REVIEW ARTICLE

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Gastroretentive drug delivery system: An overview

Bhumika Mangla[1], Vikas Rana[2], Anurekha Jain[1]

[1]Department of Pharmacy, Jayoti Vidyapeeth Women University, Jaipur, Rajasthan, India, [2]Department of Pharmacy, Punjabi University, Patiala, Punjab, India

ABSTRACT

Gastroretentive drug delivery system retains the dosage form for a long span. In this review, we have summarized about factors affecting gastric retention and effervescent and non-effervescent drug delivery systems with the diagram in detail. It also includes *in vitro* evaluation techniques to evaluate the performance of gastroretentive systems. Marketed formulations regarding gastroretentive drug delivery systems are summarized. Detail about mucoadhesive formulations and their role in gastroretention is also discussed in this review. This review gives a full view on gastroretentive systems.

Key words: Effervescent, floating, gastroretentive, non-effervescent

INTRODUCTION

Gastroretentive system ensures that the dosage form remains within the gastric region for the longer duration of time. This provides the advantage that the gastric retention time (GRT) for such drug is improved in comparison to conventional dosage form and also the minimum effective concentration of drug remains maintained in systemic circulation for longer duration.[1]

Gastroretentive drug delivery systems prolong the dosing intervals and hence patient compliance is improved.[2] Gastroretentive drug delivery systems provide the support for reducing the frequent dosing of the drug by producing a controlled delivery within the stomach for longer duration. Although formulations or novel dosage forms such as nanoparticle, microspheres, and liposome can also be used for controlled release (CR) effect, but gastroretentive system is considered a much better alternative for improved absorption through the stomach.[3]

GASTRIC EMPTYING TIME (GET) AND MOTILITY

GET occurs during both fasting as well as fed states. GET is the time required to pass drug from the stomach to the small intestine. It is the rate limiting step for drug absorption because the intestine is the major site for absorption. In general, bioavailability of the drugs is increased by rapid gastric emptying. For drugs that degrade in gastric environment, faster onset is required.[4] The drugs which are poorly soluble at alkaline pH and are majorly absorbed from the stomach or proximal part of the intestine their dissolution is promoted by delayed gastric emptying. However, the pattern of motility is distinct in the two states. The interdigestive series of electrical events takes place during the fasting states, which cycle both through the stomach and intestine every 2–3 h.[5] This is defined as the interdigestive myoelectric cycle or migrating myoelectric cycle, which further consists of following 4 phases that are summarized in Figure 1 and Table 1.

FACTORS INFLUENCING GASTRIC RETENTION OF DOSAGE FORMS

The anatomy and physiology of the stomach contain parameters to be considered in the development of gastroretentive dosage forms.

Important parameters controlling the gastric retention are as follows:

Density of Dosage Forms

The density of a dosage form affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms which are having density lower than the gastric contents can float to the surface, while high-density systems sink to bottom of the stomach.[7] Both the positions may isolate the dosage system from the pylorus part of the stomach. A density of <1.0 g/cm^3 is required to show floating property.[8] Streubel *et al.* prepared the single-unit floating tablets based on polypropylene[9] foam powder and matrix-forming polymer and the incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% wt/wt foam powder (based on the mass of tablet) showed *in vitro* release for at least 8 h. It was thus concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively. The Chitosan-Carbopol 940 mixed matrices that were used to modify release rates in hydrophilic matrix tablets prepared by direct compression, and incorporation of the highly porous low-density copolymer and poly(styrene-divinylbenzene) Copolymer in the matrix tablets provides densities that were lower than the density of the release medium and 17% w/w low-density copolymer (based on the mass of the tablet) was sufficient to achieve proper *in vitro* floating behavior for at least 8 h.[10]

Address for correspondence:
Department of Pharmacy, Jayoti Vidyapeeth Women University, Jaipur, Rajasthan, India

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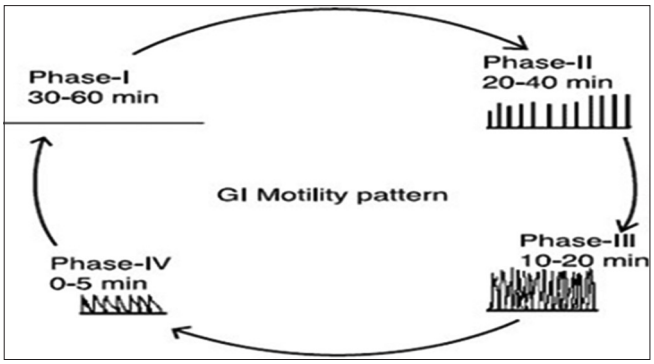

Figure 1: The schematic representation of the gastrointestinal motility pattern

Table 1: Different phases involved in interdigestive myoelectric cycle

Phase-1(basal phase)	It lasts for 40–60 min with contractions which are rare
Phase-2(preburst phase)	It lasts for 40–60 min with intermittent action potential and contractions. The intensity and frequency increase gradually as the phase progresses
Phase-3(burst phase)	It lasts for 4–6 min and it includes intense and regular contractions which remain for short period this is the reason that all the undigested material is swept out of stomach down to small intestine. It is also called as housekeeper wave
Phase-4	The period of transition from phase-3 to phase-1 remains for 0–5 min

Source: Talukder *et al.* (2004)[6]

Shape and Size of the Dosage Form

Shape and size of the dosage forms are important in designing the indigestible single-unit solid dosage forms.[11] Due to the larger size of the dosage form, it will not quickly pass through the pyloric antrum into the intestine.[12] Garg and Sharma[13] reported that tetrahedron- and ring-shaped devices had the better gastric residence time as compared to other shapes. The diameter of the dosage unit is also an important formulation parameter. Dosage forms that are having a diameter of more than 7.5 mm show a better gastric residence time as compared with one having 9.9 mm.

Single- or Multiple-unit Formulation

Multiple unit formulations show a more predictable release profile. The insignificant impairing of performance due to the failure of units allows coadministration of units with different release profiles or containing incompatible substances, and thus, they permit a larger margin of safety against dosage form failure compared with single-unit dosage forms.[11] Sungthongjeen *et al.*[14] developed a multiple-unit floating system which was prepared by extrusions spheronization and consisted of drug-loaded core pellets, and then, it was coated with double layers of an inner gas forming layer (sodium bicarbonate) and a outer with gas-entrapped membrane of an aqueous colloidal polymer dispersion. Thus, this system achieved immediate floating and buoyancy over a period of 24 h with sustained drug release. Sungthongjeen *et al.*[15] prepared the floating multilayer coated tablets in which theophylline was inside the core of the tablet, and it was further coated with a protective layer of hydroxypropyl methylcellulose (HPMC) and a gas forming layer of sodium bicarbonate and a polymeric membrane of high flexibility (Eudragit RL30D), respectively. The polymeric film had high flexibility (Eudragit RL30D) and was capable to entrap generated CO2 and had subsequent good floating properties. Ichigawa *et al.*[16] developed a floating system by coating the sustained release granules with tartaric acid layer, sodium bicarbonate layer, and polymeric film which consisted of polyvinyl acetate and shellac.

Food Intake and Its Nature

Food intake, viscosity and volume of food, caloric value, and frequency of feeding are the factors that have a profound effect on the gastric retention of dosage forms. The presence or absence of food influences the GRT of the dosage form. Usually, the presence of food in the gastrointestinal tract (GIT) improves the gastric retention for a longer period, by allowing its stay at the absorption site. Again, increase in acidity and caloric value slows down GET, which thus improves the gastric retention of dosage forms (Garg et al, 2008).[5] Sugihara *et al.*[17] studied the effect of food intake on gastroretentive and mucoadhesive submicron-sized chitosan-coated liposomes. In this study, chitosan-coated liposomes and uncoated liposomes containing fluorescent dye were orally administered to fasted or fed rats. The stomach and small intestine of rats were removed after a certain duration of time. The dye retentive properties were quantitatively confirmed by measuring the amount of dye in each part.

Effect of Gender, Posture, and Age

In general, females have slower gastric emptying rates than male partner. The postural effect does not have any significant difference in the mean GRT for individuals in the upright, ambulatory, and supine state. However, in elderly persons, gastric emptying is slowed down.[18] Timmermans e*t al.*[19] studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process using *in vivo* gamma scintigraphy. In this study, floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units) were considered. Then, the floating and non-floating were compared, and it was concluded that, regardless of their sizes, the floating dosage units remained buoyant on the gastric contents throughout their residence in the GIT. It was also observed that the floating units had the longer gastric residence time for small and medium units, while no significant difference was seen between the two types of large unit dosage forms, and it was further concluded that in supine position large dosage forms (both conventional and floating) experience prolonged retention.

Formulation techniques

Due to physiological variation in the gastric environment, the aim to achieve retention of drug in the stomach could be fulfilled by modifying drug delivery systems. Thus, various approaches have been used to retain drug in the gastric environment for the longer duration of time. The detail is shown in Figure 2. The different patented technologies are summarized in Table 2.

HIGH-DENSITY (SINKING) SYSTEM OR NON-FLOATING DRUG DELIVERY SYSTEM (FDDS)

This approach involves the formulation of dosage forms with the density more than the density of normal stomach content

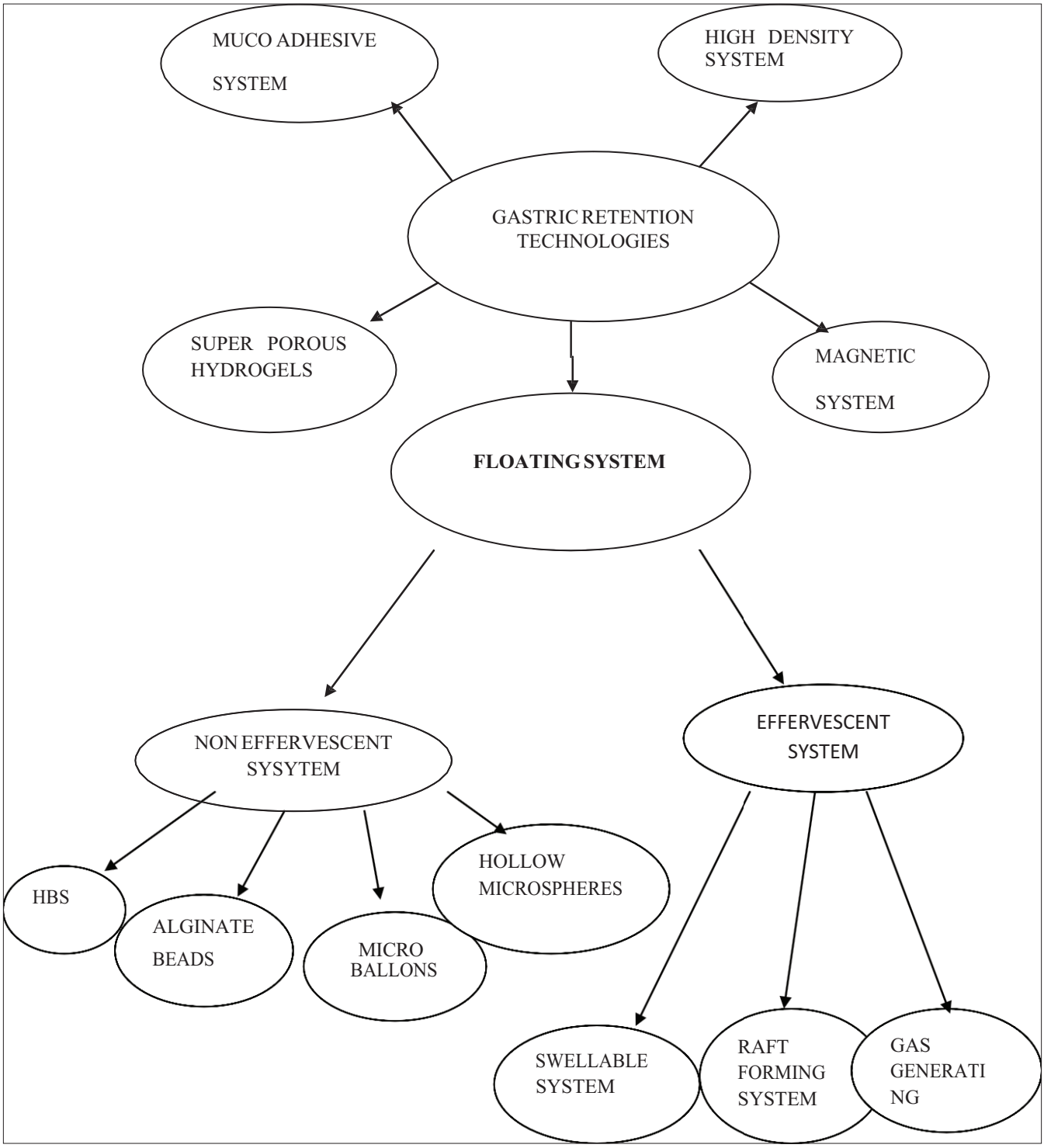

Figure 2: Different approaches to achieve gastric retention

(~1.004 g/cm^3). They are formulated by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide, and titanium oxide.[20] The materials increase the density up to 1.5–2.4 g/cm3. A density that seems to be necessary for significant prolongation of gastric residence time must be close to 2.5 g/cm Rouge *et al.*[21] performed a comparative study with an immediate release system, a high-density system, and a low-density system. The results depicted gastric residence times of 0.5, 1, and 2 h, respectively, indicating that the high-density system did not demonstrate any significant extension of the gastric residence time. However, the effectiveness of this system in human beings was not observed[22] and no such system existed in market. Devereux *et al.* [23] prepared pellets with density of at least 1.5 g/mland showed that they have significantly higher residence time both in fasted and fed state. Tuleu *et al.*[24] also prepared three types of non-disintegrating pellets with the same

Table 2: Various gastroretentive patented technologies

Drug	Dosage form	Purpose of patent	Polymer used	Evaluation	Reference
Metformin hydrochloride	The formulation consists of gastric retention pellet of metformin hydrochloride	Gastroretention patent for mucoadhesive delivery system	HPMC, Na alginate, Na-CMC, carbomer 934, Chitosan	Adhesion studies were done using texture analyzer. *In vitro* dissolution tests were performed according to the dissolution test method of USP XXII. *In vivo* study was performed, and the concentration of metformin in the solution was measured by HPLC	[39]
Rosiglitazone	A CR oral dosage form of rosiglitazone in the form of pellets	Gastroretentive technology for swelling and expanding systems	Polymeric matrix is HMC, a CMC, oral combination of alkyl celluloses, is poly (ethylene oxide)	This solid polymeric matrix on imbibitions of water swells, and retains within HEC, HPC, HPMC, hour, ≥40 weight percent of the rosiglitazone after immersion in simulated gastric fluid	[40]
Heparin and insulin	A bilayered SR tablet or caplet composition of heparin and insulin	Gastroretentive technology for swelling and expanding systems	The release-controlling polymer was polyethylene oxide, polyethylene, and Carbopol® 934 P	The *in vitro* dissolution of both SNAC and heparin in simulated intestinal fluid was measured. It was believed that this formulation could be retained in the stomach for much longer that the 4 h	[41]
Flouroquinolones, amoxicillin, cephalexin, metformin, gliclazide, diltiazem, metoprolol	Bouyant biconvex caplets were formed	Patent for floating mechanism	Methyl cellulose, HPMC, and HPC with the exclusion of low substituted HPC were used as gelling agents	Dissolution study was done in 0.1 N HCl using USP type-II apparatus at 100 rpm	[42]
Methotrexate alone or in combination with folates	Monolithic SR tablet of methotrexate alone or in combination with folates	Patent covering swelling, floating and mucoadhesive mechanisms	Polymers used are cellulose derivative such as a hydrophilic polymer which comprises Carbopol, HPC, and HMC etc.	*In vitro* dissolution was done in USP 23 paddle app 2 at a paddle speed of 50 rpm in 900 ml SGF (pH 1.2, no enzyme) at 37±0.20C for 24 h. Floating time and floating lag time and bioadhesive strength was measured.	[43]
Acyclovir	A CR oral tablet	Gastroretentive technology for swelling and expanding systems	Stearyl macrogol glyceride polyethylene oxide, Crospovidone etc.	Swelling studies were determined in 0.1 N HCL and combination of a swelling enhancerand polymer resulted in faster rate of swelling, as was desired for gastroretention	[44]
Bupropion HBr	Matrix type CR tablet dosage form	Gastroretentive Technology for swelling and expanding systems	Combination of polymers such as EC and the was HEC and HPMC	*In vitro* dissolution of formulations in different USP-3 Media, i.e., SGF, pH 1.2, acetate Buffer ph 4.5, and phosphate buffer ph 6.8 over 16 h is done.	[45]
Gabapentin and metformin	Gabapentin SR and metformin SR tablets	Gastroretentive technology for swelling and expanding systems	Combination of HPC and HPMC was used in sustain release study.	The bioavailability of gabapentin SR tablets, made by wet granulation process, was evaluated in healthy human volunteers.	[46]
Nadolol and metoprolol	Oral CR matrix tablet formulation of nadolol, and metoprolol	Gastroretentive technology for swelling and expanding systems	The first component was PVA combined with PVP, and second component was cellulose ether polymer	The acute reduction in airway function (FEV-i) was measured in subjects with mild asthma with the first 10 mg dose of once-daily corgard (nadolol). The peak serum levels of nadolol occurred in 3.5 h after administration	[47]
Parathyroid hormone	Gastro retentive drug delivery system enclosed in a capsule consisting of parathyroid hormone	Gastroretentive technology for swelling and expanding systems	Polymers selected were cross-linked hydrolyzed gelatin and polymeric strips comprised of eudragit L100, ethylcellulose, and triacetin	The results of the stability study in various buffer solutions showed that the peptide showed decreased stability at PH>7 and at pH=1.2	[48]
Thrombin inhibitor	A monolayered SR dosage form of Thrombin inhibitor	Patent for floating mechanism	HPMC, HPC, PVA	A pharmacokinetic study in dogs by giving iv bolus dose was done. The slug capsules increased the APTT to the therapeutic range of 1.5–2.5 at the 24 h time point.	[49]

(Contd...)

Table 2: (*Continued*)

Drug	Dosage form	Purpose of patent	Polymer used	Evaluation	Reference
Amoxicillin and clavulanic acid	SR gastroretentive amoxicillin and clavulanic acid	Patent for floating mechanism	HPMC. Suitable coatings of applied of HPMC, HPC, HEC, MC or PVP, combinations of different polymers were used	A pharmacokinetic evaluation of the therapeutic system was done in twelve healthy male volunteers in fed conditions	[50]
Botulinum toxin type A	Botulinum toxin type A oral formulation consisting of polymeric microspheres	Gastroretentive patent for mucoadhesive delivery system	A carrier polymer of polylactides, polyglycolides, and polyanhydrides	-	[51]

APTT: Activated partial thromboplastin time, HPMC: Hydroxypropyl methylcellulose, PVA: Polyvinyl alcohol, HEC: hydroxethyl cellulose, HPC: Hydroxypropyl cellulose, CR: Controlled release, PVP: Polyvinyl pyrrolidone

size and different densities and found that with an increase in density GI transit time increases.

FDDS

FDDS or hydrodynamically controlled systems are low-density systems that float over the gastric contents because of their sufficient buoyancy and remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate.[25] The drug is released slowly from the floating system at a desired rate. The residual system is removed from the stomach after the release of drug. According to buoyancy retention principle, a minimal gastric content is needed to allow the proper achievement of the buoyancy; however, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.[26] The mechanisms of the floating system are shown in Figure 3.[27]

The major requirements for FDDS are that the contents should be released slowly to serve as a reservoir, specific gravity must be maintained lower than gastric contents (1.004–1.01 g/cm^3) and be cohesive gel barrier. The inherent low density can be provided by the entrapment of air as in case of hollow chambers or it can be achieved by the incorporation of low-density materials (e.g., fatty material, oils, or foam powder).[28,29]

These approaches have been used for the design of floating dosage forms (FDFs) of single- and multiple-unit systems. Streubel *et al.*[9] proposed a single-unit floating system consisting of polypropylene foam powder, matrix-forming polymers, drug, and filler. The good floating behavior of these systems could be successfully combined with drug release patterns. Single-unit dosage forms are concerned with problems such as sticking together or being obstructed in the GIT which may produce irritation. Multiple unit floating systems reduce the inter and intra subject availabilities in drug absorption as well as lower the possibility of dose dumping. Based on the mechanism of buoyancy, two different technologies that have been utilized are non-effervescent and effervescent in the development of FDDS and various polymers are described in Table 3.

Non-effervescent Systems

Non-effervescent FDDSs are prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides,

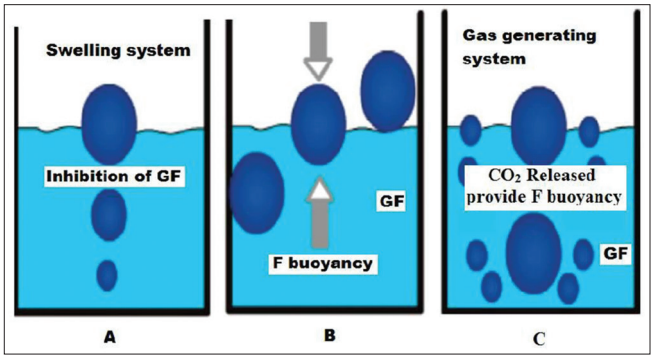

Figure 3: Mechanisms of floating system (Patel et al., 2012)

or matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate.[30] In the first approach, the drug is intimately mixed with a gel-forming hydrocolloid so that when comes in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment.[31] The air trapped by the swollen polymer provides buoyancy to these dosage forms. The excipient used most commonly includes HPMC, polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate (Alg), calcium chloride, polyethylene oxide, and polycarbonates.[5] This system can be further divided into the subtypes.

Hydrodynamically balanced systems

Hydro-dynamically balanced systems contain drug with gel forming hydro-colloids that remain buoyant on the stomach content.[32] They are single-unit dosage form, containing one or more gel-forming hydrophilic polymers such as HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenans, or alginic acid.[33,34] The polymers are mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to a dosage form for a long period in gastric juice as shown in Figure 4 (Dhiman *et al.,* 2011).[35] The continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and provides buoyancy to dosage form fatty excipient can be incorporated to give low-density formulations reducing

Table 3: Various polymers and their formulation for floating drug delivery systems

Polymer	Drug	Formulation	*In vitro* performance	Retention time	Reference
Sodium alginate	Cloxacillin	Multiple unit alginate-based floating system	The alginate beads showed drug entrapment efficiency of 64.63±0.78%, density of 0.90±0.05 g/cm^3, and drug release of 56.72±0.85% in simulated gastric fluid (pH 1.2)	The beads showed prolonged sustained release ofcloxacillin over 8 h in simulated gastric fluid (pH 1.2)	[52]
HPMC, Eudragitated 30D, PEG-6000	Zolpidem tartarate	Multipartic ulate floating drug delivery system	The dosage form of zolpidem tartrate showed release according to biphasic profile of dissolution, where the first phase is immediate release phase for inducing the sleep and the second phase is modified release phase for maintaining the sleep upto 10 h	The system floated for about 10 h	[53]
Guar gum, locust bean gum, HPMC K 100M	Ofloxacin	Floating matrix tablets of ofloxacin	Formulation prepared with guar gum started floating after 7.83 min and remains buoyant for 8 h till they were completely eroded	The formulations showed drug release from 8 to 12 h	[111]
HPMC, EC, Chitosan	Rabeprazole sodium	Floating microspher es	The microspheres showed drug release for about 12 h	The microspheres were retained for about 12 h	[54]
EC and PEG	Ranitidine hydrocloride	Floating microspheres	The microspheres showed drug loading, entrapment, and encapsulation as 23–32, 86–96 and 75–86% (w/w), respectively	The drug loaded microspheres floated for 10 h and sustained the drug release over 4–6 h	[55]
Sodium alginate, locust bean gum and xanthan gum	Acyclovir	Floating tablet	Floating lag time was from 15 to 120 s and tablet of each batch remained buoyant up to 16 h best formulation remain buoyant up to 24 h	Formulation containing 60% of Locust bean gum and 40% sodium alginate showed drug release for 24 h	[56]
Metolose 90 SH100, 000 SR	Zn-acetate	Floating matrix tablets	Lag time varied from 1 to 4 min with varying amount of effervescent agent and floated for about 4 h	The formulation showed *in vitro* drug release for about 4 h	[57]

HPMC: Hydroxypropyl methylcellulose, EC: Ethyl cellulose

the erosion. Madopar LP®, based on this system, was marketed during the 1980's (Bardonnet *et al.,* 2006).[36] Ali *et al.*[37] developed a hydrodynamically balanced system of metformin as a single-unit floating capsule using various grades of low-density polymers which were prepared by physical blending of metformin and the polymers in varying ratios.

The formulation was optimized on the basis of *in vitro* buoyancy and *in vitro* release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0), and the effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules that were prepared with HPMC K4M and ethyl cellulose (EC) gave the best *in vitro* percentage release and were taken as the optimized formulation. Singh *et al.*[38] (2010) prepared hydrodynamically balanced system of directly compressible floating-bioadhesive tablets of tramadol using varying amounts of Carbopol 971P (CP) and HPMC. This system was characterized by *in vitro* drug release profile, buoyancy characteristics and *ex vivo* bioadhesive strength using texture analyzer and optimized using a 3^2 central composite design.

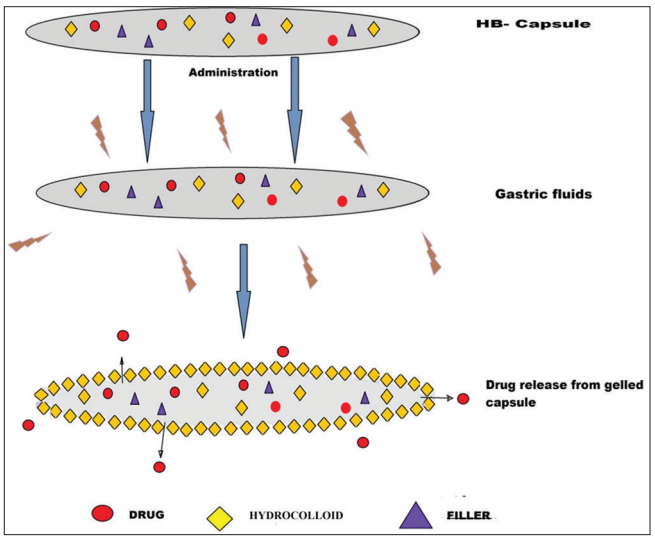

Figure 4: Mechanism of hydrodynamically balanced system

Microballoons/hollow microspheres

Microballoons/hollow microspheres which are loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion/evaporation methods to prolong the GRT of the dosage form [Figure 5].[7,59] Commonly used polymers for these systems are polycarbonate, cellulose acetate, calcium Alg, Eudragit S, agar, and low methoxylated pectin. The buoyancy and drug release from dosage form are dependent on the quantity of polymers, the plasticizer polymer ratio, and the solvent used for the formulation. Such type of microballoons floated continuously over the surface of an acidic dissolution media containing a surfactant for >12 h.[5] Hollow microspheres are considered to be one of the promising buoyant systems because they combine the advantages of multiple-unit system and good floating. Junyaprasert[60] and Pornsuwannapha prepared hollow microspheres of acyclovir by solvent evaporation diffusion method using Eudragit S 100 as a controlled polymer and found that the highest % yield of the hollow microspheres was obtained with the use of 5:8:2 of dichloromethane:ethanol:isopropanol as a solvent system and stirring at 300 rpm for 60 min. With the increase of drug-to-polymer ratio, the size and percent

drug content were increased. Ma *et al*.[61] prepared multi-unit floating Alg microspheres employing inotropic gelation method. In this technique calcium carbonate was used as gas forming agent and drug release was delayed by adding Chitosan (Cs) into the gelation medium and by coating with Eudragit, respectively. Hence, it was found that the drug encapsulation efficiency of Cs–Alg microspheres was much higher than that the Ca–Alg microspheres and coating the microspheres with Eudragit RS extended the drug release significantly.

Alg beads

Talukdar and Fassihi[62] developed a multiple-unit floating system. They were made using a combination of Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium Alg. Multiunit FDFs were developed from freeze-dried calcium Alg. Spherical beads can be prepared by dropping a sodium Alg solution into an aqueous solution of calcium chloride of approximately 2.5 mm in diameter, causing precipitation of calcium Alg.[63] In another study, floating systems comprising of a calcium Alg core separated by an air compartment from

membrane of calcium Alg or calcium Alg/polyvinyl alcohol (PVA) were developed. The porous structure that was generated by leaching of PVA, (a water-soluble additive in coating composition) was found to increase the membrane permeability preventing the collapse of air compartment.[64] Shishu *et al*.[65] prepared a multiple-unit type oral FDF of 5-fluorouracil (5-FU) to prolong gastric residence time, target stomach cancer, and increase drug bioavailability. The floating bead was prepared by dispersing 5-FU together with CaCO3 into a mixture of sodium Alg and HPMC solution and then dripping the dispersion into an acidified solution of calcium chloride, and hence, calcium Alg beads were formed by inotropic gelation and carbon dioxide was developed from the reaction of carbonate salts with an acid. Jaiswal *et al.* (2009)[66] prepared the multi-unit gastroretentive sustained release dosage form of a water-soluble drug, ranitidine hydrochloride by emulsion gelation technique, and prepared beads using sodium Alg as the polymer and oil were entrapped in the beads by gently mixing or homogenizing oil and water phase containing sodium Alg which was then extruded in to calcium chloride solution. Hence, the beads successfully delivered the drug in the stomach for a prolonged duration of time.

Microporous compartment system

This approach utilizes the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls.[7] The peripheral walls of the device were completely sealed to prevent any direct contact of the undissolved drug with the gastric surface. The buoyancy chamber in the stomach containing entrapped air causes the delivery system to float in the gastric fluid.[67] The gastric fluid that enters through the aperture dissolves the drug and causes continuous transport of the dissolved drug across the intestine for drug absorption [Figure 6].[68]

Effervescent FDFs

Gas generating systems

These are matrix type of systems that are prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, for example, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when they come in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms as shown in Figure 7.[1] *In vitro* studies, the lag time before the unit floats is <1 min, and the buoyancy is prolonged for 8–10 h.[69] *In vivo* experiments in fasted dogs, they showed that mean gastric residence time was increased up to 4 h, compressing the gas generating components in a hydrocolloid-containing layer and the drug in another layer which was formulated for a sustained release effect, thereby producing a bilayered tablet. The different floating systems available in the market are given in Table 4.

Swelling system

This type of dosage form swell to an extent that prevents their exit from the pylorus. Therefore, the dosage form is retained in the stomach for a longer period of time. Such systems may be named as "plug type systems." Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release when it comes in contact with gastric fluid, the polymer imbibes the water and swells.[76] The diagrammatic representation of drug release from swellable system is shown in Figure 8.[7] Arza *et al*.[77] (2009) developed swellable, floating, and sustained release tablets made using a combination of hydrophilic polymer HPMC, swelling

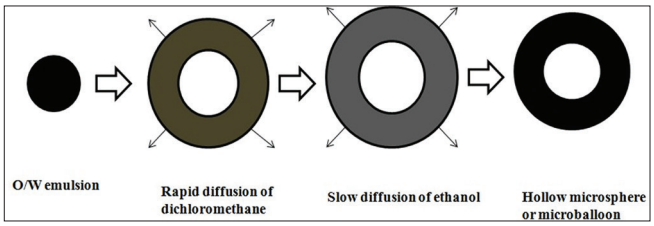

Figure 5: Formulation of floating hollow microsphere or microballoon

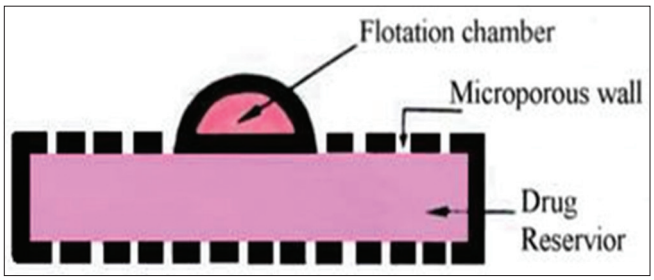

Figure 6: Microporous compartment system (Shah *et al*., 2009)

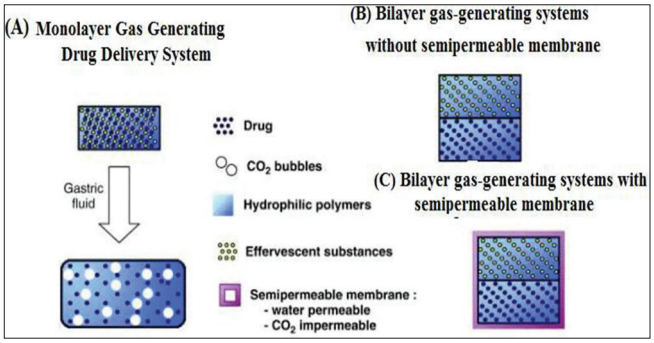

Figure 7: Different types of effervescent generating systems (Majethiya *et al*., 2013)

Table 4: Floating drug delivery systems available in the market

Name of product	Active ingredient	Category	Name of company
Zanocin OD	Ofloxacin	Effervescent floating system	Ranbaxy, India
Inon ace tablets	Siméthicone	Foam-based floating system	Sato Pharma, Japan
Prazopress XL	Prazosin Hcl	Effervescent and swelling-based floating system	Sun Pharma, Japan
Cafeclor LP	Cefaclor	Minextab Floating®	Galenix, France
Gabapentin GR	Gabapentin	Polymer-based swelling technology: AcuForm™(In phase three clinical trial)	Depomed, USA
Tramadol LP	Tramadol	Minextab Floating®	Galenix, France
Baclofen GRS	Baclofen	Coated multi-layer floating and swelling system	Sun PHarma, India
Riomet OD	Metformine Hcl	Effervescent floating system	Ranbaxy, India
Conviron	Ferrous sulfate	Antacid	Ranbaxy, India
Cytotec	Misoprostol	Bilayer floating capsule	PHarmacia Limited, UK
Cifran OD	Ciprofloxacin (1 mg)	Antibiotic	Ranbaxy, India
Almagate flotcoat	Al and Mg antacid	Antacid	-
Topalkan	Alginic acid, Aluminum and Magnesium salts	Antacid	Pierre, Fabre drug, Fabrace
Madopar HBS capsule	Levodopa (100 mg) and benserazide (25 mg)	Antiparkinsonial	Roche, USA
Liquid Gaviscon	Al Hydroxide (95 mg), Mg carbonate (358 mg)	Antacid (in reflux esophagitis)	Glaxo Smithline, India
Valrelease Capsule	Diazepam (15 mg)	Anti anxiety	Hoffman-La Roche, USA

Source: (Srikanth *et al.*, 2011; Jain *et al.*, 2005; Fagregas *et al.*,1994; Degtiareva *et al.*,1994; Erni *et al.*,1987; Washington *et al.*,1986)[70-75]

agents (crospovidone, sodium starch glycolate, and croscarmellose sodium), and effervescent substance (sodium bicarbonate). It was found that combination of HPMC K100M, crospovidone, and sodium carbonate showed good swelling, drug release, and floating characters which is even better than the CIFRAN OD®.

Raft-forming systems

Raft-forming systems have received attention for the delivery of antacids and drug delivery for GI infections and disorders.[78] This system floats on gastric contents of the stomach. The mechanism involved behind 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 its low bulk density due to the formation of CO2. Usually, this system contains a gel-forming agent and alkaline bicarbonates or carbonates which are responsible for the formation of CO2 and thus make the system less dense and float on the gastric fluids. The

system contains a gel-forming agent, for example, alginic acid, sodium bicarbonate, and acid neutralizer, which forms a foaming sodium Alg gel called (raft) when it comes in contact with gastric fluids. This raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e., gastric acid) into the esophagus, thus acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd. describes a raft-forming formulation for the treatment of *Helicobacter pylori* infections in the GIT. The composition includes drug, alginic acid, sodium bicarbonate, CaCO3, mannitol, and a sweetener. These ingredients were granulated, and then, citric acid was added to the granules. The formulation thus produced effervescence which resulted in floating.[79,80]

Raft-forming drug delivery systems are a revolution in oral drug delivery system. These systems are liquids at room temperature, but when come in contact with body fluids or change in pH undergo gelation, these possess a unique property of temperature dependent and cation-induced gelation. Gelation involves

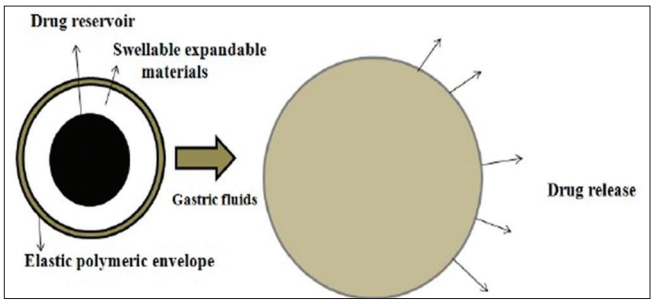

Figure 8: Drug release from swellable systems (Nayak et al., 2010)

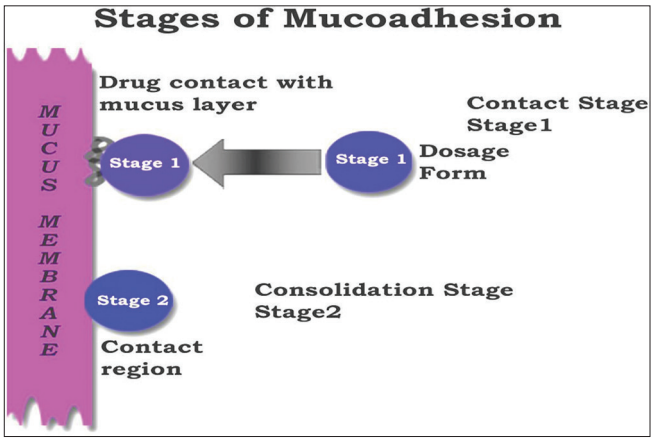

Figure 9: Stages of mucoadhesion (Alexander et al., 2011)

the formation of the double helical junction zones followed by aggregation of the double helical segments which form three-dimensional networks by complexation with cations and hydrogen bonding.[81] Various raft-forming system developed for retaining drugs in the stomach for a longer duration of time is summarized in Table 5.

Advances in raft-forming approach

The Algs were used conventionally as an excipient in drug products depending on the thickening, gel-forming, and stabilizing properties. Alg-based raft-forming formulations have been marketed worldwide for over 30 years under various brand names, which includes Gaviscon.[82] They are used for the symptomatic treatment of heartburn and esophagitis and appear to act by a unique mechanism which is quite different from that of traditional antacids. In the presence of gastric acid, Algs precipitate, thus forming a gel. Alg-based raft-forming formulations usually contain sodium or potassium bicarbonate which in the presence of gastric acid gets converted into carbon dioxide which becomes entrapped within the gel precipitate, converting it into foam which floats on the surface of the gastric contents, much like a raft on water. The *in vitro* and *in vivo* studies demonstrated that Alg-based raft system entraps carbon dioxide as well as antacid components contained in the formulations. Thus, they provide a relatively pH-neutral barrier. Several studies have demonstrated that the Alg raft can move preferentially into the esophagus in place, or ahead,

Table 5: Different floating systems and their evaluation

Drug	Floating system (polymer and effervescent agent)	Evaluation	Reference
Cefuroxime axetil	HPMC K4M, HPMC 15 M, HPMC100M, $NaHCO_3$	Lag time - 2 min duration more than 12 h and showed *in vitro* release for 12 h and *in vivo* radiographic studies indicated drug in stomach for about 6 h	[97]
Metformin hydrochloride and glibenclamide	HPMC K100 and $NaHCO_3$	Lag time - 27 s and duration more than 8 h and showed *in vitro* release for more than 8 h	[98]
Diltiazem hydrochloride	HPMC K4M, Na CMC, Carbopol 934	Lag time 1–3 min and duration of 17 h and gave 100% drug release in 12 h	[99]
Pioglitazone hydrochloride	HPMC5LV, HPMC 15 LV, HPMC50LV, ethyl cellulose, $NaHCO_3$	Lag time 60–80 s And duration 18–20 h and gave *in vitro* drug release for more than 24 h	[100]
Propanolol HCl	Badam gum, $NaHCO_3$	Lag time<3 min and duration of 6–16 h for different formulations and gave *in vitro* release for more than 12 h	[101]
Cetrizine dihydrochloride and bergenin	HPMC, $NaHCO_3$	Lag time<2 min and duration more than 10 h and sustain release for more than 12 h was obtained and *in vivo* studies proved that drug was retained in stomach for more than 5 h	[102]
Clarithromycin and esomeprazole	Xanthan gum, guar gum, HPMC K4M, $NaHCO_3$ agent and porous carrier calcium silicate, polypropylene and aerosol	It explained the role of porous carriers, cellulosic polymers, and natural gums on drug release profiles of esomeprazole core in clarithromycin coat gastroretentive tablets in duodenal ulcer treatment. and drug release for more than 12 h was obtained with minimum lag time	[103]
Furosemide	HPMC K4M, HPMC K 15 M, HPMC K 100M, Chitosan, $NaHCO_3$	Lag time <1 min and duration 8 h and *in vitro* drug release for more than 8 h	[104]
Norfloxacin	Guar gum, Na CMC, HPMC 15M, $NaHCO_3$	Lag time - 2.75 min–7 min and duration more than 24 h and provided sustain release for more than 12 h	[105]
Dextromethorphan hydrobromide tablets	HPMC as gel material, sodium bicarbonate as gas generating agent, hexadecanol as floating assistant agent.	Lag time-3 min and duration more than 24 h. The data of physical parameters were all lie within the limits. Drug release at 12 h was more than 85%.	[106]
Baclofen	Methocel K 100, Methocel K15 M, HPMC E-6 LV, $NaHCO_3$	Lag time - 3–4 min, duration of floating more than 10 h and drug release for more than 10 h and X-ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.50±0.7 h	[107]
Glipizide	HPMC, EC and MC, $NaHCO_3$	Buoyancy 10-16 h and *in vitro* release were found in the range of 59.25–79.50%. in 8 h	[108]
Lornoxicam	HPMC K15, $CaCO_3$	Lag time - <1 min, duration more than 24 h released 55% drug after 8 h	[109]
Tizanidine	HPMC K4M, HPMC K 15 M, HPMC K100M	Buoyancy - 12 h and drug release for more than 12 h and t-50 was 5.4 h in radiographic studies and in-vivo studies in human volunteers showed that mean gastric residence time was 6.2±0.2 h	[110]
Ofloxacin	Guar gum, locust bean gum, HPMC K100 and $NaHCO_3$	Formulation with locust bean gum and HPMC gave lag time 2–3 min, duration more than 12 h, and drug 97.8% and 97.33% in 12 h	[111]
Aceclofenac	HPMC E5 M and Eudragit RS 100, $NaHCO_3$	Formulation gave floating time –08–12 h and showed *in vitro* drug release for more than 8 h	[112]
Nimodipine and its inclusion complex with beta cyclodextrin	HPMCK4M, HPMC K 15 M, HPMC15, HPMC K100M, Eudragit RSPO, $NaHCO_3$	Floating duration 24 h and gave release over 24 h with the 99.89%	[113]
Ciprofloxacin	Carbopol 971P, Xanthan gum, HPMC K 100M, crospovidone, Na, CMC, $NaHCO_3$	Lag time<20 s and duration more than 24 h and gave *in vitro* release for more than 24 h	[114]

(Contd...)

Table 5: *(Continued)*

Drug	Floating system (polymer and effervescent agent)	Evaluation	Reference
Nizatidine	HPMC K4M, HPMC K 15 M, Na CMC, $NaHCO_3$	Lag time for best formulation HPMC K4M<1 min and floating more than 12 h and drug release for 12 h and during *in vivo* in healthy human volunteers was observed and MRT in the stomach was found to be 320 min	[115]
Norfloxacin	HPMC K4M, HPMC K100M, and Xanthan gum, Citric acid	Duration of floating more than 24 h, and tablets were retained in stomach for 205±8.4 min in fasting human volunteers and in-vivo studies were also carried out in healthy human volunteers and compared with the marketed formulation	[116]
Stavudine	HPMC K100M, Na CMC, $NaHCO_3$	Lag time<1 min and *in vitro* release more than 12 h and floating duration more than 10 h	[117]
Atorvastatin calcium	Methocel K4M and Methocel K15M, $NaHCO_3$ and citric acid	Lag time<1 min and floating time of 20 h of best formulation and showed *in vitro* release for more than 8 h	[118]
Famotidine	HPMC K100M, HPMC K 15 M, $NaHCO_3$, Citric acid	Lag time<40 s and duration more than 12 h and showed *in vitro* release for more than 8 h	[119]

HPMC: Hydroxypropyl methylcellulose

of acidic gastric contents during the gastroesophageal reflux; some studies further suggest that the raft can act as a physical barrier to reduce the reflux episodes. Although some Alg-based formulations contain antacid components which can provide significant acid neutralization capacity. The efficacy of these formulations so as to reduce heartburn symptoms does not appear to be totally dependent on the neutralization of bulk gastric contents. The strength of the Alg raft is dependent on several factors which include the amount of carbon dioxide generated and entrapped in the raft, the molecular properties of the Alg, and the presence of aluminum or calcium in the antacid components of the formulation. Raft formation occurs rapidly, often within a few seconds of dosing; hence, Alg-containing antacids are thus comparable to traditional antacids for the speed of onset of relief. Since the raft can be retained in the stomach for several hours, thus they provide the additional advantage of longer-lasting relief than that of traditional antacids Alg-based raft-forming formulations have been used to treat reflux symptoms in infants and children and also in the management of heartburn and reflux during the pregnancy.

The Gaviscon is effective when used alone, and it is compatible and does not interfere with the activity of antisecretory agents such as cimetidine. Even in case of the introduction of new antisecretory and promotility agents, Alg-rafting formulations will continue to have a role in the treatment of heartburn and reflux symptoms. Their unique non-systemic mechanism of action provides rapid and long-duration relief in case of heartburn and acid reflux symptoms. Besides Gaviscon, other marketed formulations are topalkan which is an effervescent floating liquid Alg preparation and consist of aluminum and magnesium mixture and other is Alg flotcoat which is also FDF and consists of aluminum and magnesium mixture.[83,84]

Advantage of raft-forming system

These systems are used for the symptomatic treatment of heartburn and esophagitis. They can also be used in laryngopharyngeal reflux (LPR) and GERD; LPR indicates the backflow of stomach contents into the laryngeal and pharyngeal region. It does not interfere with the activity of promotility agent and antisecretory agents such as cimetidine.[85] The raft system provides a rapid and long duration of action and may show its action within seconds. It does not interfere with the function of pyloric sphincter. This system helps us to achieve better patient compliance and is also well tolerated.[78,80]

EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS

Various parameters to be evaluated for stomach specific drug delivery system are as follows.

For Single-unit Dosage Forms (e.g., Tablets)

During preliminary optimization studies, tablets were evaluated for official tests such as weight variation and friability. Apart from these studies, the formulation will be examined for unofficial tests as detailed as follows.

Floating lag time and floating duration

The buoyancy of the tablets is determined at 37±0.5°C in 100 ml of simulated gastric fluid at pH 1.2 (without pepsin, USP). The duration for which tablet floats is observed visually. The evaluation is conducted in triplicate for each batch of tablets.[86]

In vitro drug release

This is determined using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±0°C in the simulated gastric fluid of pH1.2 without pepsin. Samples are withdrawn at particular time intervals from the dissolution medium with replacement, and then, they are analyzed for their drug content after appropriate dilution.[87] The *in vitro* drug release data from drugs are evaluated kinetically using various mathematical models scuh as zero-order, first-order, Higuchi, and Korsmeyer–Peppas model.[88-92]

Zero-order model: F = K0 t, where F represents the fraction of drug released in time t, and K0 is the apparent release rate constant or zero-order release constant. The graph is plotted between cumulative percent drug release and time.

First-order model: Ln (1–F) = $K1^{st}$, where F represents the fraction of drug released in time t, and K1 is the first-order release constant. The graph is plotted between log cumulative percent drug release and time.

Higuchi model: F = KHt½, where F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant. The graph is plotted between cumulative percent drug release and square root of time.

Korsmeyer–Peppas Model: F = Kptn, where F represents the fraction of drug released in time t, Kp is the rate constant, and n is the release exponent, indicative of the drug release mechanism. The graph exists between log percentage drug release and log time.

The Korsmeyer–Peppas model was employed in the *in vitro* drug release behavior analysis to distinguish between the competing release mechanisms, i.e., Fickian release (diffusion- CR), non-Fickian release (anomalous transport), and case-II transport (relaxation-CR). In case of spheres, a value of $n \leq 0.43$ indicates the Fickian release. When the value of n is between 0.43 and 0.85, there is an indication of non-Fickian release (both diffusion controlled and swelling controlled drug release). When, $n \geq 0.85$, it is case-II transport and this indicates polymer dissolution and polymeric chain enlargement or relaxation.

In vivo evaluation for gastroretention

This is carried out by means of X-ray or Gamma scintigraphic monitoring which helps to locate the dosage form in the GIT and through which one can predict and correlates the GET and the passage of dosage form in the GIT.[93] Ozdemir *et al.*[58] (2000) developed bilayer floating tablets of furosemide and for *in vivo* studies; the part of the drug was replaced by BaSO4 in the release layer. The duration during which tablets stayed in the stomach was examined by radiograms, and it was concluded that tablets stayed in the stomach for about 6 h.

Water uptake studies

Water uptake studies are performed by an equilibrium weight gain method using USP dissolution test apparatus. The tablets are accurately weighed and placed in a dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°Cat particular speed of rotation. At regular intervals, the tablet was removed from the dissolution vessel, blotted with tissue paper to remove excess water, and reweighed. The percentage water uptake (i.e., the degree of swelling due to absorbed medium) is calculated using the following equation:

% water uptake = (Wt/W0)*100

Where *W*o and *Wt* are weights of dry and swelled tablet at time *t*, respectively.[86]

For Multiple Unit Dosage Forms (e.g., Floating Beads)

Besides the *in vitro* release, duration of floating, and *in vivo* gastroretention tests, the multiple unit dosage forms are also evaluated for:

Morphological and dimensional analysis

The beads and microspheres shape and size are analyzed with the help of scanning electron microscopy. The size can also be measured using an optical microscope.[87]

Floating properties

The time taken by the floating drug formulation to reach to the upper one-third of the dissolution vessel is called buoyancy lag time, and the time for which the formulation constantly floats on the surface of the medium called duration of floating is measured simultaneously as a part of dissolution studies.[65]

SUPERPOROUS HYDROGELS

The conventional hydrogels, which are having pore size ranging between 10 nm and 10 μm, have very slow process of water absorption and require several hours to reach an equilibrium state during which premature evacuation of the dosage form may occur, while in case of superporous hydrogel, having average pore size (>100 μm), swell to equilibrium size within a minute, due to their rapid water uptake by capillary wetting through numerous interconnected open pores.[94] Moreover, they swell gradually to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is mostly achieved by a co-formulation with a hydrophilic particulate material, Ac-Di-Sol (croscarmellose sodium). Gupta and Shivakumar[95] developed superporous hydrogels of rosiglitazone using chitosan with glyoxal as a cross-linking agent. They were prepared by gas blowing method. Due to its high swelling properties in acidic pH, it was characterized as superporous hydrogel and used as gastroretentive drug delivery system.

MAGNETIC SYSTEMS

Magnetic systems involve the incorporation of the small magnet inside the core or matrix of the system, and another magnet is externally applied on the abdomen region. However, this system provides satisfactory results, but there is a problem of placing the magnet externally at the right position with great accuracy and precision.[36] Urbina *et al.*[96] developed multiple controlled drug delivery vehicles using magnetic nanoparticle- polymer composites and two types of nanoparticle-polymer composites were prepared and their potential in drug delivery system with multiple controls (magnetically and thermally controlled delivery) was evaluated, and hence, it was proved that magnetic-polymer nanoparticle composites can be used for gastroretentive drug delivery.

BIOADHESIVE OR MUCOADHESIVE DRUG DELIVERY SYSTEMS

Bioadhesive drug delivery systems are aimed to localize a delivery device within the human to enhance the drug absorption in a site-specific manner. In this approach, bioadhesive polymers adhere to the epithelial surface in the stomach and increase GRT of the dosage forms.[7] Mucoadhesion is based on the principle that dosage form can stick to the mucosal surface by different mechanism. The different mechanisms are summarized in Table 6, and various mucoadhesive formulations are detailed in Table 7.

CONCLUSION

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper GIT, and they can be delivered efficiently, thereby maximizing their absorption and enhancing absolute bioavailability. Under certain circumstances, the prolongation

Table 6: Different theories of mucoadhesion

Theory of mucoadhesion	Description	Reference
Wetting theory	This theory is based on the ability of bioadhesive polymers to spread and develop the intimate contact with the mucous layers	[120]
Diffusion theory	This theory proposes the physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate	[121]
Adsorption theory	According to this theory, bioadhesion is due to secondary forces such as Van der Waal forces and hydrogen bonding	[122]
Electronic theory	This theory states that there exist the attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Thus, the different stages are shown in Figure 9 (Alexander *et al.*, 2011)	[123]

Table 7: An overview of various mucoadhesive formulations

Drug	Category	Polymer	Performance	Evaluation	Reference
Domperidone	D2 receptor antagonist	Myrr oleo gum resin	99.99% in 0.1 N HCl for 24 h	19.868±49.778 N	[124]
Neostigmine bromide	Parasympathomimetics	Carbopol 974PNF, HPMC K 15 M	87.86–84.5% in 8 h in pbs, pH 6.4	-	[125]
Theophylline	CNS stimulant	HPMC, Carbopol, Chitosan	97% in 10 h in HCl at pH 1.2	0.4962±0.015 N 0.6413±0.015N 0.7149±0.009N	[126]
Lisinopril	ACE inhibitor	HEC, HPMC, Carbopol 934	97.1% in 10 h in pbs, pH 6.8	0.3608 N	[127]
Baclofen	Antispastic agent	Carbopol 974 p, methocel K 15	98% in 8 h in pbs, pH 6.8	0.1091±0.006 N	[128]
Terbutaline sulfate	β2 receptor agonist	HPMC	95.5% in 12 h in pbs, pH 7.4	-	[129]
Acyclovir	Antiviral	Sodium alginate	98.5% in 8 h in 0.1 N HCl	-	[130]
Montelukast	Leukotrine receptor antagonist	PVP K 30, Eudragit RL 100	67.35–93.62 in 8 h in 0.5% SLS	-	[131]
Theophyllin anhydrous	CNS stimulant	Karaya gum and guar gum	90% in 12 h in HCl pH 1.2	0.3002±0.007 N	[132]
Itraconazole	Antifungal	Carbopol 934 HPMC	100% In 3 h in 0.1 N HCl	0.01916±0.012 N 0.3392±0.021 N	[133]

CNS: Central nervous system, HPMC: Hydroxypropyl methylcellulose

of gastric residence time of a delivery system is desirable for achieving a better therapeutic benefit of the drug substance. For instance, the drugs that show absorption in the proximal part of the GIT and the drugs which are degraded or less soluble in alkaline pH may be benefitted by prolonging the gastric residence time. Prolonged gastric retention of therapeutic moiety offers many advantages such as improved bioavailability, reduction of drug wastage, and possible reduction of dose size. A controlled drug delivery based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper GIT, and they can be delivered efficiently, thereby maximizing their absorption and enhancing absolute bioavailability. To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, and magnetic systems) are interesting and present their own advantages and disadvantages. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

REFERENCES

1. Majethiya KA, Patel MR. Gastroretentive drug delivery system. Int J Pharm Biol Sci 2013;2:103-20.
2. Bhardwaj L, Sharma P, Malviya R. A short review on gastroretentive formulation for stomach specific drug delivery: Special emphasis on floating *in situ* gel system. Afr J Basic Appl Sci 2011;3:300-12.
3. Garg S, Sharma S. Gastro retentive drug delivery systems. Pharmatech 2003;5:160-6.
4. Mathur P, Saroha K. Floating drug delivery system an innovative acceptable approach in gastroretentive drug delivery. Arch Appl Sci Res 2010;12:257-70.
5. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res 2008;7:1055-66.
6. Talukder R, Fassihi R. Gastroretentive delivery systems: A mini review. Drug Dev Ind Pharm 2004;30:1019-28.
7. Nayak AK, Das MR. Gastroretentive drug delivery systems. Asian J Pharm Clin Res 2010;3:2-10.
8. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS PharmSciTech 2005;6:E372-90.
9. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: Effects of formulation and processing parameters on drug release. Eur J Pharm Sci 2003;18:37-45.
10. Raval JA, Patel JK, Li NH. Formulation of floating mixed matrix tablets using low density copolymer. Int Res J Pharm 2011;1:1-7.
11. Pandey A, Kumar G, Kothiyal P, Barshiliya Y. Review on current approaches in gastro retentive drug delivery system. Asian J Pharm Med Sci 2012;2:60-76.
12. El-Kamel AH, Sokar MS, Al-Gamal S, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm 2001;220:13-21.
13. Garg S, Sharma S. Gastro retentive drug delivery systems. Pharmatech 2003;5:160-6.

14. Sungthongjeen S, Paeratakul O, Limmatvapirat S, Puttipipatkhachorn S. Preparation and *in vitro* evaluation of a multiple-unit floating drug delivery system based on gas formation technique. Int J Pharm 2006;324:136-43.
15. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur J Pharm Biopharm 2008;69:255-63.
16. Ichigawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. I: Preparation and *in vitro* evaluation of floating and sustained-release characteristics. J Pharm Sci 1991;80:1062-6.
17. Sugihara H, Yamamoto H, Kawashima Y, Takeuchi H. Effects of food intake on the mucoadhesive and gastroretentive properties of submicron-sized chitosan-coated liposomes. Chem Pharm Bull (Tokyo) 2012;60:1320-3.
18. Patel CJ, Sangeeta A, Dhruv M, Pinkesh P, Alpesh Y, Kishor P. Formulation and evaluation of gastroretentive floating matrix tablets of domperidone. Int J Pharm Res Dev 2012;4:141-6.
19. Timmermans J, Gansbeke VB, Moes AJ. Assessing by Gamma Scintigraphy the *in vivo* Buoyancy of Dosage Forms having Known Size and Floating Force Profiles as a Function of Time. Vol. 1. Paris, France: APGI; 1989. p. 42-51.
20. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm 1993;100:81-92.
21. Rouge N, Allémann E, Gex-Fabry M, Balant L, Cole ET, Buri P, *et al.* Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta Helv 1998;73:81-7.
22. Moes AJ. Gastric retention systems for oral drug delivery. Pharmatech 2003; 4(4):157-9.
23. Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol 1990;42:500-1.
24. Tuleu C, Andrieux C, Boy P, Chaumeil JC. Gastrointestinal transit of pellets in rats: Effect of size and density. Int J Pharm 1999;180:123-31.
25. Pande SD, Vaidya PV, Gulhane PN. Floating drug delivery system (FDDS): A new way for oral drug delivery. Int J Pharm Clin Sci 2013;3:1-13.
26. Gopalakrishnan S, Chenthilnathan A. Floating drug delivery systems a review. J Pharm Sci Technol 2011;3:548-54.
27. Patel CJ, Sangeeta A, Dhruv M, Pinkesh P, Alpesh Y, Kishor P. Formulation and evaluation of gastroretentive floating matrix tablets of domperidone. Int J Pharm Res Dev 2012;4:141-6.
28. Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: Effect of some additives, hardening agent or coating on release behavior of metronidazole. Eur J Pharm Sci 2005;24:363-73.
29. Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J Control Release 1999;61:43-50.
30. Kaushik A, Dwivedi A, Kothari P, Govil A. Floating drug delivery system a significant tool for stomach specific release of cardiovascular drugs. Int J Drug Dev Res 2012;4:116-29.
31. Hilton AK, Deasy PB. *In vitro* and *in vivo* evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992;86:79-88.
32. Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984;10:313-39.
33. Reddy LH, Murthy RS. Floating dosage systems in drug delivery. Crit Rev Ther Drug Carrier Syst 2002;19:553-85.
34. Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug Carrier Syst 1998;15:243-84.
35. Dhiman S, Singh TG, Rehni AK, Sood S, Arora S. Gastroretentive: A controlled release drug delivery system. Asian J Pharm Clin Res 2011;4:5-13.
36. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of *Helicobacter pyl*ori. J Control Release 2006;111:1-18.
37. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, *et al.* Formulation and development of hydrodynamically balanced system for metformin: *In vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2007;67:196-201.
38. Singh B, Rani A, Babita NA, Kapil R. Formulation optimization of hydrodynamically balanced oral controlled release bioadhesive tablets of tramadol hydrochloride. Sci Pharm 2010;78:303-23.
39. Weon YK, Kim WD, Kim SJ, Kim K. Gastric Retention-Type Pellet and the Preparation Method Thereof, WO PCT Applications No. 2008010690; 2008.
40. Boehm G, Dundon J. Rosiglitazone Formulations. EP Patent No. 1732513; 2006.
41. Liao J, Liu P, Dinh S, Singh B, Majuru S, Bhargava PN. Gastric Retention and Controlled Release Delivery System, US Patent Applications No. 2008153779; 2008.
42. Chaudhari M, Chandwani DO, Yelegaonkar SR. Gastroretentive Formulations and Manufacturing Process Thereof, US Patent No. 2008220060; 2008.
43. Dervieux T, Olmstead K. Sustained Release Methotrexate Formulations and Methods of use Thereof, US Patent Application No. 2008268045; 2008.
44. Pilgaonkar P, Rustomjee M, Gandhi A, Bagde P. Controlled Release Pharmaceutical Compositions with Improved Bioavailability, US Patent Application No. 2007196396; 2007.
45. Oberegger W, Zhou F, Maes P, Turchetta S, Jackson G, Massardo P, Saleh MA. Modified Release Formulations of a Bupropion Salt, US Patent No. 7241805; 2007.
46. Aurora J, Sant V. Gastric Retention Drug Delivery System, US Patent Application No. 2007092565; 2007.
47. Franklin EA, Flashner M, Garner JW, Wurtman D, Bond AR. Improved Pharmacokinetic Profile of Beta-Adrenergic Inverse Agonists for the Treatment of Pulmonary Airway Diseases, PCT Application No. 2007011972; 2007.
48. Lapidot N, Afargan M, Kirmayer D, Moor E, Mardor Y. A Gastro-Retentive System for the Delivery of Macromolecules, PCT Application No. 200709399; 2007.
49. Wang WW, Ryan JJ. Gastroretentive Sustained Release Formulations, US Patent Application No. 2007269512; 2007.
50. Kerc J, Opara J, Osel JM. Therapeutic System Comprising Amoxicillin and Clavulanic Acid, US Patent Application No. 2006121106; 2006.
51. Donovan S. Botulinum Toxin Formulations for Oral Administration, US PCT Application No. 2004043430; 2004.
52. Malakar J, Nayak AK, Pal D. Development of cloxacillin loaded multiple-unit alginate-based floating system by emulsion-gelation method. Int J Biol Macromol 2012;50:138-47.
53. Amrutkar PP, Chaudharib PD, Patil SB. Design and *in vitro* evaluation of multiparticulate floating drug delivery system of zolpidem tartarate. Colloids Surf B 2012;89:182-7.
54. Kumar SK, Jaykar B, Kavimani S. Formulation and evaluation of gastroretentive floating drug delivery system of rabeprazole sodium. Int J Biopharm 2011;2:57-62.
55. Saravanan M, Anupama B. Development and evaluation of ethylcellulose floating microspheres loaded with ranitidine hydrochloride by novel solvent evaporation-matrix erosion method. Carbohydr Polym 2011;85:592-8.
56. Akelesh T, Sapkal SB, Sivakumar R, Jothi R, Venkatnarayanan R. Formulation development of gastro retentive floating tablet of acyclovir using natural gums. Der Pharm Lett 2011;3:254-61.
57. Baki G, Bajdik J, Pintye-Hódi K. Evaluation of powder mixtures and hydrophilic gastroretentive drug delivery systems containing zinc acetate and sodium bicarbonate.

J Pharm Biomed Anal 2011;54:711-6.
58. 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;26:857-66.
59. Reddy LH, Murthy RS. Floating dosage systems in drug delivery. Crit Rev Ther Drug Carrier Syst 2002;19:553-85.
60. Junyaprasert VB, Pornsuwannapha S. Floating properties and release characteristics of hollow microspheres of acyclovir. Drug Deliv 2008;15:331-41.
61. Ma N, Xu L, Wang Q, Zhang X, Zhang W, Li Y, *et al.* Development and evaluation of new sustained-release floating microspheres. Int J Pharm 2008;358:82-90.
62. Talukder R, Fassihi R. Gastroretentive delivery systems: Hollow beads. Drug Dev Ind Pharm 2004;30:405-12.
63. Dhiman S, Singh TG, Rehni AK, Sood S, Arora S. Gastroretentive: A controlled release drug delivery system. Asian J Pharm Clin Res 2011;4:5-13.
64. Jain NK. Progress in Controlled and Novel Drug Delivery Systems. 1st ed. New Delhi: CBS Publishers and Distributor; 2004. p. 84-5.
65. Shishu, Gupta N, Aggarwal N. Stomach-specific drug delivery of 5-fluorouracil using floating alginate beads. AAPS PharmSciTech 2007;8:48.
66. Jaiswal D, Bhattacharya A, Yadav IK, Singh HP, Chandra D, Jain DA. Formulation and evaluation of oil entrapped floating alginate beads of ranitidine hydrochloride. Int J Pharm Pharm Sci 2009;1:128-40.
67. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled Drug Delivery. Delhi, India: Vallabh Prakashan; 2006. p. 197-217.
68. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Technol Res 2009;1:623-33.
69. Patel N, Nagesh C, Chandrashekhar S, Patel J, Jani D. Floating drug delivery system: An innovative acceptable approach in Gastro retentive drug delivery. Asian J Pharm Res 2012;2:7-18.
70. Srikanth MV, Ram BJ, Sunil SA, Rao NS, Murthy RK. Gastroretentive drug delivery systems: Novel approaches and its evaluation: A review. Int J Pharm Sci Rev Res 2011;10:203-16.
71. Jain SK, Jain NK, Agrawal GP. Gastroretentive floating drug delivery: A overview. Drug Deliv Technol 2005;5:7-15.
72. 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;20:1199-212.
73. Degtiareva H, Bogdanov A, Kahtib Z, Kharchenko NV. The use of third generation antacid preparations for the treatment of patients with nonulcerous dyspeosia and peptic ulcer complicated by reflux esophagus. Lik Sprava 1994;5-6:119-22.
74. Erni W, Held K. The hydrodynamically balanced system: A novel principle of controlled drug release. Eur Neurol 1987;27:215-75.
75. Washington N, Washington C, Wilson CG, Davis SS. What is liquid graviscon? A comparison of four international formulations. Int J Pharm 1986;34:105-10.
76. Soni RP, Patel AV, Patel RB, Patel MR, Patel KR, Patel NM. Gastroretentive drug delivery systems. Int J Pharm World Res 2011;2:1-2.
77. Arza RA, Gonugunta CS, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS Pharm Sci Technol 2009;10:220-6.
78. Bhavsar DN, Varde NM, Sini S, Shah VH, Upadhyay UM. Advances in GRDDS: Raft forming system a review. J Drug Deliv Ther 2012;2:123-8.
79. Nasa P, Mahant S, Sharma D. Floating systems: A novel approach toward gastroretentive drug delivery System. Int J Pharm Pharm Sci 2010;2:2-7.
80. Punitha S, Sabitha G, Vishal K, Rajasekar S. Floating drug delivery system-chronotherapeutic approach. Int Res J Pharm 2011;2:38-45.
81. Kubo W, Konno Y, Miyazaki S, Attwood D. *In situ* gelling pectin formulations for oral sustained delivery of paracetamol. Drug Dev Ind Pharm 2004;30:593-9.
82. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: Alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther 2000;14:669-90.
83. Makwana A, Sameja K, Parekh H, Pandya Y. Advancement in controlled release gastroretentive drug delivery system: A review. J Drug Deliv Ther 2012;2:12-21.
84. Sayeed A, Kinagi MB, Mohiuddin H, Gada S. Gastroretentive drug delivery system: A review. Pharm Lett 2011;3:121-37.
85. Debjit B, Chiranjib B, Chandira M, Jayakar B, Kumar KP. Floating drug delivery system-a review. Der Pharm Lett 2009;1:199-218.
86. Nagarwal RC, Ridhurkar DN, Pandit JK. *In vitro* release kinetic and bioavailability of gastroretentive cinnarizine hydrochloride tablet. AAPS Pharm Sci Technol 2010;11:294-303.
87. Khan AD, Bajpai M. Floating drug delivery system: An overview. Int J Pharmtech Res 2010;2:2497-505.
88. Korsmeyer RW, Gurny R, Doelkar E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25-35.
89. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials a review. Biomaterials 1996;17:1553-61.
90. Karasulu E, Karasulu HY, Ertan G, Kirilmaz L, Guneri T. Extended release lipophilic indomethacin microspheres: Formulation factors and mathematical equations fitted drug release rates. Eur J Pharm Sci 2003;19:99-104.
91. Siepmann J, Peppas NA. Higuchi equation: Derivation, applications, use and misuse. Int J Pharm 2011;418:6-12.
92. Costa P, Lobo JM. Modelling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.
93. Chandel A, Chauhan K, Parashar B, Kumar H, Arora S. Floating drug delivery systems: A better approach: A review. Int Curr Pharm J 2012;1:110-8.
94. Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. J Control Release 2000;65:73-82.
95. Gupta NV, Shivakumar HG. Research on development of a gastroretentive drug delivery system based on superporous hydrogel. Trop J Pharm Res 2010;9:257-64.
96. Urbina MC, Zinoveva S, Miller T, Sabliov CM, Monroe WT, Kumar CS. Investigation of magnetic nanoparticle-polymer composites for multiple-controlled. Drug Deliv J Phys Chem C 2008;112:11102-8.
97. Rao GK, Mandapalli PK, Manthri R, Reddy VP. Development and *in vivo* evaluation of gastroretentive delivery systems for cefuroxime axetil. Saudi Pharm J 2013;21:53-9.
98. Kumari DS, Balasubramaniam V, Velrajan G, Deepthi N, Sushma R. Formulation and evaluation of bilayer floating tablets of metformin hydrochloride and glibenclamide. Res J Pharm Technol 2013;6:105-11.
99. Gaikwad VD, Yadav VD, Jadhav PD. Formulation and evaluation of floating matrix tablets of diltiazem hydrochloride. Asian J Pharm 2012;6:245-51.
100. Rangapriya M, Manigandan V, Natarajan R, Mohankumar K. Formulation and evaluation of floating tablets of pioglitazone hydrochloride. Int J Pharm Chem Sci 2012;1:1046-54.
101. Meka VS, Nali SR, Songa AS, Kolapalli VR. Characterization and *in vitro* drug release studies of a natural polysaccharide *Terminalia catappa* gum (Badam gum). AAPS PharmSciTech 2012;13:1451-64.
102. He S, Li F, Zhou D, Du J, Huang Y. Formulation and evaluation of novel coated floating tablets of bergenin and cetirizine dihydrochloride for gastric delivery. Inf Health Care 2012;38:1280-8.

103. Kumar PR, Doddayya H, Reddy SR. Studies on core in coat gastroretentive tablet using porous carriers with cellulosic polymers and natural gums. J Appl Pharm 2012;1:511-23.
104. Verma A, Sahua AK, Singh SK. Preparation of hydrophilic swelling controlled release floating matrix tablets containing HPMC and chitosan. Int J Pharm Pharm Sci 2012;4:82-7.
105. Thahera PD, Ashok M, Latha K, Shailaja T, Nyamathulla S, Uhumwangho MU. Research on formulation and evaluation of norfloxacin gastro retentive drug delivery systems using natural polymers. Int Curr Pharm J 2012;1:155-64.
106. Hu L, Li L, Yang X, Liu W, Yang J, Jia Y, *et al*. Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: *In vitro* and *in vivo* evaluation in healthy volunteers. Eur J Pharm Sci 2011;42:99-105.
107. Gande S, Rao YM. Sustained-release effervescent floating matrix tablets of baclofen: Development, optimization and *in vitro-in vivo* evaluation in healthy human volunteers. Daru 2011;19:202-9.
108. Sivabalan M, Vani TP, Reddy VP, Jose NG. Formulation and evaluation of gastroretentive glipizide floating tablets. Int J Compr Pharm 2011;2:1-4.
109. Sathiyaraj S, Devi RD, Hari VB. Lornoxicam gastro retentive floating matrix tablets: Design and *in vitro* evaluation. J Adv Pharm Technol Res 2011;2:156-62.
110. Someshwar K, Chithaluru K, Ramarao T, Kumar K. Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharm 2011;61:217-26.
111. Patil P, Rao BS, Kulkarni SV, Basavaraj SC, Ammanage A. Formulation and *in vitro* evaluation of floating matrix tablets of ofloxacin. Asian J Res Pharm Sci 2011;1:17-22.
112. Reddy AB, Rani BS, Tony DE, Raja DS, Sindhura L, Kumar NS. Aceclofenac floating tablets-a promising sustained release dosage form. Int J Drug Dev Res 2011;3:290-300.
113. Patil A, Majahar S, Irfani G. Floating tablets of nimodipine and its inclusion complex with β-cyclodextrin for controlled release. Int J Pharmtech Res 2011;3:619-25.
114. Mostafavi A, Emami J, Varshosaz J, Davies NM, Rezazadeh M. Research on development of a prolonged-release gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characteriation in healthy human volunteers. Int J Pharm 2011;409:128-36.
115. Reddy GJ, Potu AR, Reddy VP, Jukanti R, Bandari S. Research on development and *in vitro-in vivo* behaviour of nizatidine floating tablets. Sch Res Libr 2011;3:454-65.
116. Guguloth M, Bomma R, Veerabrahma K. Development of sustained release floating drug delivery system for norfloxacin: *In vitro* and *in vivo* evaluation. PDA J Pharm Sci Technol 2011;65:198-206.
117. Verma S, Narang N. Development and *in vitro* evaluation of floating matrix tablets of anti-retroviral drug. Int J Pharm Pharm Sci 2011;3:208-11.
118. Sharmin F, Masum MA, Islam SM, Reza MS. Preparation and evaluation of gastro retentive floating tablets of atorvastatin calcium. J Pharm Sci 2011;10:79-85.
119. Pahwa R, Chhabra L, Lamba AK, Jindal S, Rathour A. Formulation and *in-vitro* evaluation of effervescent floating tablets of an antiulcer agent. J Chem Pharm Res 2012;4:1066-73.
120. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev 2005;57:1556-68.
121. Shaikh R, Raj ST, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci 2011;3:89-100.
122. Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhe-sive drug delivery systems. Drug Dev Ind Pharm 1993;19:143-94.
123. Dodou D, Breedveld P, Wieringa PA. Mucoadhesives in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm 2005;60:1-16.
124. Arora G, Malik K, Rana V. Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using *Salvia plebeian* gum. J Adv Pharm Technol Res 2011;2:163-9.
125. Rao JV, Gangadi JR, Kumar S, Venu K, Jayaveera KN. Intranasal microspheres of neostigmine bromide with carbopol 974P and HPMC. Int J Pharm Technol 2010;2:1158-98.
126. Senthil V, Gopalakrishnan S, Sureshkumar R, Jawahar N, Ganesh GN, Nagasamyvenkatesh D. Mucoadhesive slow-release tablets of theophyline: Design and evaluation. Asian J Pharm 2010;4:64-8.
127. Guda A, Gudas GK, Bingi M, Debnath S, Rajesham VV. Design and evaluation of controlled release mucoadhesive buccal tablets of lisinopril. Int J Curr Pharm Res 2010;2:24-7.
128. Gavaskar B, Venkateswarlu E, Kumaraswamy D, Dooda D, Nagaraju M. Formulation and evaluation of mucoadhesive tablets of baclofen. Int J Pharm Technol 2010;2:396-409.
129. Chanda R., Nath L. K., and Mahapatra S. (2009). Formulation development of oral mucoadhesive coated terbutaline sulphate tablets using some natural materials extracted from edible fruits available in India. Iran. J. Pharm. Res., 5(1): 3-12.
130. Bhanja SB, Ellaiah P, Martha SK, Murthy KV. Preparation and in-vitro evaluation of mucoadhesive microcapsules of acyclovir. Int J Pharm Tech 2010;2:907-23.
131. Rao R, Suryakar VB, Thube K. Development of mucoadhesive film for buccal administration of montelukast. Int J Pharm Tech 2010;2:1-15.
132. Deshmukh VN, Jadhav JK, Sakarkar DM. Formulation and in vitro evaluation of theophylline anhydrous bioadhesive tablets. Asian J Pharm 2009;3:54-8.
133. Madgulkar A, Kadam S, Pokharkar V. Development of trilayered mucoadhesive tablet of itraconazole with zero-order release. Asian J Pharm 2008;2:57-60.

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