Mixing and homogenizing function: achieved through grinding due to stomach contraction.

Size restriction function: during the fed state, the particle sizes of food emptied through the pylorus is less than 1 millimetre[3].

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 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period[4].

ADVANTAGES

1. The bioavailability of drugs can be significantly enhanced for those which get metabolised in the upper GIT by gastroretentive drug delivery approaches.
2. The site specific drug delivery is useful in the treatment of disorders related to stomach and the small intestine.
3. Continuous input of drug following controlled release gastroretentive delivery produces systemic drug concentrations within a narrower range as compared to immediate release oral dosage forms[5].
4. These are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response[6].

DISADVANTAGES

1. Floating system is not feasible for 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 and work efficiently-coat, water.
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[7].

FACTORS AFFECTING THE FLOATING DRUG DELIVERY SYSTEM

1. Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;
2. Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm;
3. Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes;
4. Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms;[8]
5. Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motor activity (or) the Migrating Myoelectric Complex (MMC) that occurs every 1.5 to 2 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer
6. Nature of meal: Feeding of indigestible polymers (or) fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
7. Caloric content: GRT can be increased by 4 to 10 h with a meal that is high in proteins and fats.
8. Frequency of feed: The GRT can increase by over 400 minutes when successive meals are given compared with a single meal[9].
9. Temperature of the meal: High or low temperature of the ingested fluid decrease the gastric emptying time.
10. Gender: Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2 hours) regardless of the weight, height and body surface.
11. Age: Elderly people and those above 70, have a significantly longer GRT.
12. Posture: Gastric retention is affected by posture 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 anti depressants (imipramine, amitriptyline)[10].

CLASSIFICATION OF DRUG DELIVERY

1. **Single unit floating dosage systems**

a. **Effervescent systems (Gas generating systems)**

Swellable polymers like HPMC, polysaccha-rides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature are used as matrices. 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[11].

b. **Non effervescent systems**

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. This system can be further divided into four sub-types.

i. **Colloidal gel barrier system**

Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption.

ii. **Microporous compartment system**

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

iii. **Alginate beads**

Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

iv. **Hollow microspheres**

The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug12. 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 formulation13.

2. **Multiple unit floating systems**

Multiple unit dosage forms may be an attractive alternate 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.

a. **Effervescent systems**

Ichikawa *et al* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two 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. CO2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0/ml.

b. **Non effervescent systems**
Not many reports were 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. 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 ratios[14].

3. **RAFT FORMING SYSTEMS**
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 CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids[15].

IN VITRO AND IN VIVO EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS

1. **Hardness, friability, assay, content uniformity** (Tablets)
These tests are performed as per described in specified monographs.

2. **Floating lag time and total floating time determination**
The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37o C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium.

3. **Weight gain and water uptake (WU)**
Weight gain is studied by considering the swelling behavior of Floating dosage form. The dosage form was immersed in simulated gastric fluid at 37oC and determining the dimensional changes like tablet diameter and/ or thickness at regular 1□h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation WU = (Wt – Wo) X 100 / Wo In which Wt and Wo are the weights of the dosage form at time t and initially respectively.

4. **Pharmacokinetic studies**
Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) were estimated. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance[16].

5. **Swelling Study**
The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes were measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.
WU = (W1 – W0) W0/ x 100
Wt = Weight of dosage form at time t.
W0 = Initial weight of dosage form[17].

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

Drug loading can be assessed by crushing an accurately weighed sample of beads or microspheres in a mortar and adding it to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by a variety of analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total microspheres. The particle size and the size distribution of the microspheres are determined in the dry state by optical microscopy. The external and cross-sectional morphology (surface characterization) is carried out by scanning electron microscopy.

7. **X-ray/gamma scintigraphy**
X-ray/gamma scintigraphy helps to locate the dosage form in the GIT and it can be used to predict and correlate the gastric emptying time and the passage of the 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 radio-nuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the radio-nuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract[18].

8. **In vitro release studies**
The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium.

9. **In vivo studies**
The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs) [19].

MARKETED PREPARATIONS [20]

List of various floating gastroretentive marketed formulations is given in table no 1 below.

DRUGS USED IN FORMULATION OF FLOATING DOSAGE FORMS [21]

Drugs reported to be used in the formulation of floating dosage forms are given in table no 2 below.

RECENT TRENDS IN FORMULATION AND OPTIMIZATION OF GRDDS

Pharmacokinetic and pharmacodynamic properties like ADME, half life, therapeutic index, dose size and first pass clearance are the key factors. Recently various formulations are made up for gastroretentive drug delivery like floating ring capsule pellets, bilayered tablets, trilayared tablets, thiolated tablets.
Modern optimization techniques using experimental designs are a vital aid to the formulator as they help in developing the best possible formulation under a given set of conditions. Statistical techniques can be employed to optimise the formulation to save time and cost. Different statistical designs such as factorial design, central composite design, Box Behnken design, D optimal design and simplex lattice design are used for optimisation[22].

APPLICATIONS

Floating microspheres are especially effective in the delivery of sparingly soluble and insoluble drugs. Floating systems can improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach. They are also used for controlled release of non steroidal anti inflammatory drugs [23]. Chitosan is used as a polymer in floating systems. It has a number of important utilizations including cholesterol lowering effects, increasing the stability of drug, as a permeation enhancer,

mucoadhesive excepient and wound healing properties[24].

FUTURE PERSPECTIVES

Further investigation may concentrate on the following concepts:

1. Identification of a minimal cut off size above that DF's retained in the human stomach for prolonged periods of time. This would permit a more specific control to be achieved in gastroretentivity.
2. Design of an array of FDDS, each having a narrow GRT for use according to the clinical need eg. Dosage and state of disease. This may be achieved by compounding polymeric matrices with various biodegradation properties.
3. Study of the effect of various geometric shapes, in a more excessive manner then previous studies, extended dimensions with high rigidity on gastroretentivity.
4. Design of novel polymers according to clinical and pharmaceutical need[25].

CONCLUSION

Drug absorption in the gastrointestinal tract is highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. By prolonging the gastric emptying time of the dosage form, controlled release of the drug can be obtained and also the drug is presented in absorbable forms at the regions of optimum absorption. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. FDDS promises to be a potential approach for gastric retention. This article gives an overview of the main concept to design the gastroretentive drug delivery systems.

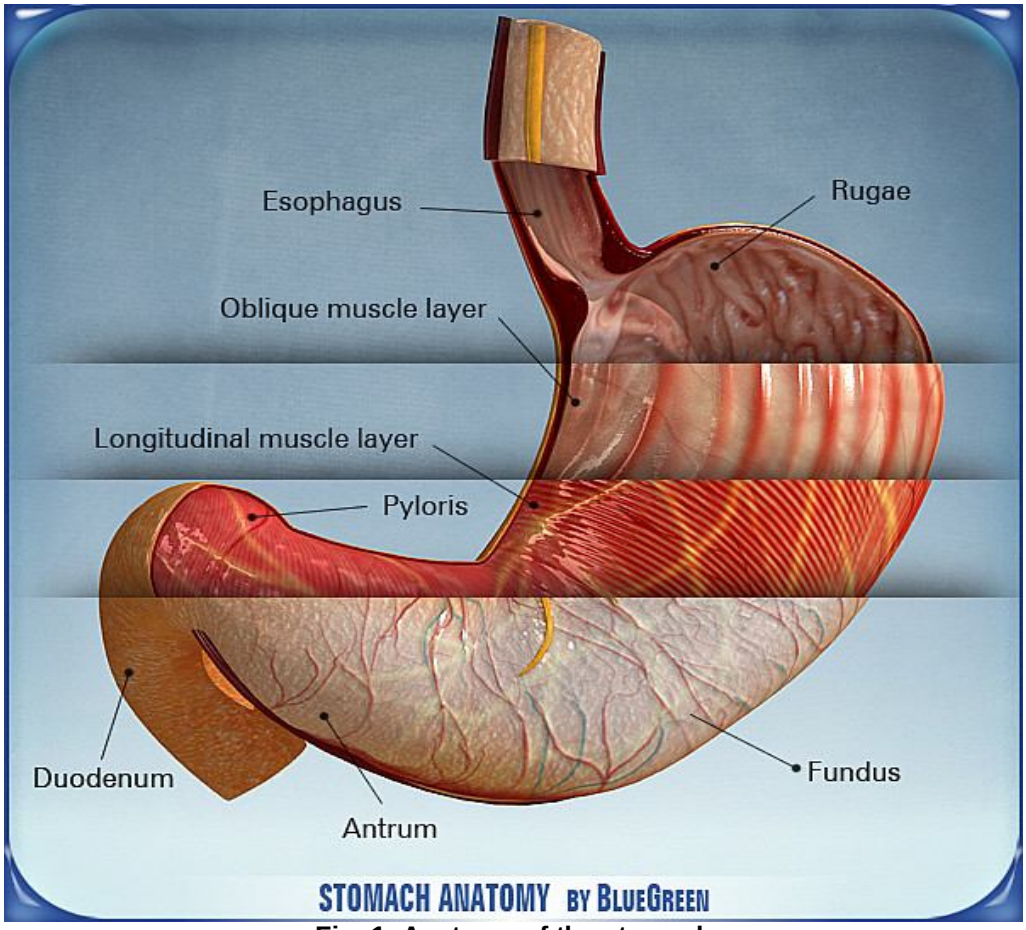

Fig. 1: Anatomy of the stomach

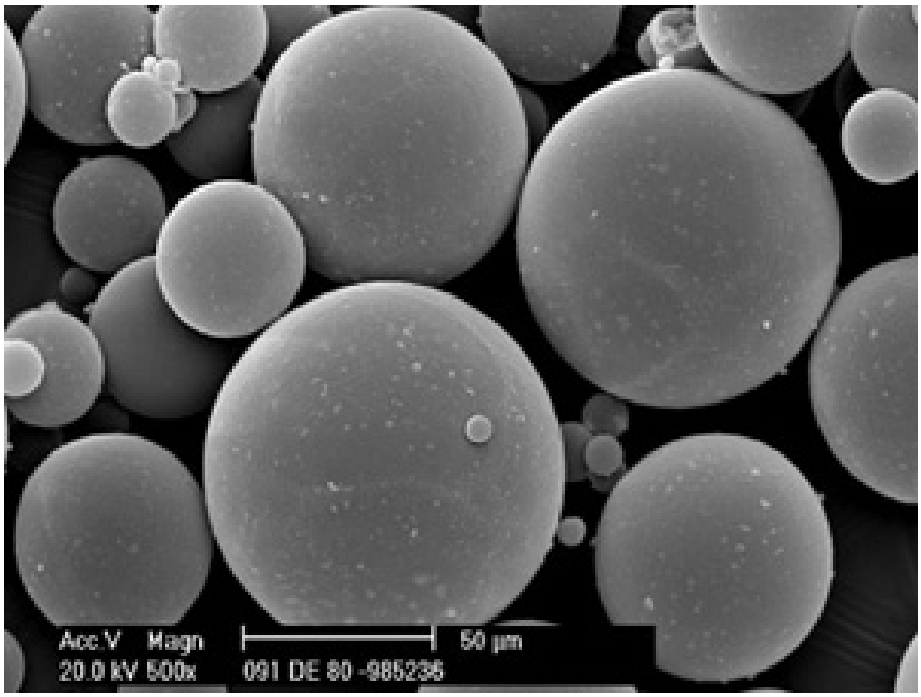

Fig. 2: Hollow microspheres

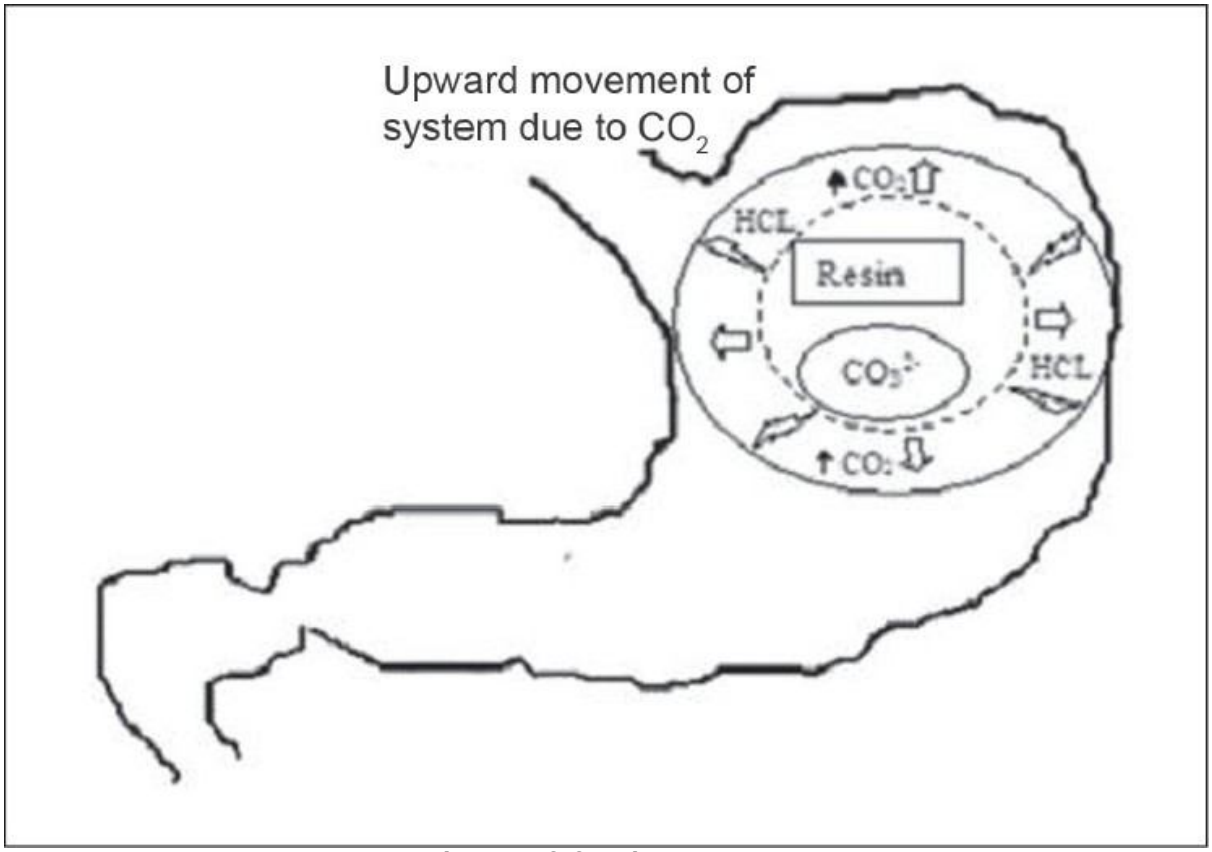

Fig. 3: Raft forming systems

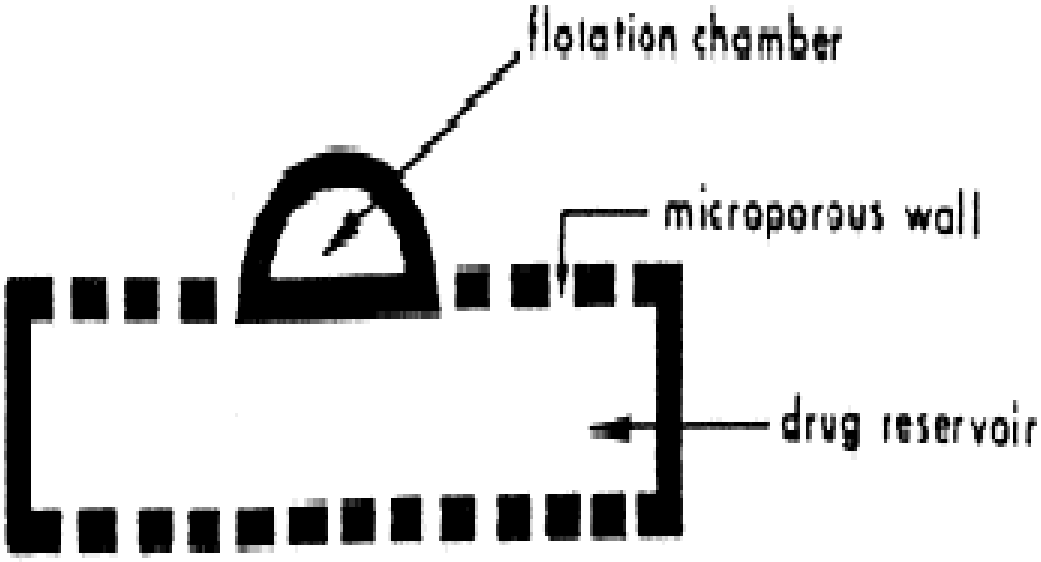

Fig. 4: Microporous compartment system

Table 1: List of various floating gastroretentive marketed formulations

S. No.	Drug	Brand name	Manufacturer
1.	Diazepam floating capsule	Valrelease®	Roche, USA
2.	Antacid preparation	Almagate Flot- Coat®	----------
3.	Aluminium- magnesium Antacid	Topalkan®	Pierre Fabre Drug, France
4.	Benserazide and L- Dopa	Madopar®	Roche products, USA
5.	Ciprofloxacin floating tablets	Cifran OD	Ranbaxy, India
6.	Effervescent floating liquid alginate preparation	Liquid Gaviscon®	Glaxo SmithKline, India
7.	Ferrous Sulphate colloidal gel forming FDDS	Conviron®	Ranbaxy, India
8.	Misoprostol bilayer floating capsule	Cytotec®	Pharmacia, USA

Table 2: Drugs used in formulation of floating dosage forms

Drug	Dosage form
Verapamil Hydrochloride	Floating microparticles
Ketoprofen	Floating microparticles
Ranitidine Hydrochloride	Floating granules
Metronidazole	Floating beads
Lansoprazole	Floating micropellets
Meloxicam	Low density multiparticulate system
Diltiazem Hydrochloride, Theophylline and Verapamil Hydrochloride	Foam based floating microparticles
Nifedipine	Hollow microsphere
Acetohydroxamic acid	Floating microsphere
Piroxicam	Floating microsphere
Residronate Sodium	Granules
Diltiazem Hydrochloride	Granules

REFERENCES

1. Khan AD and Bajpai M. Floating drug delivery system: An overview. Int J PharmTech Res. 2010;2(4):2497-2505.
2. Surana AS and Kotecha RK. An overview on various approaches to oral controlled drug delivery system via gastroretention. Int J Pharm Sci Review & Res. 2010;2(2):68-72.
3. Jain AK and Umashankar H. A review on floating drug delivery system. Int J Pharm studies & Res. 2011;2(3):01-06.
4. Arora S, Ali J, Ahuja A, Khar RK and Baboota S. Floating drug delivery systems: A review. AAPS PharmSciTech. 2005; 6(3):E372-E390.
5. Kadam SM, Kadam SR, Patil US, Ratan GN and Jamkandi VG. Review on floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. Int J Res

Ayurveda & pharm. 2011;2(6):1752-1755.
6. Thakur N, Gupta BP, Patel D, Chaturvedi SK, Jain NP and Banweer J. A comprehensive review on floating oral drug delivery system. Drug Invention Today. 2010;2(7):328-330.
7. Mayavanshi AV and Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A review. Res J Pharm & Tech. 2008;1(4):345-348.
8. Bhowmik D, Chiranjib B, Chandira M, Jayakar B and Sampath Kumar KP. Floating drug delivery system: A review. Sch Res Lib. 2009;1(2):199-218.
9. Geetha A, Rajendra Kumar K, Krishna Mohan CH, Sateesh V and Raju PN. A review on floating drug delivery systems. Int J Pharm Res & Biomedical Analysis. 2012;1(1):1-13.
10. Binoy B and Jayachandran Nair CV. Floating drug delivery system- A new approach in gastric retention- A review. J Drug Del Res. 2012;1(3):18-31.
11. Chandel A, Chauhan K, Parashkar B, Kumar H and Arora S. Floating drug delivery systems: A better approach. Int Current Pharm J. 2012;1(5):110-118.
12. Garg R and Gupta GD. Progress in controlled gastroretentive delivery systems. Tropical J Pharm Res. 2008;7(3):1055-1066.
13. Nayak AK, Maji R and Das B. Gastroretentive drug delivery systems: a review. Asian J Pharm & Clinical Res. 2010;3(1):02-10.
14. Roy Chowdhary and Verma P. Floating drug delivery- A new era in novel drug delivery system. Int J Pharm Res & Bio-Sci. 2012;1(5):91-107.
15. Shah SH, Patel JK and Patel NV. Stomach specific floating drug delivery system: A review. Int J PharmTech Res. 2009;1(3):623-633.
16. Narang N. An updated review on: Floating drug delivery system (FDDS). Int J Allied Pharmaceutics. 2011;3(1):01-07.
17. Sharma N, Agarwal D, Gupta MK and Khinchi M. A comprehensive review on floating drug delivery system. Int J Res Pharmaceutical & Biomedical Sci. 2011;2(2):428- 441.
18. Shaha SH, Patel JK, Pundarikakshudu K and Patel NV. An overview of a gastro-retentive floating drug delivery system. Asian J Pharm Sci. 2009; 4(1): 65-80.
19. Gholap SB, Banerjee SK, Gaikwad DD, Jaadhav SL and Thorat RM. Hollow microsphere: A review. Int J Pharm Sci Review & Res. 2010;1(1):74-79.
20. Mathur P, Saroha K, Syan N, Verma S, Nanda S and Valecha V. An overview on recent advancements and developments in gastroretentive buoyant drug delivery system. Pelagia Rdes Lib. 2011;2(1):161-169.
21. Sharma S, Nanda A and Singh L. Gastroretentive drug delivery system: An overview. Int J Res Pharm & BioMed Sci. 2011;2(3):954-958.
22. Shaikh S, Khurshid M, Nazim S and Khan T. Recent trends in gastroretentive drug delivery system. Int J Pharm Res & Dev. 2013;5(9):80-88.
23. Jagtap YM, Bhujbal RK and Ranpise NS. Floating microspheres: A review. Brazilian J Pharm Sci. 2012;48(1):18-30.
24. Kataria S, Middha A, Sandhu P, Bilandi A and Kapoor B. Microsphere: A review. Int J Res Pharm & Chem. 2011;1(4):1184-1198.
25. Patil JM, Hirlekar RS, Gide PS and Kadam VJ. Trends in floating drug delivery system. J Sci & Industrial Res. 2006;65:11-21.