An Extensive Insight on Gastroretentive Drug Delivery Systems

Manish R. Bhise
Department of Pharmaceutics
Dr. Rajendra Gode College of Pharmacy,Malkapur,Dist-Buldana, (MS), India

Suresh G. Sudke
Department of Pharmaceutics
Gourishankar Education Society's Satara College of Pharmacy, Degaon, Satara, MS, India

Pramod V.Burakle
Department of Pharmaceutical Chemistry
Dr. Rajendra Gode College of Pharmacy, Malkapur,Dist-Buldana, (MS), India

Vishal B.Patond
Department of Pharmaceutics
Dr. Rajendra Gode College of Pharmacy,Malkapur,Dist-Buldana, (MS), India

Abstract-The objective of present overview on extensive insight on gastroretentive drug delivery systems is to explore the various gastroretentive approaches which became a leading drug delivery system in site specific oral controlled drug delivery. Recently, many attempts have been made to enhance the oral bioavailability and therapeutic effectiveness of drug with narrow absorption window, low stability at alkaline pH, solubility in acidic conditions and local activity in the stomach. The review further enlighten over the physiological state of the stomach and the factors affecting gastric retention of drug delivery systems. The physiological difficulties to achieve gastric retention and way out to conquer these difficulties are also focused. The various gastroretentive approaches designed and developed till date are high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems. The advanced gastrointestinal technologies such as expandable, superporous hydrogel; bio/mucoadhesive, magnetic, ion-exchange resin; and low- and high density systems have also been enumerated.

Keywords: Gastric retention, Oral controlled release, Floating dosage form, Drug delivery system.

I.INTRODUCTION

Oral administration is the most convenient and preferred means of drug delivery to the systematic circulation. The oral controlled drug delivery have recently increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained or controlled release formulations are designed to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a longer period of time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract [1]. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in acidic pH environment[3].

Gastroretentive drug delivery system (GRDDS) is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking)systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5, 6, 7],mucoadhesive systems that causes Bioadhesion to

stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9, 10], superporous hydrogel systems[11], magnetic systems [12] etc.

II.PARAMETERS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The most important parameters controlling the gastric retention time of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.)[14]. The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters [15]. The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm [13].

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the gastric retention timeof the dosage form. Usually the presence of food in the gastrointestinal tract improves the gastric retention time of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms [16].

Physiological factors

Several studies have reported that various extrinsic factors including the nature of meal, caloric content (caloric density and nature of the calories), frequency of ingestion, posture, sleep, and physical activity can affect the GRT of drugs in the stomach [17,18,19,20]. Furthermore, the GRT is influenced by posture, and the effect is different for floating and non-floating dosage forms [17]. In the upright position, the floating system floats in the gastric fluid for a prolonged amount of time which can eventually increase the GRT.However, in similar conditions, the non-floating system remains in the lower part of the stomach and the gastric emptying rate is faster as a result of peristaltic contractions [17]. In contrast, in the supine position, the non-floating system has a longer GRT compared to the floating system [21, 22].

Patient related factors

Patient-related factors such as gender, age, illness, and emotional state can influence GRDDS.A recent study reported that gender affected the gastric emptying time and intraluminal pH [23].The authors demonstrated that females had slower gastric emptying times than males [23]. Hormonal influences could explain the longer GRT in females than in males. Another study showed that males secreted more gastric acid compared to females [24]. Likewise, the age of the patient also affects the GRT. Elderly patients have a longer GRT compared to younger patients [25]. The nature of a patient's illness may also affect the GRT of the dosage form. For instance, patients with Parkinson's disease havea prolonged GRT that is frequently accompanied by constipation [26]. Likewise, in diabetic patients, gastric emptying is decreased by 30–50% [27]. The emotional condition of a patient may also influence GRDDS. It was reported that a decrease in gastric emptying rate was observed in patients suffering from depression, whereas an increased rate was observed in patients experiencing anxiety [18, 21].

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach [28]. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm^3 is required to exhibit floating property [29].

Effect of gender, posture and age

Generally females have slower gastric emptyin grates than male. The effect of posture does not haveany significant difference in the mean gastric retention time for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down [30].

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric

retention time due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine [32].Dosage forms having a diameter of more than 7.5mm show a better gastric residence time compared with one having 9.9 mm [31]. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes [33].

Potential drug candidates for gastroretentive drug delivery systems

1. Drugs those are unstable in the intestinal or colonic environment. For e.g. captopril, ranitidine hydrochloride (HCl), metronidazole.
2. Drugs that have narrow absorption window in gastrointestinal tract. For e.g., L-DOPA, paraaminobenzoic acid, furosemide, riboflavin etc.
3. Drugs that disturb normal colonic microbes. For e.g. antibiotics against Helicobacter pylori.
4. Drugs that exhibit low solubility at high pH values. For e.g. diazepam, chlordiazepoxide, verapamil HCl.
5. Drugs those are locally active in the stomach. For e.g.misroprostol, antacids etc.

Drugs those are unsuitable for gastroretentive drug delivery systems

1. Drugs that is unstable in the gastric environment. For e.g. erythromycin etc.
2. Drugs that have very limited acid solubility. For e.g.phenytoin etc.
3. Drugs intended for selective release in the colon. Fore.g. 5- amino salicylic acid, corticosteroids etc.

III.APPROACHES TO ACHIEVE GASTRICRETENTION

Low density systems

Low-density/floating systems are the most practical and extensively studied gastroretentive dosage forms [34,35,36,37]. The floating system was first introduced by Davis in 1968. In this system, the bulk density of the dosage form is lower than that of the gastric fluid (1.004 g/cm^3) shown in [Figure 1A]. This property allows the system to remain buoyant in the stomach for a prolonged period of time while the drug is released at the desired rate from the system during the GRT [34,35,38].This system is classified into two subtypes based on the mechanism buoyancy: non-effervescent floating and effervescent floating systems.

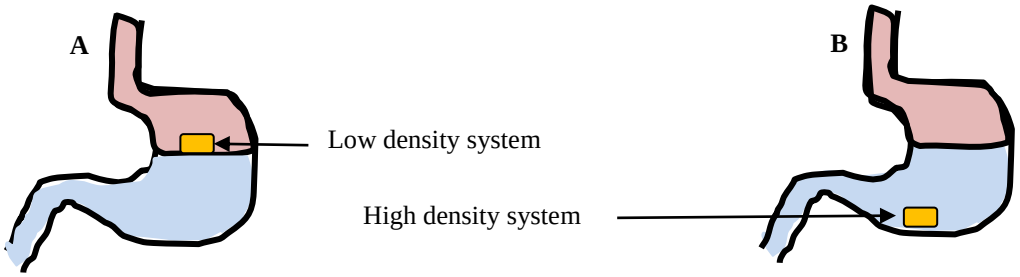

Figure 1. (A) Low density and (B) high density gastroretentive systems

Non-effervescent floating systems

In non-effervescent systems, highly swellable cellulose derivatives or gel-forming polymers are used [39]. The non-effervescent systems involve mixing the drug with a gel-forming polymer. Various non-effervescent systems include the hydrodynamically balanced system (HBS), single- and double-layer floating tablets, and microballoons/hollow microspheres. The HBS system was first designed by Sheth and Tossounian in 1984 [40]. It is a single unit dosage form composed of one or more gel-forming hydrophilic polymers. HPMC, hydroxy propyl cellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose, carrageenan, agar, and alginic acid are some of the polymers that are used to design the HBS system [35,41]. In this system, the drug is mixed with the polymer and filled in the gelatin capsule.

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm^3). These formulations are prepared by coating drug on aheavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide as shown in [Figure 1B][42]. The materials increase density by up to 1.5-2.4 gm/cm^3. A density close to 2.5 gm/cm^3 seems necessary for significant

prolongation of gastric residence time [43]. But, effectiveness of this system in human beings was not observed [44] and no such system has been marketed.

Effervescent floating systems

Effervescent floating systems include a gas generating agent or volatile liquids. This approach has been applied for single- and multiple-unit systems. In the gas generating floating system, effervescent agents such as sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid areused in combination with hydrophilic polymers [45, 46]. When this system comes into contact with gastric fluid, carbon dioxide is liberated due to the reaction of the effervescent agent with gastric fluid. The liberated carbon dioxide gas is entrapped in the hydrocolloid matrix, which provides the tablet buoyancy and influences the drug release properties [47]. In volatile liquid systems, volatile liquids such as ether and cyclopentane are introduced into an inflatable chamber, which volatilize at body temperature allowing inflation of the chamber in the stomach [48]. Hydrophilic polymers are often used to control the drug release rate in this system. Effervescent floating systems can be categorized into single- and double-layer effervescent floating tablets and multiple unit effervescent floating systems [49, 35]. Single-layer effervescent tablets are formulated by intimately mixing effervescent agent, polymer, drug, and excipients. However, in bilayer effervescent floating tablets, one layer comprises the drug, polymer, and carbon dioxide gas-generating agent, whereas the other layer constitutes an immediate-release drug and excipients without carbon dioxide and polymer [Figure 2].

In a recent study, sodium bicarbonate in hydroxypropyl methylcellulose (HPMC) matrix formulation was used to improve the GRT by increasing the hydration volume of dosage form and increasing the surface area of drug discussion [49].In addition, an increase in the amount of sodium bicarbonate decreased the drug release rate from the matrix, which could be due to obstruction of the discussion path by carbon dioxide gas bubbles [49]. Another study also utilized this approach to evaluate the in vitro and in vivo behaviors of ciprofloxacin hydrochloride effervescent floating tablets [50].

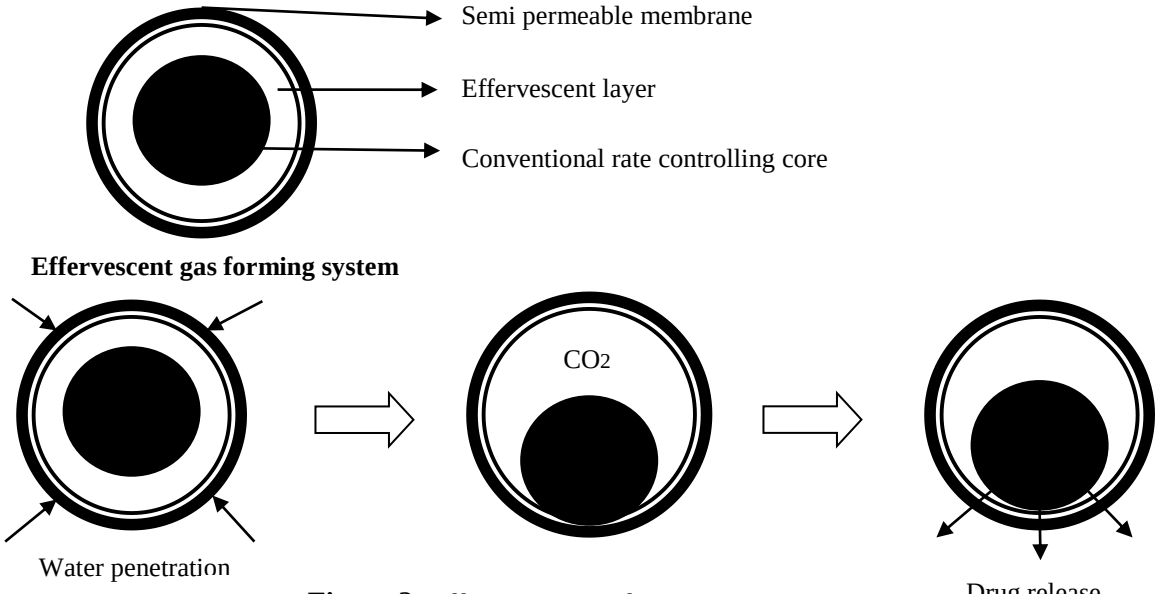

Figure 2: Effervescent gas forming system

Microballoons/ hollow microspheres

Microballoons/ hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion/evaporation methods [18] to prolong the gastric retention time (GRT) of the dosage form [Figure 3].Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin etc. The buoyancy and drug release rate from dosage form are dependent on quantity of polymers, plasticizer, polymer ratio and the solvent used in the formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12hours [51]. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple unit system and good floating.

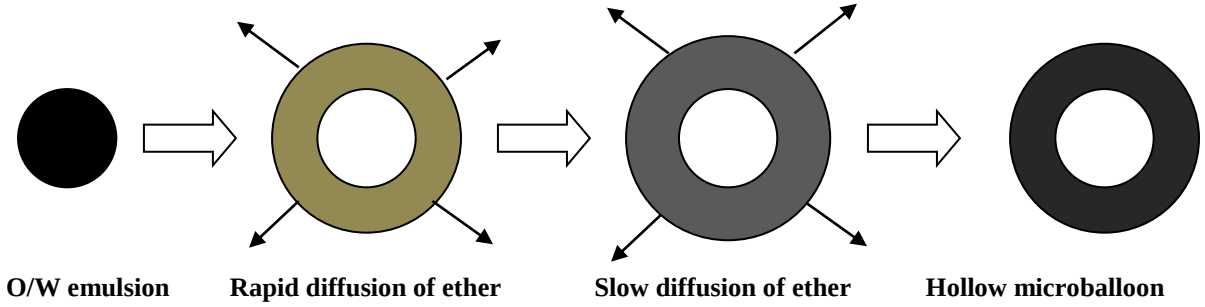

Figure 3. Formulation of floating hollow microsphere or microballoon

Hydrodynamically balanced systems

Sheth andTossounian [52] first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose, sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans and alginic acid are commonly used excipients todevelop these systems [53, 54]. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with gastric fluid and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice fora long period [Figure 4]. Because, continuous erosion of the surface allows water penetration into the inner layers maintaining surface hydration and buoyancy of the dosage form [54].

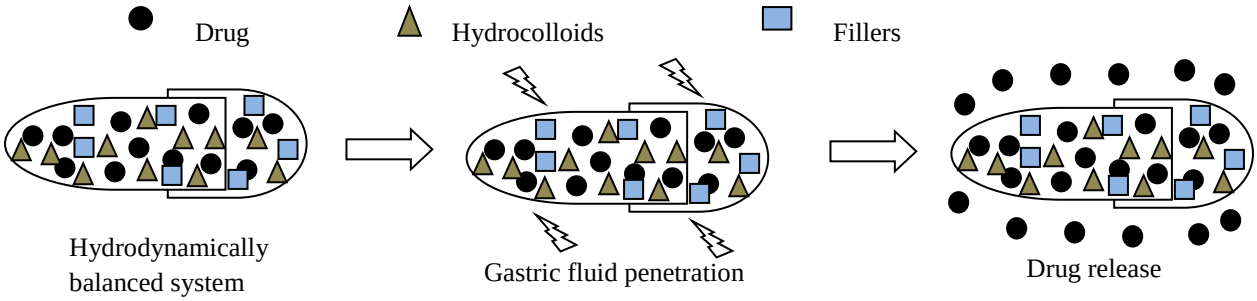

Figure 4: Hydrodynamically balanced system

Alginate beads

Talukdar and Fassihi [55] developed a multiple-unit floating system based on cross-linked beads. They were made by using $Ca^{2+}$and low methoxylated pectin (anionic polysaccharide) and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can float for over12 hrs. These beads improve gastric retention time more than 5.5 hrs [51, 56].

Microporous compartment system

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls [57]. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug [Figure 5]. In the stomach the floating chamber containing entrapped air causes the delivery system to float in the gastric fluid [58]. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

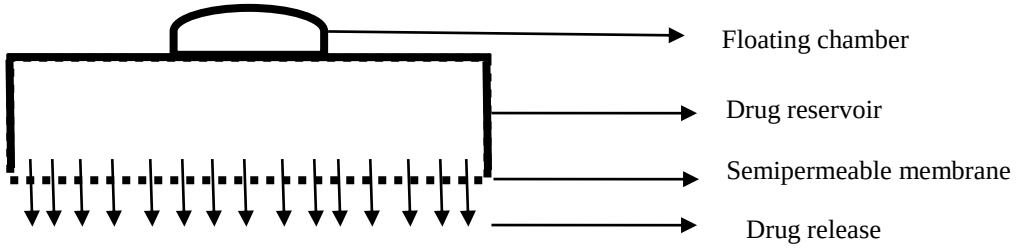

Figure 5: Microporous gastroretentive drug delivery system

Expandable systems

Expandable drug delivery systems are designed to have a longer GRT through an increase in their volume or shape. Initially, they were used for veterinary purposes and, subsequently, their applications were extended to humans [59]. Three general configurations need to be considered for the proper functioning of the system: small size for easy oral intake, expanded form in the stomach to prevent passage through the pyloric sphincter, and size reduction of the system after complete drug release to enable evacuation [34, 60, 61]. This system is also termed as a plug type system because its ability to block the pyloric sphincter. Expansion of the system occurs by two methods, swelling and unfolding, which allow for volume and shape modification respectively [60, 62].

The main mechanism for swelling and drug release from the system is discussion. These systems utilize hydrophilic polymers (for e.g., HPMC, polyethylene oxide, and carbopol) that can absorb water from the gastric fluids and increase the volume of the system. Likewise, in unfolding systems, the polymer and drug are in a folded/compressed state inside the gelatin capsule. When they come into contact with the gastric fluid, gelatin is dissolved and releases the mechanically preferred expanded configuration. Different geometrical forms of biodegradable polymer can be prepared and compressed within a capsule [61].It is crucial to select a suitable biodegradable polymer with an appropriate molecular weight, viscosity grade, and swelling properties to maintain the sustained release profile of the dosage form [61, 63].

Various novel polymers have the ability to swell promptly in contact with the GI fluid. Sivaneswari et al.developed and characterized a novel expandable GRDDS of levetiracetam based on an unfolding mechanism. In their study, the drug was loaded onto a polymeric patch made of HPMC, carbopol 934 P, and xanthum gum, which was designed to adhere to the gastric mucosa, where the drug was released in a sustained manner [64].

Superporous hydrogel systems

In 1998, the superporous hydrogel was presented as a different category of water-absorbent polymer system. This system has gained popularity in the controlled-release formulation due to its high mechanical strength and elastic properties [65]. It has a pore size greater than 100 μm, and as a result, it swells rapidly to an equilibrium size due to water uptake by capillary wetting through numerous pores. Highly swellable polymers such as crosscarmallose sodium and sodium alginate are used in this system (61, 66)

Bioadhesive or mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner [Figure 6]. In this approach, bioadhesive polymers are used and theycan adhere to the epithelial surface in the stomach [67]. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can adhere to the mucosal surface by different mechanism. These mechanisms [68, 69] are:

1. The diffusion theory, which proposes physical entanglement of mucin, strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
2. The absorption theory, suggests that Bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
3. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
4. The electronic theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose, and polylactic acid. Even though some of these polymers are effective at producing

bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract.

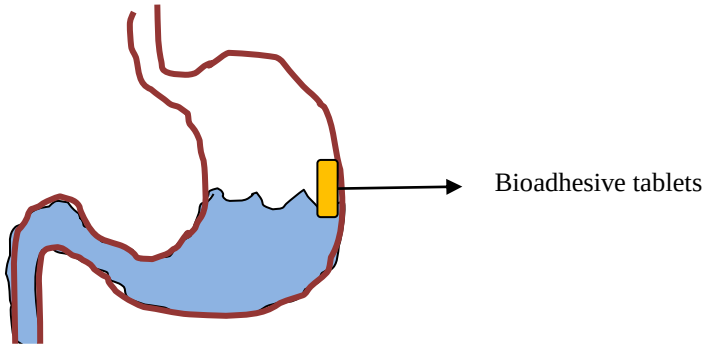

Figure 6: Bioadhesive drug delivery systems

Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations [70, 71] are required to develop an expandable system to prolong gastric retention time.

1) An expanded gastroretentive form
2) A final small form enabling evacuation following drug release from the device
3) A small configuration for oral intake

Thus, gastroretentionability is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers.

Swellable systems are also retained in the gastrointestinal tract due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. [72]

Raft forming systems

Raft-forming systems are GRDDS formulated with effervescent excipients and gel forming polymers in order to achieve the sustained drug delivery system. [Figure 7] illustrates the concept of these systems, which mainly focuses on achieving localized effects because floating raft act as a blockades between esophagus and stomach, thus they can be used for effective management of gastric esophageal reflux disease. When raft forming system comes in to contact with gastric fluids they swell and form a viscous cohesive gel leading to the formation of a continuous layer term as a raft. [73, 74]

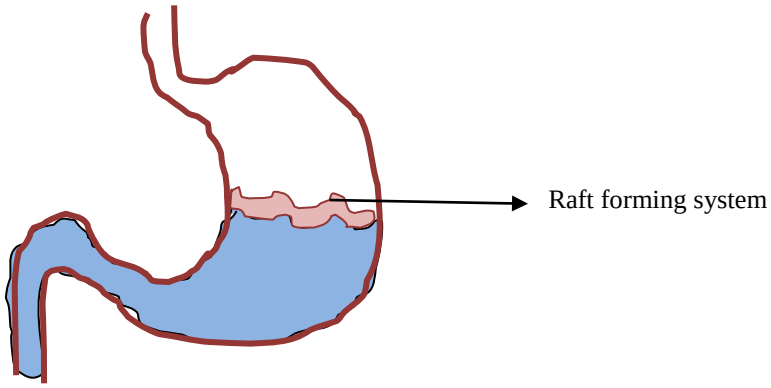

Figure 7. GRDDS based on raft-forming systems.

Magnetic systems

The gastric retention time is based on addition of small internal magnet inside drug delivery system, and a magnet placed on the abdomen over the position of the stomach [Figure 8]. Although magnetic system seems to work, the external magnet must be positioned with adegree of precision that might compromise patient compliance [69].

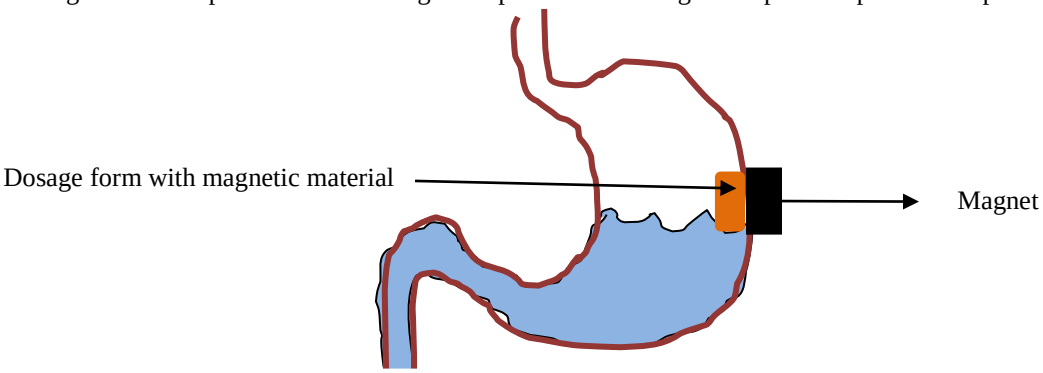

Figure 8. GRDDS based magnetic system

Ion exchange resin Systems

The ion-exchange resin system consists of the water insoluble cross-linked polymer (resin) that can be either cationic or anionic. In general, it is designed to release the drug in a controlled manner. The suitable resins can be chosen according to the drug properties. In case of GRDDS, drugs should be released in the stomach and hence this system is applicable to cationic drugs. Therefore, cationic resin can be selected. A specific amount of resin is poured on a known drug concentration and mixed homogeneously for a certain period. The drug ions from the solution get adsorbed onto the resin matrix and displace cations from the resin. Such loaded drug resin complexes are called resinates. When the resinates come into contact with the hydrogen ions in the acidic environment of the stomach, hydrogen ions are exchanged with the drug ions present in the resinates matrix. As a consequence, the drug ions are released into the gastric fluid while the resin particles are eliminated through the large intestine [75] Even though this system alone may not be suitable to increase the GRT, the ion exchange resin can be combined with floating delivery systems or bioadhesive systems to prolong the GRT [76]. Some of its limitations may be difficulty in estimating the amount of bound resin with drug, and safety issues concerning its ingesting.

IV.EVALUATION PARAMETERS OF GRDDS

Evaluation parameters

In-vitro evaluation of GRDDS can be used to predict the in-vivo performance. The routine evaluation methods of gastroretentive drug delivery systems are available in tablet, capsule, beads, microcapsules or microspheres, film forms. The evaluation test for these dosage forms are summaries in Table 1.

Table 1. Evaluation tests for various gastroretentive dosages forms

Evaluation test	Tablets	Capsules	Films	Microballoon or microspheres	Beads or granules
Physical appearance	+	+	+	+	+
Surface morphology	-	-	+	+	+
Weight	+	+	+	-	-
Thickness	+	-	+	-	-
Diameter	-	-	-	+	+
Flowability	-	-	-	+	+
Particle size distribution	-	-	-	+	+
Average particle size	-	-	-	+	+
Density	+	-	-	+	+
Moisture content	-	-	+	-	-
Swelling index	+	+	-	+	+
Water uptake	+	-	+	+	+
Moisture loss	-	-	+	-	-
Folding endurance	-	-	+	-	-
Tensile strength	-	-	+	-	-
Hardness	+	+	-	-	+
Friability	+	+	-	-	+
Floating ability	+	+	+	+	+
Drug content	+	+	+	+	+
In-vitro release	+	+	+	+	+
Kinetic analysis	+	+	+	+	+
Stability study	+	+	+	+	+
Mucoadhesive strength [a]	+	+	+	+	+

Where, [a] indicates the test for mucoadhesive dosage form.

Floating ability such as floating lag time, floating efficiency and total floating time have been used for the assessment of floating behavior of low density systems. Furthermore, floating force is also used to measure the floating capacity of the floating tablet. The mucoadhesive strength of the polymeric dosage form can be evaluated using dissolution medium and tested for at least 8 hr to ensure the floating mechanism, drug release, and gel strength.

In-vivo evaluation parameters

In order to provide the evidence of in-vivo efficacy of GRDDS, a well-designated in-vivo study in an animal model or humans is required. In-vivo studies provide information about the GRT and bioavailability of the drug. Selection of a suitable animal model is the first requirement for a successful in-vivo study. For example, in small animals such as mouse, rat, guinea pig, and rabbit, there might be an issue of animal handling especially for large dosage forms [62, 77]. As a result, measurements of the GRT and bioavailability are still difficult. Various diagnostic imaging techniques including gamma scintigraphy, radiology, gastroscopy, ultrasonography, and magnetic resonance imaging (MRI) can be applied for in-vivo evaluations of GRDDS [60, 62, 79, 78]. Gamma scintigraphy studies have been conducted to determine the location and extent of GRDDS and their transit through the GIT. In this technique, small amounts of stable isotope are added to the dosage form during its preparation [62]. Then, this isotope is converted into emitting material by irradiating the dosage form in a neutron source. Gamma rays are released and captured as an image after processing by a computer. This method can also be used for the identification of dissolution and disintegration properties of the dosage form. A good safety profile and relatively low doses of radiation are the major advantages of the technique [60, 62]. Commonly used drugs in formulation of gastroretentive dosage forms and some gastroretentive products available in the market are listed in Table 2 and Table 3 respectively.

Table 2. Commonly used drug in formulation ofgastroretentive dosages forms[29, 58]

Dosage form	Drug
Floating tablets	Acetaminophen, Acetylsalicylic acid,Ampicillin, Amoxicillin trihydrate,Atenolol, Captopril, Cinnerzine,Chlorpheniramine maleate, Furesamide, Quinapril, Ciprofloxacin,Diltiazem, Fluorouracil, Isosorbidedinitrate,Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone,Nimodipine, Losartan, Sotalol,Propranalol, Theophylline,Verapamil, Metoprolol, Nicorandil, Nisoldipine
Floating capsules	Chlordiazepoxide HCl, Diazepam,Furosemide, L-DOPA, Benserazide,Nicardipine, Misoprostol, Propranolol,Pepstatin, Lisinopril
Floating microspheres	Aspirin, Diltiazem, Griseofulvin, p-nitro aniline,Ibuprofen, Terfenadine, Tranilast, Lacidipine, Propranalol, Nifedipine, Verapamil, Furesamide, Carvedilol
Floating granules	Diclofenac sodium, Diltiazem, Indomethacin,Prednisolone
Powders	Several basic drugs
Films	Cinnerzine, Furesamide, Captopril
Beads	Diltiazem, Furesamide, Verapamil, Captopril

Table 3. Gastroretentive products available inthe market[58, 23]

Sr. No.	Brand Name	Active ingredients
1.	Cifran OD ®	Ciprofloxacin
2.	Prazopress XL®	Prazosin HCl
3.	Coreg CR®	Carvedilol
4.	Covera HS®	Verapamil
5.	Sular®	Nisoldipine
6.	Topalkan ®	Aluminum -magnesium antacid
7.	Valrelease ®	Diazepam
8.	Liquid Gavison ®	Aluminium hydroxide

V.ADVANTAGES OF GASTRORETENTIVEDRUG DELIVERY SYSTEMS

1. Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomachand small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

2. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract that act concomitantly to influence the magnitude of drug absorption [24].

3. For drugs with relatively with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

4. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time as well as the gastric emptying time. As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

5. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature isof special importance for drug with a narrow therapeutic index [55].

6. The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.

7. Reduction of fluctuation in drug level in plasma which improve selectivity in receptor activation.

8. Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

VI.FUTURE PERSPECTIVES OF GRDDS

Developing GRDDS will help to overcome the drawbacks associated with conventional dosage form; although further work is needed on its shortcomings. To date, many studies have been performed on GRDDS utilizing the

single system approach such as floating, expandable, and mucoadhesive systems. The GRT of the conventional dosage form is one of the main challenges in the pharmaceutical industry, especially for drugs that are absorbed from the upper part of the intestine. Even though various GRDDS technologies have been extensively explored to achieve successful gastroretentive systems, most have their own limitations.

VII.CONCLUSIONS

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 gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Although, this microorganism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period. An important feature to take into account is the stomach physiology. The timewhen the drug is taken (during or apart from the meal) is an important parameter. 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

REFERENCES

[1]Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv 2006; 3(2): 217- 33.
[2] Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm 1998; 174: 47-54.
[3] Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.
[4] Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multipleunit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta Helbetiae 1998; 73: 81-7.
[5] Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J Microencapsul 2003; 20: 329-47.
[6] Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm 2007; 334: 35-41.
[7] Shrma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm 2006; 313: 150-58.
[8] Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo UY, Digenis GA. An in vitro- in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm 1997; 44: 39-52.
[9] Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J ControlRelease 2003; 90: 143-62.
[10] Deshpande AA, Shah N, Rhodes CT, Malik W. Development of a novel controlled-release system forgastric retention. Pharm Res 1997; 14: 815-19.
[11] Park K. Enzyme-digestible swelling as platforms for longterm oral drug delivery: synthesis and characterization. Biomaterials 1988; 9: 435.
[12] Fujimori J, Machida Y, Nagai T. Preparation of a magnetically-responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharma Sci 1994; 4: 425-30.
[13] Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Rubinstein, MH, editors. Physiological Pharmaceutical: Biological barriers to drug absorption. Chichester, U.K.: Ellis Horwood. 1989; 47-70.
[14] Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using Gastroretentive technologies. Curr Opin Pharmacol 2006; 6: 501-8.
[15] Larhed AW, Artursson P, Grasjo J, Bjork K. Diffusion of drugs in native and purified gastrointestinal mucus. J Pharm Sci 1997; 86(6): 660-65.
[16] Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm 1989; 53: 107-17.
[17] Lopes, C.M.; Bettencourt, C.; Rossi, A.; Buttini, F.; Barata, P. Overview on gastroretentive drug deliverysystems for improving drug bioavailability. Int. J. Pharm. 2016; 510: 144–158.
[18]Talukdar, R.; Fassihi, R. Gastroretentive delivery systems: A mini review. Drug Dev. Ind. Pharm. 2004; 30:1019–1028.
[19] Streubel, A.; Siepmann, J.; Bodmeier, R. Drug delivery to the upper small intestine window usinggastroretentive technologies. Curr. Opin. Pharmacol. 2006; 6: 501–508.
[20] Arora, S.; Ali, J.; Ahuja, A.; Khar, R.K.; Baboota, S. Floating drug delivery systems: A review. AAPSPharmSciTech 2005; 6: E372–E390.
[21] Garg, R.; Gupta, G. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res. 2008; 7:1055–1066.
[22] Nguyen, N.Q.; Debreceni, T.L.; Burgstad, C.M.; Wishart, J.M.; Bellon, M.; Rayner, C.K.; Wittert, G.A.;Horowitz, M. E_ects of posture and meal volume on gastric emptying, intestinal transit, oral glucosetolerance, blood pressure and gastrointestinal symptoms after Roux-en-Y gastric bypass. Obes. Surg. 2015;25: 1392–1400.
[23] Wang, Y.T.; Mohammed, S.D.; Farmer, A.D.;Wang, D.; Zarate, N.; Hobson, A.R.; Hellström, P.M.; Semler, J.R.;Kuo, B.; Rao, S.S. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using thewireless motility capsule: Influence of age, gender, study country and testing protocol. Aliment. Pharmacol.Ther. 2015; 42: 761–772.
[24] Feldman, M.; Barnett, C. Fasting gastric pH and its relationship to true hypochlorhydria in humans. Dig. Dis.Sci. 1991; 36: 866–869.
[25] Mojaverian, P.; Vlasses, P.H.; Kellner, P.E.; Rocci, M.L. E_ects of gender, posture, and age on gastric residencetime of an indigestible solid: Pharmaceutical considerations. Pharm. Res. 1988; 5: 639–644.
[26] Krygowska-Wajs, A.; Cheshire, W.P.; Wszolek, Z.K.; Hubalewska-Dydejczyk, A.; Jasinska-Myga, B.;Farrer, M.J.; Moskala, M.; Sowa-Staszczak, A. Evaluation of gastric emptying in familial and sporadicParkinson disease. Parkinsonism Relat. D. 2009; 15: 692–696.
[27] Triantafyllou, K.; Kalantzis, C.; Papadopoulos, A.; Apostolopoulos, P.; Rokkas, T.; Kalantzis, N.; Ladas, S.Video-capsule endoscopy gastric and small bowel transit time and completeness of the examination inpatients with diabetes mellitus. Dig. Liver Dis. 2007; 39: 575–580.
[28]Dubernet C. Syste`mes a` liberation gastrique prolonge`e. In: Falson-Rieg F, Faivre V, Pirot F, editors. Novelles formes me`dicamenteuses. Editions Me`dicales Internationales. Editions TEC and DOC. Cachan. 2004; 119-33.
[29] Arrora S, Ali J, Khar RK, Baboota S. Floatng drug delivery systems: A review. AAPS Pharm Sci Tech 2005; 6(3): 372-90.

[30] Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr ML. Effects of gender, posture and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm Res 1988; 10: 639-44.
[31]Arrora S, Ali J, Khar RK, Baboota S. Floatng drug deliverysystems: A review. AAPS Pharm Sci Tech 2005; 6(3): 372-90.
[32] El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF.Preparation and evaluation of ketoprofen floating oral delivery system. Int J Parm 2001; 220: 13-21.
[33] Garg S, Sharma S. Gastroretentive drug delivery systems.Business Briefing: Pharmatech 2003; 160-66.
[34] Lopes, C.M.; Bettencourt, C.; Rossi, A.; Buttini, F.; Barata, P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int. J. Pharm. 2016; 510: 144–158.
[35] Prajapati, V.D.; Jani, G.K.; Khutliwala, T.A.; Zala, B.S. Raft forming system—An upcoming approach ofgastroretentive drug delivery system. J. Control. Release 2013; 168: 151–165
[36] N Abduljabbar, H.; M Badr-Eldin, S.; M Aldawsari, H. Gastroretentive ranitidine hydrochloride tablets withcombined floating and bioadhesive properties: Factorial design analysis, in vitro evaluation and in vivoabdominal X-ray imaging. Curr. Drug Deliv. 2015; 12: 578–590.
[37] Choi, B.; Park, H.; Hwang, S.; Park, J. Preparation of alginate beads for floating drug delivery system: Effectsof CO2 gas-forming agents. Int. J. Pharm. 2002; 239: 81–91.
[38] Rossi, A.; Conti, C.; Colombo, G.; Castrati, L.; Scarpignato, C.; Barata, P.; Sandri, G.; Caramella, C.; Bettini, R.;Buttini, F. Floating modular drug delivery systems with buoyancy independent of release mechanisms to sustain amoxicillin and clarithromycin intra-gastric concentrations. Drug Dev. Ind. Pharm. 2016; 42: 332–339.
[39] Kim, S.; Hwang, K.-M.; Park, Y.S.; Nguyen, T.-T.; Park, E.-S. Preparation and evaluation of non-e_ervescentgastroretentive tablets containing pregabalin for once-daily administration and dose proportionalpharmacokinetics. Int. J. Pharm. 2018; 550: 160–169.
[40] Sheth, P.; Tossounian, J. The hydrodynamically balanced system (HBS.): A novel drug delivery system fororal use. Drug Dev. Ind. Pharm. 1984; 10: 313–339.
[41] Reddy, L.H.V.; Murthy, R. Floating dosage systems in drug delivery. Crit. Rev. Ther. Drug 2002; 19: 553–585.
[42] Vyas SP, Khar RK. Gastroretentive systems. In: Controlleddrug Delivery. Vallabh Prakashan, Delhi, India. 2006; 197-217.
[43] Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm 1993; 100(13): 81-92.
[44] Moes AJ. Gastric retention systems for oral drug delivery. Business Briefing: Pharmatech 2003: 157-59.
[45] Thapa, P.; Jeong, S. Effects of formulation and process variables on gastroretentive floating tablets with a high-dose soluble drug and experimental design approach. Pharmaceutics.2018; 10: 161.
[46] Rahim, S.A.; Carter, P.; Elkordy, A.A. Influence of calcium carbonate and sodium carbonate gassing agentson pentoxifylline floating tablets properties. Powder Technol. 2017; 322: 65–74.
[47] Baumgartner, S.; Kristl, J.; Vre˘cer, F.; Vodopivec, P.; Zorko, B. Optimisation of floating matrix tablets andevaluation of their gastric residence time. Int. J. Pharm. 2000; 195:125–135.
[48] Talukder, R.; Fassihi, R. Gastroretentive delivery systems: A mini review. Drug Dev. Ind. Pharm. 2004;30:1019–1028.
[49] Jiménez-Martínez, I.; Quirino-Barreda, T.; Villafuerte-Robles, L. Sustained delivery of captopril from floatingmatrix tablets. Int. J. Pharm. 2008; 362,:37–43.
[50] Tadros, M.I. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride:Development, optimization and in vitro–in vivo evaluation in healthy human volunteers. Eur. J. Pharm.Biopharm. 2010; 74: 332–339.
[51] Garg R, Gupta GD. Progress in controlled gastroretentivedelivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.
[52] Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984; 10: 313-39.
[53] Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug Carrier Syst 1998; 15(3): 243-84.
[54] Reddy LH, Murthy RS. Floating dosage system in drug delivery. Crit Rev Ther Drug Carrier Syst 2002; 19(6): 553-85.
[55] Talukdar R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev Ind Pharm 2004; 30: 405-12.
[56] Whiteland L, Fell JT, Collett JH. Development of gastroretentive dosage form. Eur J Pharm Sci 1996;4(suppl.): S182.
[57] Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 405 5178; October 25, 1977.
[58] Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006; 197-217.
[59] Garg, R.; Gupta, G. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res. 2008; 7:1055–1066.
[60] Klausner, E.A.; Lavy, E.; Friedman, M.; Ho_man, A. Expandable gastroretentive dosage forms. J. Control.Release 2003; 90:143–162.
[61] Bardonnet, P.; Faivre, V.; Pugh, W.; Pi_aretti, J.; Falson, F. Gastroretentive dosage forms: Overview andspecial case of Helicobacter pylori. J. Control. Release 2006; 111: 1–18.
[62] Mandal, U.K.; Chatterjee, B.; Senjoti, F.G. Gastro-retentive drug delivery systems and their in vivo success:A recent update. Asian J. Pharm. Sci. 2016; 11: 575–584.
[63] Sivaneswari, S.; Karthikeyan, E.; Chandana, P. Novel expandable gastro retentive system by unfoldingmechanism of levetiracetam using simple lattice design–Formulation optimization and in vitro evaluation.Bull. Fac. Pharm. Cairo Univ. 2017; 55,:63–72.
[64] Chen, Y.C.; Ho, H.O.; Lee, T.Y.; Sheu, M.T. Physical characterizations and sustained release profiling ofgastroretentive drug delivery systems with improved floating and swelling capabilities. Int. J. Pharm. 2013;441: 162–169.
[65] Omidian, H.; Rocca, J.G.; Park, K. Advances in superporous hydrogels. J. Control. Release 2005; 102: 3–12.
[66] Bhalla, S.; Nagpal, M. Comparison of various generations of superporous hydrogels based on chitosan-acrylamide and in vitro drug release. ISRN Pharm. 2013; 62:48-41.
[67] Moes A. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993; 10: 143-95.
[68] Faivre V. Aspects theoriques de la bioadhesion. In: Falson- Rieg V, Faivre V, Pirot F. ed. Nonvelles forms medicamenteuses , Editions Medicales Internationales, Editions TEC and DOC, Cachan. 2004; 1-24.
[69] Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. J Control Release 2000; 65(1-2): 63- 71.
[70] Klusner EA, Lavy E, Friedman M, Hoffman A. Expandable gasrtroretentive dosage forms. J ControlRelease 2003; 90(2): 143-62.
[71] Klusner EA, Lavy E, Stepensley D, Friedman M, HoffmanA. Novel gasrtroretentive dosage form: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharm Res 2002; 19: 1516-23.
[72] Klusner EA, Lavy E, Barta M, Cserepes E, Friedman M, Hoffman A. Novel gasrtroretentive dosage form: evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm Res 2003; 20(9): 1466-73.

[73] Prajapati, V.D.; Jani, G.K.; Khutliwala, T.A.; Zala, B.S. Raft forming system—An upcoming approach ofgastroretentive drug delivery system. J. Control. Release 2013; 168: 151–165.
[74] Abouelatta, S.M.; Aboelwafa, A.A.; El-Gazayerly, O.N. Gastroretentive raft liquid delivery system as anew approach to release extension for carrier-mediated drug. Durg Deliv. 2018; 25: 1161–1174.
[75] Gaur, P.K.; Mishra, S.; Bhardwaj, S.; Puri, D.; Kumar, S.S. Ion Exchange Resins in Gastroretentive DrugDelivery: Characteristics, Selection, Formulation and Applications. J. Pharm. Sci. Pharmacol. 2014; 1:304–312.
[76] Anand, V.; Kandarapu, R.; Garg, S. Ion-exchange resins: Carrying drug delivery forward. Drug Discov. Today2001; 6: 905–914.
[77] Turner, P.V.; Brabb, T.; Pekow, C.; Vasbinder, M.A. Administration of substances to laboratory animals:Routes of administration and factors to consider. J. Am. Assoc. Lab. Anim. Sci. 2011; 50: 600–613.
[78] Badve, S.S.; Sher, P.; Korde, A.; Pawar, A.P. Development of hollow/porous calcium pectinate beads forfloating-pulsatile drug delivery. Eur. J. Pharm. Biopharm. 2007; 65: 85–93.
[79] Pawar, V.K.; Kansal, S.; Garg, G.; Awasthi, R.; Singodia, D.; Kulkarni, G.T. Gastroretentive dosage forms: Areview with special emphasis on floating drug delivery systems. Durg Deliv. 2011;18: 97–110.