



FLOATING SYSTEMS: A NOVEL APPROACH TOWARDS GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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ABSTRACT

Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which prolong the gastric emptying time. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems, have been employed. Floating drug delivery systems have a bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releasing the drug slowly at the desired rate from the system. Dosage forms available as gastric floating systems include tablets, capsules, granules and microspheres. This review on GRDDS attempts to compile the available information with all the possible mechanisms used to achieve gastric retention.

Keywords: Gastroretentive drug delivery systems, Floating tablet, Buoyancy capabilities.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day¹. This results in a significant fluctuation in drug levels. Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits². The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantages in prolonging the gastric emptying time. 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 system³, low density systems⁴⁻⁶, raft systems incorporating alginate gels⁷⁻⁹, bioadhesive or mucoadhesive systems¹⁰, high density systems¹¹⁻¹³, super-porous hydrogels¹⁴ and magnetic systems¹⁵⁻¹⁷. Swellable, floating and sustained release tablets are developed by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (croscopolidone and croscarmellose) and effervescent substances (sodium bicarbonate and citric acid).

Objective

The present study attempts to give an insight into the gastroretentive drug delivery systems, and gastric floating tablets, in particular. These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems, recently. The study highlights these advantages with reference to the various types of gastroretentive drug delivery systems, as well as provides an overview of the recent advances that have taken place in this arena.

Gastroretentive drug delivery systems

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby, improve the bioavailability of drugs. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in gastrointestinal absorption of drugs with narrow therapeutic absorption window, as well as, controlling release of drugs having site specific- absorption limitation. Drugs that could take advantage of gastric retention include the drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlorthalidone and cinnarizine), the drugs prone for degradation in the intestinal pH (e.g. captopril), and the drugs for local action in the stomach (e.g. misoprostol). Antibiotics, catecholamines, sedatives, analgesics, anticonvulsants, muscle relaxants, antihypertensives and vitamins can also be administered in HBS dosage form.

Approaches to gastric retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach, for example, bioadhesive approach in which the adhesive capacity of some polymer with glycoprotein is closely applied to the epithelial surface of stomach.

Other approaches include: high density and low density approach.

1) High density approach

For preparing such type of formulations, the density of the pellets should be higher than the stomach fluid. It would be at least 1.50 g/ml. In this type, the drug can be coated or mixed with heavy, non-toxic materials such as barium sulfate, titanium dioxide, etc.

2) Low density approach

Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time. This type is also called as Hydrodynamically Balanced System (HBS).

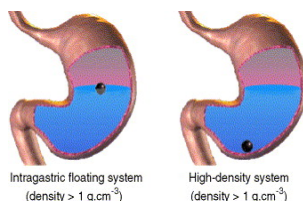


Fig. 1: Diagram of Gastroretentive drug delivery system (low density and high density systems)

Table 1: Conventional v/s Gastroretentive drug delivery system:

Conventional drug delivery system	Gastroretentive drug delivery system
-High risk of toxicity	-Very low risk of toxicity
-Less patient compliance	-Improves patient compliance
-Not suitable for delivery of drugs with narrow absorption window in small intestine region.	-Suitable for delivery of drugs with narrow absorption window in small intestine region.
-Not much advantageous for	-Very much advantageous for
Drugs having rapid absorption through GIT	Drugs acting locally in the stomach.
Drugs which degrade in the colon.	Drugs which degrade in the colon.
Drugs acting locally in the stomach.	Drugs having rapid absorption through GIT
Drugs which are poorly soluble at an alkaline pH	
-No risk of dose dumping.	-Possibility of dose dumping.

Floating Drug Delivery systems and its mechanism:

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they 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 as shown in fig. 2(a). 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

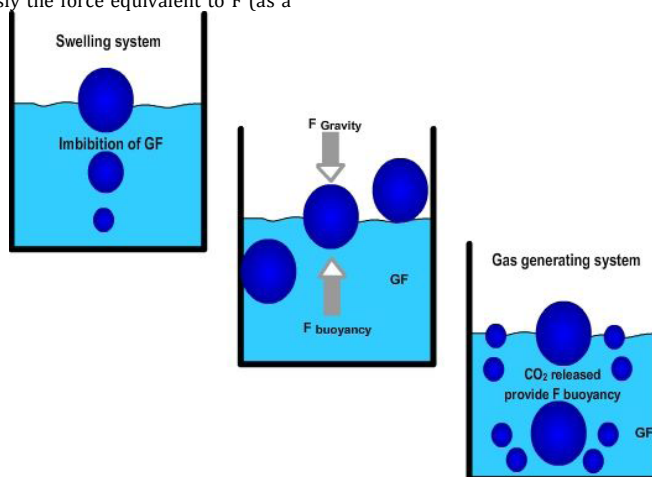


Fig. 2: Mechanism of floating systems, GF= Gastric fluid

Classification of floating system

- 1). Single Unit Floating Dosage Systems
 - a) Effervescent system
 - b) Non-effervescent Systems
- 2). Multiple Unit Floating Dosage Systems
 - a) Effervescent Systems
 - b) Non-effervescent Systems
 - c) Hollow microspheres
- 3). Raft forming system

1). Single Unit Floating Dosage Systems:**a) Effervescent systems**

Effervescent floating drug delivery systems generate gas (CO₂), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid¹⁹.

Penners *et al* prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swells rapidly in an aqueous environment and thus, stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas formed, the density of the system was reduced and thus, the system tended to float in the gastric environment²⁰.

M.Jaimini *et al* prepared the effervescent floating tablet of famotidine. They found that the addition of gel-forming polymer methocel (K100 and K15M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve in vitro buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed²¹.

b) Non effervescent system

Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration, this dosage form swells in contact with gastric fluids and attains a bulk density of less

than 1 g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form.

Iannuccelli *et al* prepared air compartment multiple unit system for prolonged gastric residence. These units were composed of a calcium alginate core separated by an air compartment from membrane of calcium alginate. The porous structure generated by leaching of polyvinyl alcohol (PVA), which was employed as water soluble additive in coating composition, was found to increase the membrane permeability preventing the air compartment shrinkage. The ability of floatation increases with increase in PVA, molecular weight²².

Wu *et al* prepared floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content, a decline in *in vitro* release of nimodipine occurred.²³

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. The main drawback of such system is "all or none" phenomenon. In such cases, there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple, unit dosage forms are designed.



Fig. 3: a) Different layers b) Mechanism of floatation via CO₂ liberation

Chen *et al* studied the effect of formulation variables on *in vitro* performance of floating sustained release of verapamil. The formulations were comprised of variables like polymers excipients, polymer content, density of capsule and amount of effervescent agents²⁵.

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 ratio²⁶.

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 variabilities 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 system, 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.

a) Effervescent system:

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 37°C, 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 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner as shown in fig.3 (a), (b)²⁴.

Thanoo *et al* developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids, as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug²⁷.

Sheth *et al* developed hydrodynamically balanced capsules containing mixture of drug and hydrocolloids containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1, thereby being buoyant on the gastric contents of stomach, until all the drug was released as shown in fig.5²⁸.

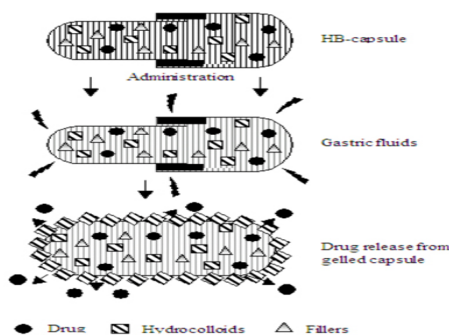


Fig. 5: Working principle of hydrodynamically balanced system

c) Hollow microspheres

Both natural and synthetic polymers have been used to prepare floating microspheres.

Joseph *et al.* developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration versus time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period²⁹.

3) Raft forming system

Raft forming systems have received much attention for the 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 CO₂. Usually, the system ingredients includes 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.

Jorgen *et al.* described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft 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 esophagus³⁰.

Evaluation of Floating Drug delivery system

1) Evaluation of powder blend for-

- a) Angle of Repose
- b) Bulk Density
- c) Percentage porosity

2) Evaluation of tablets for-

- a) Buoyancy capabilities
- b) *In vitro* floating and dissolution behaviour

c) Weight variation

- d) Hardness & friability

e) Particle size analysis, surface characterization (for floating microspheres and beads):

- f) X-Ray/Gamma Scintigraphy
- g) Pharmacokinetic studies

1) Evaluation of powder blend³¹

a) Angle of repose

Angle of repose is defined as "the maximum angle possible between the surface of the pile of powder and the horizontal plane." Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

$$\tan \theta = h/r \quad \text{----}$$

(1)

b) Bulk density

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk .Bulk density is defined as:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}} \quad \text{---- (2)}$$

When particles are packed, it is possible that a large amount of gaps may be present between the particles. Therefore, trapping of powder allows the particles to shift and remove the voids to minimum volume. The volume occupied by the powder in this condition represents the bulk volume. Substituting this volume for a given weight of powder in equation (2) gives the bulk density.

c) Percentage porosity

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc.

$$\% \text{ porosity, } \epsilon = \frac{\text{void volume} \times 100}{\text{Bulk volume}} \quad \text{---- (3)}$$

$$\% \text{ porosity, } \epsilon = \frac{(\text{bulk volume} - \text{true volume}) \times 100}{\text{True density}} \quad \text{---- (4)}$$

2) Evaluation of floating tablets

a) Measurement of buoyancy capabilities of the FDSS

The floating behaviour is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal. 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 water³².

b) *In Vitro* floating and dissolution behaviour

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started". A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of *in vitro* performance of floating dosage forms³².

Pillay *et al.* applied a helical wire sinker to the swellable floating system of theophylline, which is sparingly soluble in water and concluded that the swelling of the system was inhibited by the wire helix and the drug release also slowed down. To overcome this limitation, a method was developed in which the floating drug delivery system was fully submerged under a ring or mesh assembly, and an increase in drug release was observed. Also, it was shown that the method was more reproducible and consistent. However, no significant change in the drug release was observed when the proposed method was applied to a swellable floating system of diltiazem, which is a highly water-soluble drug. It was thus concluded that the drug release from swellable floating systems was dependent upon uninhibited swelling, surface exposure, and the solubility of the drug in water³³.

c) Weight variation

In practice, composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however provides an average weight but contains a problem of averaged value. To help alleviate this problem, the United States pharmacopeia (USP) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP

test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit³⁴.

d) Hardness & friability

Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. Some devices which are used to test hardness are Monsanto tester, strong Cobb tester, Pfizer tester, etc. The laboratory friability tester is known as the Roche Friabilator. This consists of a device which subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm & drop the tablet to a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging, that may be required for these types of tablets³⁴.

e) Particle size analysis, surface characterization (for floating microspheres and beads): The particle size and the size distribution of beads or microspheres are 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)³².

f) X-Ray/gamma scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), 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. 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 GIT³².

g) Pharmacokinetic studies

Pharmacokinetic studies are an integral part of the in vivo studies and several works have been reported on these. Sawicki 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 t_{max} and AUC (0-infinity) values (3.75 h and 364.65ng/ml -1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (t_{max} value 1.21 h, and AUC value 224.22 mg/ml-1h)³².

Table 2: Good candidates for gastroretentive drug delivery system³⁵

S.no.	Drug	Category	Half life	Peak time(hrs)	Bioavailability
1.	Verapamil	Calcium channel blocker	6	1-2	20-35%
2.	Nifedipine	Calcium channel blocker	2	0.5-0.2	45-65%
3.	Omeprazole	Proton pump inhibitor	1-2	1	35-60%
4.	Atenolol	Antihypertensive	4	3	40-50%
5.	Propranolol	Antihypertensive	4-5	4	26%
6.	Verapamil	Antihypertensive	6	1.8	35%
7.	Diltiazem	Calcium channel blocker	3-4.5	50min.	40%
8.	Lidocaine	Local anaesthetic	1.5-2	4	35%
9.	Clarithromycin	Antibiotic	3-4	2-2.5	50%
10.	Ramipril	ACE inhibitor	2-4	3-5	28%

Drugs available As Floating Drug Delivery System

Tablets

- Atenolol³⁶
- Ampicillin³⁷
- Fluorouracil³⁸
- Ciprofloxacin³⁹
- Furosemide⁴⁰
- Acetaminophen⁴¹
- Captopril⁴²

Capsules

- Diazepam⁴³

- Furosemide⁴⁴

- Propranolol⁴⁵

Granules

- Indomethacin⁴⁶
- Diclofenac Sodium⁴⁷
- Prednisolone⁴⁸

Microspheres

- Ibuprofen⁴⁹
- Ketoprofen⁵⁰
- Tranilast⁵¹
- Terfenadine⁵²

Table 3: Some of the marketed formulations available as GRDDS⁴²

Brand name	Delivery system	Drug	Category	Company name
Topalkan®	Floating liquid alginate preparation	Al - Mg	Antacid	Pierre Fabre Drug, France
Convicon®	colloidal gel forming FDDS	Ferrous sulphate	Antianemic	Ranbaxy, India
Cifran OD®	Gas-generating floating form	Ciprofloxacin	Antibiotic	Ranbaxy, India
Valrelease®	Floating capsule	Diazepam	CNS depressant	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide and L-Dopa	Antiparkinsons	Roche Products, USA

Recent advances in stomach specific floating dosage forms:

Sungthongjeen *et al* have prepared a floating multilayer coated tablets based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methyl cellulose), a gas forming layer (sodium

bicarbonate) and a gas-entrapped membrane, respectively. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability.

The obtained tablets enabled to float due to the CO₂-gas formation and the gas entrapment by polymeric membrane. The effect of

formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter the time to float and faster drug release than those using wet-granulated cores. The increased amount of a gas forming agent did not affect time to float but increased the drug release from the floating tablets, while increasing the coating level of gas entrapped membrane increased the time to float (more than 8 hours) and slightly retarded, but sustained drug release⁵³.

Rajnikanth *et al* 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* (*H.pylori*). Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water, to which varying concentrations of the 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* than the corresponding clarithromycin suspension⁵⁴.

CONCLUSION

Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

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