Review on Gastroretentive Drug Delivery System

Vedant S.Ganorkar[1], Dr. Nishan Bobade[2], Tushar S Bochare[3], Vaishnavi Chavan[4]
[1,2,3,4]*Vidhyabharti College of Pharmacy Amravati*

Abstract- The goal of this review on gastroretentive drug delivery systems was to gather the most recent research with a special emphasis on the various gastroretentive methodologies that have recently emerged as leading approaches in the area of site-specific oral controlled release drug delivery. We have outlined key elements influencing stomach retention in order to comprehend the numerous physiological challenges involved in achieving it. After that, we evaluated the several gastroretentive strategies that have been created and developed to date, including high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, ultra porous hydrogel, and magnetic systems. The benefits of gastroretentive medication delivery devices were then thoroughly discussed.

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

INTRODUCTION

The most practical and preferable method of delivering any medicine to the systemic circulation is oral administration. The pharmaceutical industry has recently shown an increased interest in oral controlled release drug delivery to gain better therapeutic benefits, such as simplicity in administering doses, patient compliance, and formulation flexibility. Drugs with short half lives and easy absorption from the gastrointestinal tract (GIT) are removed from the systemic circulation swiftly. These medications must be dosed frequently to get the desired therapeutic effect. The creation o f oral sustainedth controlled release formulations is an effort to bypass this restriction by graduall y releasing the medication into the gastrointestinal tract (GIT) while maintaining an effective dru g concentration. lengthy time in the systemic circulation. Such a drug delivery would be kept in the stomach after oral administration and release the medication under controlled circumstances, allowing the drug to be constantly provided to its absorption sites in the gastrointestinal tract (GIT) [1]. The two main drawbacks of these drug delivery systems are short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), both of which can cause incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine), which can reduce the effectiveness of the dose that was administered [2]. It is necessaryto create a site-specific oral controlled release dose form. is desirable to extend the drug delivery's stomach residence period. Long-term gastric retention enhances drug bioavailability, prolongs the time it takes for the medication to leave the stomach, minimises drug waste, and increases the solubility of drugs that are less soluble in high pH environments [3]. Additionally, a prolonged GRT in the stomach may be helpful for local actions in the upper part of the small intestine, such as the treatment of peptic ulcers, etc. It is possible to target site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects by using a strategy called gastroretentive drug delivery. The gastric retention time (GRT) of medications can be greatly extended when using gastroretentive dose forms, which can stay in the gastric region for extended periods. Many gastroretentive drug delivery methods have been designed and developed over the past few decades, including high density (sinking) systems that are retainedin the bottom of the stomach [4], low density (floating) systems that cause buoyancy in gastric fluid [5, 6, 7], mucoadhesive systems that cause bioadhesion to stomach mucosa [8], and unfoldable,extendible, or swellable systems that restrict emptying of the dosage forms through the pyloric systems using magnets, etc. The current review examines a number of recently popular gastroretentive methods. Techniques in the realm of oral controlled release medication delivery systems that are site-specific.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The structure and physiology of the stomach contain variables that should be taken into account when creating gastroretentive dose forms. The particle size

should be between 1 and 2 mm in order to pass through the pyloric valve and enter the small intestine [13]. The density, size, and shape of the dosage form, the type of food consumed, the caloric content and frequency of consumption, posture, gender, age, sex, sleep, body mass index, physical activity, and thediseased states of the individual (such as chronic disease, diabetes, etc.) are the most crucial factors influencing the gastric retention time (GRT) of oral dosage forms. and the use of medications that may affect gastrointestinal transit time, such as atropine and propantheline, which function as anticholinergic agents. Codeine and metclopramide are two examples of opiates and prokinetic drugs, respectively [14]. Important criteria include the drug's molecular weight and lipophilicity in relation to its ionisation state [15].Density of dosage forms the density of a dose form also influences the rate of gastric emptying and establishes where the system is located in the stomach. While high density systems sink to the bottom of the stomach, dosage forms with a density lower than the gastric contents might float to the surface [16]. The dose system may be separated from the pylorus in either position. For an object to have floating properties, its density must be less than 1.0 gm/cm3 [17].Shape and size of dosage forms designing indigestible single unit solid dosage forms requires consideration of the shape and size of the dosage forms. Non-floating dose forms can be big, medium, or small units, and their size has a significant impact on their mean stomach residence periods. The gastric retention time (GRT) will often increase with dose form size since larger dosage forms make it more difficult for them to move swiftly via the pyloric antrum and into the intestine [18]. When compared to dosage forms with a 9.9 mm diameter, those with a diameter of more than 7.5 mm exhibit a longer stomach residence duration [17]. Ring-shaped Compared to other shapes, tetrahedron- shaped devices have a longer stomach residency time [19].Food intake and its nature the amountof food consumed, its viscosity and volume, caloric content, and feeding frequency all have a significant impact on the retention of dosage forms in the stomach. The gastric retention time (GRT) of the dose form is influenced by the presence or absence of food in the gastrointestinal tract (GIT). The gastric retention time (GRT) of the dosage form is often improved by the presence of food in the gastrointestinal tract (GIT), and as a result, the medication absorption increases by allowing it to remain at the absorption site for a longer amount of time. Again, a risein acidity and caloric content results in a decrease in gastric emptying time (GET), which can enhance the retention of dose forms in the stomach [20]. Effects of gender, posture and age in general, females empty their stomachs more slowly than males. Individuals in an upright, ambulatory, and supine state do not significantly differ in their mean gastric retention times (GRT) as a result of their posture. Gastric emptying is slowed down in elderly people [21].

POTENTIAL DRUG CANDIDATE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

1) Medicines that act locally in the stomach, such as antacids and misroprostol.
2) Medicines with a limited window of absorption in the gastrointestinal tract (GIT), such asriboflavin, para aminobenzoic acid, furosemide, and L-DOPA.
3) Drugs that are unstable in the intestinal or colonic environment, such as metronidazole, captopril, and ranitidine HCl.
4) Substances that disrupt the regular colonic microbiota medication to treat Helicobacterpylori.
5) Medicines with low solubility at high pH levels, such as verapamil HCl, chlordiazepoxide,and diazepam.

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Medicines with a very low acid solubility, such as phenytoin, etc.
2) Drugs that are unstable in the stomach, such as erythromycin, etc.
3) Drugs designed for colonic selective release such as corticosteroids and 5-aminosalicylic acid,etc.

APPROACHES TO ACHIEVE GASTRIC RETENTION

Non-floating drug delivery systems or high density (sinking) systems this method calls for the development of dose forms whose density must be greater than that of the typical contents of the stomach (1.004 gm/cm3). These formulations are made by coating the medication on a substantial core or by

combining it with inert substances as iron powder, barium sulphate, zinc oxide, titanium oxide, etc. [22]. The materials can raise density by 1.5–2.4 gm/cm3 or more. For a meaningful extension of the stomach residence period, a density of close to 2.5 gm/cm3 appears to be required [23]. However, no evidence of this method's usefulness in humans has been found[24] and no system has been sold.Floating drug delivery systems one of the crucial methods for achieving stomach retention and obtaining adequate medication bioavailability is the use of floating drug delivery devices [25]. For medications with an absorption window in the stomach or upper small intestine, this administration strategy is preferred [26]. This floats in the stomach without slowing down gastric emptying rate since its bulk density is lower than that of gastric fluids, and the medicine is released gradually as the system's targeted rate. The stomach's residual system is emptied after the medication has been released. As a result, the gastricretention time (GRT) was extended and the variability in plasma drug concentration was better managed. The following [22] are the main requirements for floating medication delivery systems:

- It must retain a specific gravity lower than gastric contents (1.004–1.01 gm/cm3) and dischargecontents gradually to act as a reservoir.
- A cohesive gel barrier is required.

By trapping air (such as in hollow chambers) [27] or by incorporating low density materials (such as fatty materials, oils, or foam powder) [5, 28, 29], the inherent low density can be produced. The design of floating dosage forms for both single-unit systems and multi-unit systems has incorporated the following strategies. A single-unit floating system made up of matrix-forming polymers, polypropylene foam powder, medication, and filler was recently presented [30]. Single- unit dose forms have a tendency to cling together or become clogged in the gastrointestinal tract (GIT), both of which might irritate the stomach. However, multiple-unit floating systems have been demonstrated to lessen the inter- and intra-subject availabilities in drug absorption as well as the likelihood of dose dumping, making them a compelling option [26]. Different multiple-unit floating systems, such as the air compartment multiple-unit system [2], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method [31], microparticles based on low density foam powder [5], beads prepared by the emulsion gelatin method [32], etc., can be widely distributed throughout the GIT, offering the possibility of achieving a longer lasting and more dependable release of drugs. Two distinctly different technologies, namely non-effervescent and effervescent systems, have been used in the creation of floating medication delivery systems based on the mechanism of buoyancy.

Non-effervescent systems

Microballoons / Hollow Microspheres: To increase the gastric retention time (GRT) of the dosage form, simple solvent evaporation or solvent diffusion / evaporation procedures [38] were used to create microballoons / hollow microspheres that were loaded with pharmaceuticals in their other polymer shelf. Polycarbonate, cellulose acetate, calcium alginate, agar, and low methoxylated pectin are among the frequently employed polymers in the development of these systems. Quantity of polymers, plasticizer to polymer ratio, and formulation solvent all affect buoyancy and drug release from dosage forms. For more than 12 hours, the microballoons floated constantly over the top of an acidic dissolving media that contained surfactant [3]. 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.

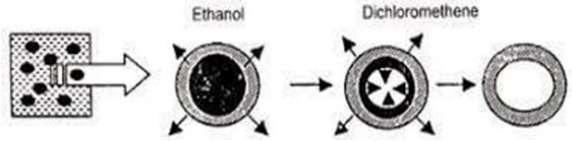

Figure 1. shows how a hollow floating microsphere or micro balloon is made.

Using cross-linked alginate beads, Talukdar and Fassihi [32] recently created a multiple-unit floating system. They were created utilising either Ca2+ low methoxylated pectin and sodium alginate or Ca2+ low methoxylated pectin and anionic polysaccharide. In this method, calcium alginate is typically precipitated by dropping a sodium alginate solution into an aqueous calciumchloride solution. The formation of a porous system, which can sustain a floating force for

morethan 12 hours, results from the separation and drying of these beads using air convection and freeze drying. The gastric retention time (GRT) is improved by these beads by more than 5.5 hours [3, 39].

This method relies on the idea that a drug reservoir is enclosed inside a microporous compartment with pores running the length of its top and bottom walls [40]. In order to prevent any direct contact of the gastric surface with the undissolved medication, the device's peripheralborders were entirely sealed. The delivery system floats in the gastric fluid inside the stomach due to the flotation chamber's airtight seal [22]. Through the opening, gastric fluid enters, dissolves the drug, and then causes the drug's continuous transportation across the intestine for drug absorption.

Effervescent (gas generating) systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) [40]. The optimal stoicheometricratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 [19]. In thissystem carbon dioxide is released and causes the formulation to float in the stomach (Figure 2 and Figure 3). Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) Ion exchange resin technology-based floating system, coating with hydroxypropyl methylcellulose (HPMC), etc. Additionally, multilayer or bilayer systems have been developed [41, 42]. The gas generating material can be included into any of the layers, and drugs and excipients can be manufactured separately. The matrix will undergo additional alterations, including a covering of a polymer that is permeable to water but not to carbon dioxide. Finding a reasonable balance between the polymers' elasticity, plasticity, and permeability is the main challenge of these formulations.

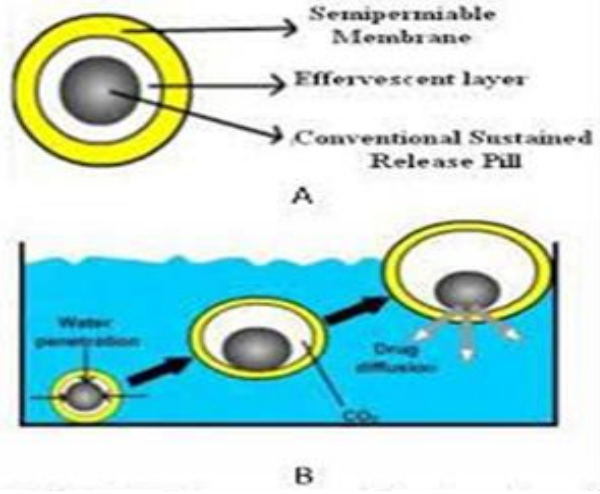

Figure 2. Effervescent (gas generating) systems devices release drugs.

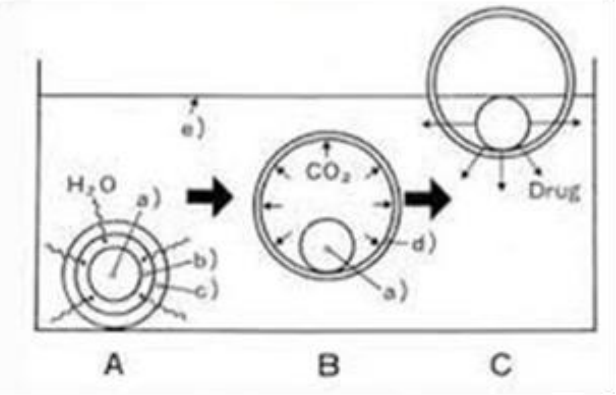

Figure 3. shows how effervescent (gas-generating)

Bioadhesive and Mucoadhesive drug delivery system

The usage of bioadhesive drug delivery is delivery system inside the body to improve drug absorption in a targeted way. This method employs bio adhesive polymers, which can cling to the stomach's epithelial surface [43]. They thereby enhance the lengthening of gastric retention. The fundamental principle of adhesion is that numerous mechanisms might cause a dose form to adhere to the mucosal surface. These systems [44, 45] consist of-

1) The wetting theory, which is based on bioadhesive polymers' propensity to diffuse and establish close contact with the mucosal layers.

2) The diffusion theory, which suggests that mucin strands physically entangle with flexible polymer chains or interpenetrate the porous structure

of the polymer substrate.

3) According to the absorption theory, secondary forces like hydrogen bonds and Vander Waalforces are what cause bioadhesion.

4) The electron theory, which suggests that the glycoprotein mucin network and the bio adhesive substance are held together by attractive electrostatic forces.

Polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG), and polylactic acids are examples of materials frequently utilised for bioadhesion. Despite the fact that some of these polymers are successful at forming bioadhesive, the rapid mucus turnover in the gastrointestinal tract (GIT) makes effective maintenance very challenging.

Expandable, unfoldable and swellable systems

If a dose form is larger than the pyloric sphincter, it will resist gastric transit. The dosage form must, however, be small enough to be taken and must not, either individually or cumulatively, result in stomach blockage. Thus, in order to create an extensible system to extend gastric retention time (GRT), their configurations [46, 47] are necessary:

1) a compact design for oral ingestion,
2) A more comprehensive gastroretentive version, and
3) a last tiny form that enables evacuation after the medication has been released from theapparatus.

So, the combination of considerable dimension with high rigidity of the dose form to withstand peristalsis and mechanical contractility of the stomach improves gastroretentivity. Recently, efforts have been made to produce effective gastroretentive medication delivery using unfoldableand swellable devices. Biodegradable polymers are used to create unfoldable systems. They come in a variety of geometric shapes, including tetrahedron, ring, planner membrane, disc, or cross with four limbs, made of bioerodible polymer and squeezed inside a capsule that extends into the stomach [48, 49]. Due to their mechanical characteristics, swellable systems are also retained in the gastro intestinal tract (GIT). The dosage form is tiny enough to be taken by the gastric fluid and the swelling is typically caused by the osmotic absorption of water (Figure 4). Expandable systems have some limitations, such as challenging storage of readily biodegradable, rapidly hydrolyzable polymers, relatively short mechanical shape memory for the unfolding system, and inefficient and expensive industrialization.50 Once more, the continual use of inflexible, big single-unit expandable drug delivery dosage forms may result in short intestinal blockage gastropathy and adhesion [19].

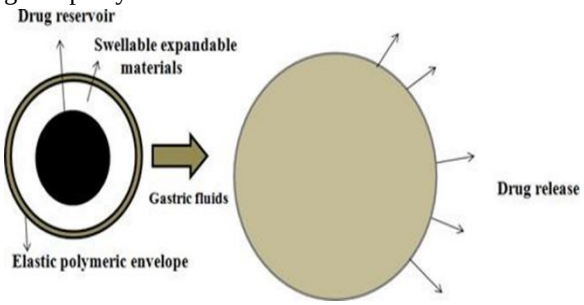

Fig 4. Drug release from swellable systems

Super porous hydrogel systems

These swellable systems are different enough from the traditional varieties to merit classificationas a separate group. Super porous hydrogels with an average pore size of over 100 micrometres are used in this method to increase gastric retention time (GRT), and they expand to equilibrium size in under a minute as a result of rapid water absorption by capillary wetting through a large number of interconnected open pores [51]. They are designed to have adequate mechanical strength to withstand pressure caused by gastric contraction and swell to a big size (swelling ratio: 100 or higher). Co-formulation of hydrophilic particle materia[l] [52] suggests doing this.

Magnetic systems

A small internal magnet is present in the dose form, and a magnet is also applied to the abdomen over the location of the stomach in this method to increase gastric retention time (GRT).Although the magnetic system appears to work, the external magnet needs to be placed precisely, which may reduce patient compliance [45].

Tables 1 and 2 respectively include some of the gastroretentive products that are commercially available as well as often utilised medications in the formulation of gastroretentive dosage forms.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Table 1. Commonly used drug in formulation of gastro retentive dosages forms [17, 22]

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several basic drugs
Films	Cinnerzine

Table 2. Gastroretentive products available in the market [22, 53]

Brand Name	Active Ingredient(s)
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoat ®	Aluminum -magnesium antacid
Liquid Gavison ®	Aluminium hydroxide,
Conviron	Ferrous sulfate
Cytotec®	Misoprostal

1) When compared to the administration of non-gastroretentive drug delivery, the bioavailability of therapeutic drugs can be greatly increased, especially for those that are metabolised in the upper GIT. The volume of medication absorption is influenced by a number of different parameters that are connected to drug absorption and transit in the gastrointestinal tract (GIT) concurrently [54].

2) Sustained release may provide a flip-flop pharmacokinetics for medications with a relatively short half-life and allow for less frequent dosage with better patient compliance.

3) Due to their smaller bulk density than the stomach juices, they can float atop the fluid without changing their intrinsic rate of employing. They also have a benefit over their traditional approach in that they can be used to get around problems with the gastric retention time (GRT) and the gastric emptying time (GET). Since these systems are anticipated to continue.

4) Gastroretentive drug delivery can result in a prolonged and sustained release of medications from dosage forms that offer local therapy in the small intestine and stomach. As a result, they are helpful for treating conditions of the stomach and small intestine.

5) Drug systemic exposure is minimised or completely avoided by the regulated, gradual release of medication in the form of a gastroretentive dosage form, which offers sufficient local action atthe sick location. The negative consequences of side effects are lessened by this site-specificdrug administration.

6) The variability of medication concentrations and effects is reduced by gastroretentive dosage forms. As a result, peak concentrations can be used to illustrate undesirable effects that are concentration dependent. This characteristic is especially crucial for medications with a limited therapeutic index [55].

7) Gastroretentive medication administration can reduce the body's defence mechanisms, increasing drug effectiveness.

8) Improving selectivity in receptor activation is feasible by reducing drug concentration fluctuations.

9) The prolonged time over a critical concentration is made possible by the sustained mode of drug release from gastroretentive dosages, which improves the pharmacological effects and time (GRT) as well as the stomach emptying time (GET). This system's continued use enhances the chemical results.

CONCLUSION

Based on the reviewed literature, it is possible to draw the conclusion that gastroretentive drug delivery offers a number of potential benefits for medications with low bioavailability because these medications' absorption is limited to the upper gastrointestinal tract (GIT) and because they can be efficiently delivered, maximising absorption and improving absolute bioavailability. To determine the best dosage form for a certain medicine, in vivo investigations are necessary due to the intricacy of the pharmacokinetics and pharmacodynamics characteristics. Eliminating Helicobacter pylori, now recognised as the primary bacterium responsible for chronic stomach ulcers, is another interesting field of research for gastroretentive drug delivery systems peptic ulcers and gastritis. Although this microorganism is highly sensitive to a variety of antibiotics, maintaining a high concentration of antibiotics within the stomach mucosa for an extended period of time is necessary for its full eradication. The physiology of the stomach is a crucial

factor to consider. The moment the medication is taken (during or after a meal) is a crucial factor.A significant problem for pharmaceutical science is to create an effective gastroretentive dose form. In fact, the drug delivery mechanism must stay in the stomach for a long enough period of time, which is not consistent with its natural physiology. All of these gastroretentive drug delivery methods (such as magnetic systems, high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, etc.) are intriguing and each have their own benefits and drawbacks. A lot of work is currently being done to develop various gastroretentive medication delivery methods. They are anticipated to become more significant in the future, which will ultimately result in increased pharmacotherapy efficacy across the board.

REFERENCE

[1] Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert OpinDrug 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 multiple- unit 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 Control Release 2003; 90: 143-62.

[10] Deshpande AA, Shah N, Rhodes CT, Malik W. Development of a novel controlled- release system for gastric retention. Pharm Res 1997; 14: 815-19.

[11] Park K. Enzyme-digestible swelling as platforms for long- term 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. p. 47-70.

[14] Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine windowusing 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] 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. p. 119-33.

[17] Arrora S, Ali J, Khar RK, Baboota S. Floatng drug delivery systems: A review. AAPS Pharm Sci Tech 2005; 6(3): 372-90.

[18] 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.

[19] Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003: 160-66.

[20] Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm 1989; 53:

107-17.

[21] 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.

[22] Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006. p. 197-217.

[23] Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm 1993; 100(13): 81-92.

[24] Moes AJ. Gastric retention systems for oral drug delivery.Business Briefing: Pharmatech 2003: 157-59.

[25] Sing BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel 2000; 63: 235-59.

[26] Sungthongjeen S, Paeratakul O, Limmatvapirat S, Puttipupathachorn S. Preparation and in-vitro evaluation of multiple-unit floating drug delivery system based on gas formation technique. Int J Pharm 2006; 324: 136-43.

[27] Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J Control release 1999; 61: 43-50.

[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] Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. Int J Pharm 2002; 241: 279-92.

[30] 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.

[31] Sato Y, Kawashima Y, Takenchi H, Yamamoto H. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Eur J Pharm Biopharm 2003; 55: 297-304.

[32] Talukdar R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev Ind Pharm 2004; 30: 405-12.

[33] 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.

[34] Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984; 10: 313-39.

[35] Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug CarrierSyst 1998; 15(3): 243-84.

[36] Reddy LH, Murthy RS. Floating dosage system in drug delivery. Crit Rev Ther Drug Carrier Syst 2002; 19(6): 553-85.

[37] Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of *Helicibacter pylori.* J Control Release 2006; 111: 1-18.

[38] Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81: 135- 40.

[39] Whiteland L, Fell JT, Collett JH. Development of gastroretentive dosage form. Eur J Pharm Sci 1996; 4(suppl.): S182.

[40] Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 405 5178; October 25, 1977.

[41] Ingani HM, Timmermans J, Moes A. Conception and in vivo investigation of per oral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm 1987; 35(12): 157-64.

[42] Krogel I, Bodmeir R. Floating or pulsatile drug delivery system based on coated effervescent cores. Int J Pharm 1999; 187(2): 175-84.

[43] Moes A. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993; 10: 143- 95.

[44] Faivre V. Aspects theoriques de la bioadhesion. In: Falson- Rieg V, Faivre V, Pirot F. ed. Nonvelles formes medicamenteuses , Editions Medicales Internationales, Editions TEC and DOC, Cachan. 2004. p. 1-24.

[45] 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.

[46] Klusner EA, Lavy E, Friedman M, Hoffman A. Expandable gasrtroretentive dosage forms. J Control Release 2003; 90(2): 143-62.

[47] Klusner EA, Lavy E, Stepensley D, Friedman M, Hoffman A. Novel gasrtroretentive dosage form: evaluation of gastroretentivity and its effect onriboflavin absorption in dogs. Pharm Res 2002; 19: 1516-23.

[48] Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained inthe stomach for controlled period of time. US Patent 473 5804. April 5, 1988.

[49] Caldwell LJ, Gardner CR, Cargill RC, Higuchi T. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 475 8436: July 19, 1988.

[50] 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.

[51] Chen J, Blevins WE, Park H, Park K. Gastric retention of superporous hydrogel composites. J Control Release 2000; 64(1-3): 39-51.

[52] Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. J Control Release 2000; 65(1-2): 73-82.

[53] Chawla G, Gupta P, Bansal AK. Gastroretentive drug delivery systems. In: Jain NK. editor. Progress in controlled and novel drug delivery systems. CBS Publishers and Distributors. New Delhi. 2004. p. 76-97.

[54] Klusner EA, Eyal S, Lavy E, Friedman M, Hoffman A. Novel levodopa gasrtroretentive dosage form: in vivo evaluation in dogs. J Control Release 2003; 88: 117-26.

[55] Hoffman A. Pharmacodynamic aspects of sustained release preparation. Adv DrugDeliv Rev 1998; 33: 185-99.