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Features & Facts of Gastroretentive Drug Delivery System – A Review

Gastroretentive İlaç Dağıtım Sisteminin Özellikleri ve Gerçekleri - Bir İnceleme

Short title: Gastroretentive Drug Delivery System

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ABSTRACT
English Oral delivery of drug was the commonly used modality on account of patient compliance and ease of administration. After oral administration of any drug, its bioavailability is affected by the residence time in stomach. Recently, gastroretentive drug delivery systems (GRDDS) are gaining wide acceptance for drugs with a narrow absorption window, decreased stability at high alkaline pH, and increased solubility at low pH. This approach aims to develop a drug delivery system which gets retained within a gastric fluid, thereby releasing its active principles in the stomach. Some of the methods used to achieve gastric retention of drugs include the use of effervescence agents, mucoadhesive polymers, magnetic material, bouncy enhancing excipient, and techniques that form plug-like devices which resisted gastric emptying. This review attempts to provide a concise account of various attributes of recently developed approaches for GRDDS.
Keywords: Bioavailability, bio/mucoadhesive system, therapeutic window, gastric emptying.

ÖZ
İlacın oral doğumu, hasta uyumu ve uygulama kolaylığı nedeniyle yaygın olarak kullanılan modalite idi.Herhangi bir ilacın oral olarak verilmesinden sonra, biyoyararlanı midedeki oturma süresinden etkilenir.Son zamanlarda, gastroretentive ilaç dağıtım sistemleri (GRDDS) dar bir emilim penceresine sahip ilaçlar için geniş bir kabul görüyor, yüksek alkali pH'da stabilite azaldı ve düşük pH'da çözünürlük arttı.Bu yaklaşım, mide sıvısı içinde tutulan ve böylece midedeki aktif prensiplerini serbest bırakan bir ilaç dağıtım sistemi geliştirmeyi amaçlamaktadır.İlaçların gastrik tutulmasını sağlamak için kullanılan yöntemlerden bazıları arasında efervesan ajanların, mukoza yapıştırıcı polimerlerin, manyetik malzemenin, zıplayan arttırıcı ekscipient ve mide boşalmaya karşı dayanıklı fiş benzeri cihazlar oluşturan

tekniklerin kullanımı yer almaktadır.Bu derleme, GRDDS için son zamanlarda geliştirilen yaklaşımların çeşitli niteliklerinin kısa bir hesabını sağlamaya çalışır.
Anahtar Kelimeler: Biyoyararlanim, biyo/mukoza sistemi, terapötik pencere, mide boşaltma.

Introduction:

Oral administration is popular despite continuous improvement in drug delivery approaches owing to patient comfort and ease of administration. Controlled release drug delivery systems are designed for oral administration. These drug delivery systems release the medication in a predetermined, predictable and controlled way. They are not suitable for drugs with low bioavailability due to stability issues or absorption issues.[1] These problems can get better through modern approaches, which are designed to increase the residence of such drugs in the stomach for an extended time. Such drug delivery systems are called gastroretentive drug delivery systems (GRDDS). GRDDS are suitable for those drugs, which are absorbed from the stomach (e.g. Albuterol),[2] labile at alkaline pH (e.g. Ranitidine and Metformin),[3] poorly soluble at alkaline pH (e.g. Furosemide and Diazepam),[4] and having a narrow window of absorption (e.g. Riboflavin, levodopa).[5]

Some of the common advantages associated with the use of GRDDS include improved patient compliance by reducing the frequency of dosing; improved therapeutic efficacy of drugs with a short half-life; site-specific delivery of medications; sustained and controlled release of drugs in the stomach; enhanced residence time of drug at the absorption site; improved bioavailability from the gastrointestinal tract; avoid dose dumping of medicines.[6]

To develop GRDDS different materials like ion-exchange resins, mucoadhesives, high-density materials, raft forming substances, magnetic substances, and super porous hydrogel are used. [7,8]

This review attempts to provide a concise account of various attributes of recently developed approaches for GRDDS.

Anatomy and physiology of the stomach:

Knowledge about the anatomy and physiology of the stomach is essential for the successful formulation of gastroretentive dosage forms. Anatomically, the stomach is divided into three areas; the proximal portion towards the esophagus is the fundus, followed by the body, which serves as a storage site for engulfed food, and the antrum, the last part which connects the body to the small intestine. Antrum helps in churning action as well as in gastric emptying.[9]

In the fasting state, a sequence of contractions occurs cyclically through the stomach and intestine every 120-180 min, called the migrating myoelectric cycle (MMC). It is further divided into four phases. The pattern of contractions changes in a fed state termed as digestive motility pattern.[10] This pattern comprises of Phase 1- (Basal phase); Phase 2- (Preburst phase); Phase 3- (Burst phase); and Phase 4.[11] Figure no.1 depicts the motility pattern in the gastrointestinal tract.

Physicochemical properties of gastroretentive drug delivery system

Physiochemical properties of gastroretentive drug delivery systems include density, size, and shape of dosage form which plays a major role in the formulation of GRDDS. The dosage forms having a density lower than the gastric contents can float to the surface, while high-density systems sink to the bottom of the stomach. For an ideal formulation, the density should be in the range of 1.0 g/cm^3 – 2.5 g/cm^3. Dosage form having a diameter of more than 7.5 mm shows better gastric residence time. Circular, spherical, or tetrahedron-shaped devices show excellent gastroretentive properties.[12]

Physiological factors affecting retention of gastroretentive drug delivery system in the stomach

The most important factors controlling the gastric retention time of dosage forms include fed or unfed state, nature of the meal, caloric content, and frequency of feed. In the case of a fasting environment, gastric retention time is less due to the increase in GI motility. Emptying of gastric contents occurs due to peristalsis. If peristalsis coincides with dosage form administration, the gastric residence is short. However, after meals, peristalsis is delayed and may help in increasing the gastric residence of the formulation. A high-calorie meal containing proteins, fats, and fibrous compounds increases gastric retention time. In the case of multiple meals, the gastric retention is more than a single meal due to persistent inhibition of peristalsis.

Also, some other factors such as sex and age affect gastric retention. As compared to males, females have a slower gastric emptying time irrespective of height, weight, and body surface. A person with an age of more than 70 exhibits longer GRT. In comparison, neonates show less gastric residence time (GRT) as compared with geriatric patients.[13,14,15]

Approaches of gastroretentive dosage form:

Continuous research and advancements in various approaches of gastroretentive dosage form over the last few years are as shown in figure no.2. These approaches of GRDDS help in delivering the medicament in a sustained and restrained way through the gastrointestinal tract.

Classification of GRDDS:

Gastroretentive drug delivery system is classified into mainly two types floating and non-floating systems. Floating systems are further classified into the effervescent system and non-effervescent system based on the mechanism of floating while nonfloating system classified into four different classes based upon the mechanism used for gastroretention. Figure no.3 depicts the classification of the gastroretentive drug delivery system.

I] High-density system:

The density of dosage form plays an important factor in the formulation of the gastroretentive drug delivery system. A High-density system uses its weight as a retention mechanism. To enhance the gastric residence of a drug in the stomach its density needs to exceed the normal stomach content (1.004g/ml).[16] Figure no.4 (A) depicts the principle of a high-density system. Clark and Newton[17] compared gastrointestinal transit of placebo pellet systems of varying density using gamma scintigraphy. They reported the gastrointestinal residence time of such formulation can be extended from an average of 5.8 hours to 25 hours, depending more on density than on the diameter of the pellets.

II] Floating or low-density system:

Another approach to increase gastric residence is to lower the density of dosage form than the normal gastric content. These systems remain buoyant due to lower density and provide continuous drug release. In this way, they increase the gastric retention time of the drug and improves its bioavailability.[18] Figure no.4 (B) depicts the principle of floating or low-density systems.

(A) Effervescent System:

This system makes use of carbonates (e.g. sodium bicarbonate) to generate in situ carbon dioxide (CO_2). Organic acids (e.g. citric acid and tartaric acid) are added to speed up the reaction, thus reducing the density of dosage form and remaining buoyant in the stomach.[19,20] It is categorized into two classes:

a.) Volatile liquid/ vacuum type: These are further classified into three types -

i) Inflatable system:

It consists of a pullout system having a space filled with volatile liquids that evaporate at body temperature. Thus, when these systems are introduced in the stomach, the chamber inflates, and the system floats. The inflatable chamber comprises a bioerodible polymer filament that is made from polymers like polyvinyl alcohol and polyethylene. When the

inflatable chamber floats in the gastrointestinal fluid, the polymer gradually dissolves and releases the drug. After some time, due to polymer dissolution, the inflatable section collapses.[22] Figure no.4 (C) depicts a floating effervescent type of inflatable system.

ii) Intragastric floating system:

It contains a chamber filled with a vacuum and also includes a microporous compartment serving as a drug reservoir.[20] Figure no.5 depicts a floating type of intragastric system. Patel and Modasiya[21] developed intragastric floating tablets of verapamil HCl using hydroxypropyl methylcellulose (HPMC), carbopol, xanthan gum as a gel-forming agent. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. Optimized formulation showed satisfactory results with short buoyancy lag time of 36 sec, total buoyancy time of more than 24 hr, and controlled drug release up to 24 hr.

iii) Intragastric-osmotically controlled system:

Osmotic control can be achieved using a biodegradable capsule comprising inflatable floating support congestion with an osmotic pressure-controlled drug delivery device.[23] Zaho and Hao[24] used fenofibrate-loaded mesoporous silica nanoparticles (MSNs) to prepare an oral push-pull osmotic pump. Polyethylene oxide (100,000) and polyethylene oxide (6,000,000) were selected as suspending agents and expanding agents, respectively. Cellulose acetate was used as a semipermeable membrane, along with polyethylene glycol 6,000 to increase flexibility and controlling the membrane permeability. The prepared system is reported to stay in the stomach for a period of 21.72 hr than 12.48 hr of reference tablet and delivers the drug in an approximately zero-order manner for 24 hr.

b) Matrix tablets:

They are of two types, single layer, and bilayer matrix tablets. The single-layer matrix tablets are prepared using a drug and a hydrocolloid forming gel, while the bilayer matrix tablet contains one immediate-release layer and another sustained release layer. Saisivam and Shakeel[25] developed single-layer floating matrix tablets of losartan potassium using different proportions of hydroxypropyl methylcellulose (HPMC-K4M) and karaya gum as retarding polymer and sodium bicarbonate as an effervescent agent by direct compression method. Results of *in vivo* study of optimized formulation showed the floatability of tablet in gastric content and prolonged the gastric residence time to approximately 12 hr. X-ray imaging study in albino rabbits, showed the residence of tablet in the stomach even after a period of 12 hr.

c) Gas generating systems:

Gas generating systems are prepared by using effervescent compounds along with hydrophilic polymers.

i) Floating capsules:

These dosage forms involve encapsulation of drugs in hydrophilic polymers like ethyl cellulose and eudragit RS-100 with effervescent agents like sodium bicarbonate, calcium carbonate, etc. Moursy and Afifi[26] developed a hydrodynamically balanced capsule containing a mixture of nicardipine hydrochloride and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolves with subsequent swelling, forming a gelatinous barrier, which remains buoyant in the gastric juice for an extended period.

ii) Floating pills:

Multiple unit types of oral floating dosage forms have been developed using a hydrophilic polymer in the outer layer and an effervescent agent in the inner layer. When it comes in contact with the gastric fluid, the outer layer of hydrophilic polymer starts to swell and then sinks, but as the effervescent agent meets with gastric content, it releases CO_2, and the system starts to float.[27,28] Meka and Kesavan[29] prepared multiple-unit minitabs of captopril based on gas formation technique to prolong the gastric residence time and to increase the overall bioavailability of the drug. They formulated drug-containing core units by the direct compression process, which were coated with three successive layers of an inner seal coat,

effervescent layer (sodium bicarbonate), and an outer gas-entrapped polymeric membrane of polymethacrylates (eudragit RL30D, RS30D, and combinations of them). They found that increasing the coating level of gas-entrapped polymeric membrane decreased the drug release.

iii) Floating systems with ion exchange resins:

These floating systems are mainly developed to prolong the gastric residence time of dosage form using ion exchange resin. They consist of drug resin complex beads loaded with bicarbonate ions and are coated with hydrophilic polymers.[30] It results in the generation of CO_2 gas when it comes in contact with the gastric fluid and causes the beads to float. Atyabi and Sharma[31] developed a floating system based on ion exchange resin which consists of resin beads, loaded with bicarbonate and negatively charged drug that was bound to the resin. Two resins, Amberlite IRA-400 and Dowex 2 x 10 were investigated and both exhibited in vitro floating times of over 24 hr using a standardized procedure. The coated dosage form stayed for over 3 hr in the stomach than the non-coated system and shows a marked increase in retention over conventional formulation.

(B) Non - Effervescent systems:

In non - effervescent floating systems, the drug comes in contact with the gastric fluid, and it swells. It maintains its shape, and its density remains less than one and hence floats in gastric juice.[32] Matrix forming polymer, gel-forming, or swellable type hydrocolloids are used for these types of floating systems. They are further classified as follows:

i. Hydrodynamically balanced systems (HBS):

These systems mainly consist of a mixture of drugs and hydrocolloids that forms a gelatinous barrier when it comes in contact with the gastric fluid due to swelling of the combination. It remains buoyant in the stomach for an extended period as its bulk density is less than one in gastric fluid. Nayak and Malakar[33] developed gastroretentive theophylline HBS capsules using hydroxypropyl methylcellulose, polyethylene oxide, polyvinyl pyrrolidone, ethylcellulose, liquid paraffin, and lactose to control the delivery of theophylline for a longer period in the stomach with a minimum floating time of 6 hrs.

ii. Microballoons:

Microballons are formulated by the gradual addition of drug-containing emulsion in a volatile solvent. On evaporation of the solvent, gas is generated in a dispersed polymer droplet, which results in the formation of an interior orifice in the microsphere of the drug with polymer. It is also called as emulsion solvent diffusion method.[34] The floating time of microspheres depends upon the type and amount of polymer used in the formulation. Gupta and Kumar[35] developed pantoprazole sodium-loaded microspheres using eudragit L100 by adopting an emulsion solvent diffusion method with a non-effervescent approach. The results of *in vitro* and *in vivo* studies showed a suitable drug release pattern in terms of increased bioavailability and efficient ulcer healing effect. Figure no.6 depicts the steps involved in the preparation of microballoons by solvent diffusion method.

iii. Alginate beads:

These systems are prepared by using a hydrocolloid gel-forming agent and sodium alginate as the interlocking agent. In the presence of gastric fluid, the hydrocolloid absorbs water and forms a barrier that results in entrapment of air in the polymer, which causes swelling of the polymer, and hence the dosage form starts to float and results in releasing the drug for a prolonged period. Ghareeb and Radhi[36] formulated trimetazidine calcium alginate floating beads using sodium alginate solution (2, 3, and 4% w/v), hydroxypropyl methylcellulose, and peppermint oil (15, 20, and 25% v/v) by emulsion gelation method. They found that oil entrapped floating beads give promising results for sustaining the release of the drug over 10 hrs.

iv. Layered tablets:

Layered tablets are more popular due to their ease of preparation, low cost, and high stability.

a. Single layered floating tablets:

These tablets were formulated by mixing drug and gas generating agents within the matrix tablet. These formulations have lower bulk density than gastric fluid, and thus they remain buoyant in the stomach by increasing gastric residence time.[37] Kim and Hwang[38] developed non-effervescent gastroretentive tablets of pregabalin once a day using wet granulation and compaction. They found that the amount of hydroxypropyl methylcellulose and crospovidone were found to be critical factors affecting *in vitro* dissolution and floating properties of the prepared tablets. Figure no.7 depicts a schematic diagram of single-layered floating tablets.

b. Double layered floating tablets:

It comprises two formulations separated by layering, one on top of the other having two different release profiles.[39,40] Vinchurkar and Mane[41] formulated a bilayer floating tablet of metoprolol succinate (sustained-release layer) and rosuvastatin calcium (immediate-release layer) by direct compression method. Hydroxypropyl methylcellulose (HPMC K100, K4M, K15M) were used as gel-forming agents while cross carmellose sodium, sodium starch glycolate, and crospovidone are used as a super disintegrant. Sodium bicarbonate is used as an effervescent agent. From the *in vitro* buoyancy study, it was observed that as the concentration of gas generating agents increases, floating lag time decreases. Also, the polymer gas generating agent ratio was found to be influencing the floating lag time and the total duration of floating.

III] Mucoadhesive and bioadhesive systems:

A Mucoadhesive and bioadhesive system uses the adhesive property for targeting a drug to a specific region of the body for an extended period. Figure no.4 (D) shows a mucoadhesive system of the gastroretentive drug delivery system. For this, bioadhesive or mucoadhesive polymers are mainly used.[42] Natural polymers such as sodium alginate, gelatin, guar gum, etc., and semisynthetic polymers such as HPMC, lectins, carbopol, sodium carboxymethyl cellulose widely used for mucoadhesion. The adhesion is mediated by hydration, bonding, or receptor interactions.[43,44] Madgulkar and Kadam[45] developed sustained-release tablets of itraconazole using mucoadhesive polymer carbopol 934P and hydroxypropyl methylcellulose (HPMC K4M). They confirmed sustained drug release and gastric retention for six hours in albino rats. Figure no.8 depicts the principle of mucoadhesive drug delivery systems.

IV] Swelling system:

These systems when comes in contact with the gastric fluid, size increases significantly than that of a pyloric sphincter and thus, after swelling, remains logged in the stomach. These are also called a 'plug type system'.[46] Controlled and sustained drug release is achieved by using an appropriate excipient. The swelling ability of polymer mainly depends upon the degree of crosslinking of the hydrophilic polymer network. The high degree of crosslinking maintains the integrity of the system, while a low degree of crosslinking causes extensive swelling results in rapid dissolution of the polymer.[47]

V] Superporous hydrogels:

Superporous hydrogels are a three-dimensional network of hydrophilic polymers that have numerous super-size pores inside them. The swelling of superporous hydrogels occurs by the mechanism of capillary wetting through interconnected open pores. To formulate superporous hydrogels, certain ingredients like initiators and cross-linkers are used to initiate the cross-linking.[48] Other ingredients involved are foam stabilizers, foaming aids, and foaming agents. Desu and Paasam[49] developed a superporous hydrogel system using N', N'-methylene bisacrylamide (BIS) as the crosslinking operator and polyvinyl alcohol as a composite specialist, ammonium persulfate and N, N-tetra methylene diamine as an initiator pair and span 80 as a surfactant. They are used as a froth stabilizer to make a permeable structure by the gas-forming method.

VI] Magnetic system:

In this system, by using a powerful magnetic field of strong magnet onto the body surface, the movement of gastroretentive formulation with a small internal magnet is controlled. Several reports tell about the positive result of this system, but the success of this system depends upon a selection of the magnet position with very high precision.[50] Groning and Berntgen[51] developed peroral acyclovir depot tablets with an internal magnet. An extracorporeal magnet was used to prolong the gastric residence time of the dosage form and to influence the duration of absorption of acyclovir. They performed *in vivo* study with five healthy male subjects and determined the plasma concentration-time profiles of acyclovir. Computer simulations were carried out to show the influence of the gastric residence time of acyclovir depot preparations on the plasma concentration-time profiles of acyclovir. Figure no.4 (E) shows a magnetic system of the gastroretentive drug delivery system.

***In-vitro* assessment:**

For gastroretentive drug delivery systems, *in vitro* assessment is very essential to predict gastric transit behavior. Following are the parameters which should be considered for designing novel gastroretentive formulations.

i. Buoyancy Lag Time

It is the time taken by gastroretentive formulations to come onto the surface of the dissolution medium. It is determined using USP dissolution apparatus containing 900ml of 0.1 N HCl solution as a testing medium maintained at 37^0C. The time required to float different dosage forms noted as floating lag time.[52]

ii. Floating Time

It determines the buoyancy of dosage form. In this test, a specific dissolution apparatus is used depending upon the type of dosage form with 900ml of dissolution medium kept at 37^0C. The floating time or floating duration of the dosage form is determined by visual observation.[52,53]

iii. Specific Gravity / Density

Specific gravity estimates are essential for both low-density and high-density GRDDS. Specific gravity is determined using the Displacement method.[53]

iv. Swelling Index

The swelling index is determined by immersing the tablets in 0.1 N HCl at 37^0C and their periodic removal at regular intervals.[53]

v. Water Uptake

In this study, the dosage is form removed out from the dissolution medium after the regular interval and a weight change is determined.[54]

Water uptake (WU) = (Wt – Wo) * 100 / Wo

Where Wt = weight of the dosage form at time t, Wo = initial weight of dosage form

vi. Weight variation

Various official methods are recommended by pharmacopeias that calculate the weight variation. Usually, the individual and average weight of 20 tablets is recorded. From this data, average weight and weight variation are calculated.[55,56]

vii. Hardness & friability

Hardness or crushing strength is determined using Monsanto tester, Strong cobb tester, Pfizer tester, etc. Friability (Strength) of tablets is determined using Roche friabilator.[57,58]

viii. *In-Vitro* dissolution tests

This test is performed to determine drug release from GRDDS in gastric fluid and intestinal fluid maintained at 37^0C at a definite time using USP dissolution type II apparatus (paddle).[59,60]

Evaluation of microsphere and beads:

An optical microscope is used to measure the particle size of beads and microspheres. Surface morphology and cross-sectional morphology are evaluated with the help of a scanning electron microscope (SEM).

***In-Vivo* assessment:**

a. Radiology

This technique is mainly used to determine the position of gastroretentive dosage form filled with barium sulfate (radio-opaque marker) inside the body system concerning time using X-ray. X-ray pictures are taken at different intervals to record the correct position of the dosage form.[61.62]

b. Scintigraphy

Similar to radiology, it is used to determine the in vivo floating behavior of the gastroretentive dosage form. In scintigraphy, 99mTc pertechnetate is used as an emitting material instead of an X-ray to engulf the formulation to record the image.[63,64]

c. Gastroscopy

Gastroscopy is used widely for visual examination of gastroretentive dosage form. In this technique, an illuminate optical, tubular, and slender instrument called an endoscope is used to look deep inside the body parts such as the stomach, esophagus, and small intestine.[65,66]

d. Ultrasonography

It is a diagnostic imaging technique in which ultrasound is used for imaging internal body structures. The main disadvantage of this test is non-detectability at entrails.[1,66,65]

e. 13C Octanoic Acid Breath Test

Radioactive 13C Octanoic acid is used to assess the extent of absorption of drugs from GRDDS. This compound gets absorbed from the duodenum, and when it is radiolabelled, then after its metabolism, the CO_2 exhaled in breath can be correlated to the amount of octanoic acid absorbed. The radiolabelled CO_2 is measured by isotope ratio mass spectroscopy.[65,66]

f. Magnetic marker monitoring

As compared with radiology and scintigraphy, this method is radiation-less and thus is non-hazardous. It involves real-time tracking of the dosage form in the gastrointestinal tract. This technique is mainly used for the determination of the gastrointestinal motility and dissolution behavior of pharmaceuticals. In this technique, the dosage form is labeled as a magnetic dipole by incorporating a trace of ferromagnetic particles and recording the magnetic dipole field by an apparatus responsive to bio-magnetic measurement.[67]

Advantages and applications of gastroretentive delivery systems:

Gastroretentive dosage forms release the drug in a controlled manner to their specific site of action. These systems help to increase the bioavailability of drugs that get metabolized in the upper part of the gastrointestinal tract such as riboflavin and levodopa, etc. For drugs that have a short half-life, gastroretentive dosage forms aids to reduce the dosing frequency and improves patient compliance by enhancing gastric residence time. Also, they provide a sustained and prolonged release of drugs in the stomach and intestine, which are helpful in local therapy.[64,65,66]

Conclusion:

Gastroretentive drug delivery systems are unique system and got important in the last three decades. It offers various advantages, viz., site-specific, slow, and controlled release of drugs from different types of gastroretentive dosage forms, thus improving patient compliance and reducing the side effects by minimizing dosing frequency. Therefore, it is expected that in the future, various pharmaceutical companies will come forward to initialize gastroretentive drug delivery technology for creating excellent advantages, prolonging patents, and a better outcome for their marketed formulations.

REFERENCES

1. Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms. Pharmaceutics. 2019;11:416-445.
2. Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. Clin Rev Allergy Immunol. 1996;14:115-38
3. Chandira RM, Palanisamy P, Jaykar B. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. Int. Res. J. Pharm. 2012;3:257-267.
4. Menon A, Ritschel W, Sakar A. Development and evaluation of a monolithic floating dosage form for furosemide. J. Pharm. Sci. 1994;83:239-245.
5. Levy G, Jusko WJ. Factors affecting the absorption of riboflavin in man. J. Pharm. Sci. 1966;55:285-289.
6. Badoni A, Ojha A. Review on gastro retentive drug delivery system. J. Pharm. Innov. 2012;1:32-42.
7. Malpure PS, Chavan BR. Gastroretentive drug delivery systems. World J Pharm Pharm Sci. 2019;8:506-528.
8. Kumar M. Approaches and recent patents on gastroretentive drug delivery systems. Recent Pat on Drug Deliv Formul. 2018;12:84-92.
9. Pund AU, Shendge R. Current approaches on gastroretentive drug delivery system. J. Drug Deliv Ther. 2020;10:139-146.
10. Gunda, RK. Formulation development and evaluation of gastroretentive drug delivery system. A review. J. Pharm. Res. 2017;8:11-20.
11. More S, Gavali K, Doke O, Kasgawadek P. Gastroretentive drug delivery system. J. Drug Deliv. Ther. 2018;8:24-35.
12. Tomar A, Upadhyay A, Gupta S. An overview on gastroretentive drug delivery system. Current approaches and advancements. Current Research In Pharma Sci. 2019;9:12-16.
13. Taylor K, Aulton M. Aulton's Pharmaceutics (4th ed) The design and manufacture of medicines. Churchill Livingstone; London; 2007: 397.
14. Gandhi A, Verma S, Imam SS, Vyas M. A review on techniques for grafting of natural polymers and their applications. Plant Arch. 2019;19:972-978.
15. Chudiwal V, Shahi S, Chudiwal S, Ahale D. Innovative technologies for gastro-retentive. Asian J. Pharm. Res. 2017;6:22-28.
16. Devkant S, Anjali S. Gastro retentive drug delivery system. A review. Asian Pac. J. Health Sci. 2014;1:80-89.
17. Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm. 1995;114;1-11.
18. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin. Drug Deliv. 2006;3:217- 233.
19. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res. 2008;7:1055-1066.
20. Thapa P, Jeong S. Effects of formulation and process variables on gastroretentive floating tablets. Pharmaceutics. 2018;10:161-186.
21. Patel A, Modasiya M, Patel V. Development and in vivo floating behaviour of verapamil HCl intragastric floating tablets. AAPS Pharmasci Tech. 2009;10:310-315.
22. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asi. J. Pharm. Clinical Res. 2010;3:1-9.
23. Nasa P, Mahant S, Sharma D. Floating systems: a novel approach towards gastro retentive drug delivery systems. Int. J. Pharm. and Pharm Sci. 2010;2:2-7.

24. Zhao Z, Wu C, Zhao Y, Hao Y, Liu Y, Zhao W. Development of an oral push–pull osmotic pump of fenofibrate loaded mesoporous silica nanoparticles. Int J Nanomedicine. 2015;10:1691-1701.
25. Saisivam S, Shakeel F. Development of floating matrix tablet of losartan potassium: In vitro and in vivo evaluation. J Drug Deliv Sci Technol. 2013;23:611-617.
26. Moursy N, Afifi N, Ghorab D. Formulation and evaluation of sustained release floating capsules of nicardipine hydrochloride. Pharmazie. 2003;58:38-43.
27. Samal HB, Dey S, Kumar D, Kumar DS, Sreenivas SA, Rahul V. Formulation, characterization and in-vitro evaluation of floating microspheres of nateglinide. Int. J. Pharm. Bio Sci. 2011;2:147-157.
28. Pal P, Sharma V, Singh L. A review on floating type gastroretentive drug delivery system. Int. Res. J. Pharm. 2012;3:37-43.
29. Meka L, Kesavan B, Yamsani M. Preparation of a matrix type multiple-unit gastro retentive floating drug delivery system for captopril based on gas formation technique: in vitro evaluation. AAPS Pharmsci Tech. 2008;9:612-638.
30. Verma R, Kumar A, Purohit S, Bhandari A. Overview of gastro-retentive drug delivery system. J. Natura Conscientia. 2011;2:423- 436.
31. Atyabi F, Sharma H, Mohammad H, Fell JT. In vivo evaluation of novel gastric retentive formulation based on ion exchange resin. J. Control. Release. 1996;42:105-113.
32. Ali A, Shahid MA, Hossain MD, Islam MN. Antibacterial bi-layered polyvinyl alcohol (PVA)-chitosan blend nanofibrous mat loaded with Azadirachta indica (neem) extract. Int. J. Biol. Macromolecules. 2019;138:13-20.
33. Nayak AK, Malakar J. Formulation and in vitro evaluation of Hydrodynamically balanced system for theophylline delivery. Journal of Basic and Clinical Pharmacy. 2011;2:133-137.
34. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asi. J. Pharm. Clinical Res. 2010;3:1-9.
35. Gupta P, Kumar M, Kaushik D. Pantoprazole sodium loaded microballons for the systemic approach: in vitro and in vivo evaluation. Adv. Pharm. Bull. 2017;7:461-467.
36. Ghareeb M, Radhi ZA. Formulation and in vitro evaluation of trimetazidine dichloride floating beads. Int. J. Pharm. Pharm. Sci. 2014;6:456-440.
37. Vinchurkar K, Balekar N. Formulation and evaluation of floating multilayered coated tablets. J. Adv. Pharm. Technol. Res.2015;212-222.
38. Kim S, Hwang KM, Park Y. Preparation and evaluation of non-effervescent gastroretentive tablets containing pregabalin. Int. J. Pharm. 2018;550:160-169.
39. Soni RP, Patel AV, Patel RB. Patel NM. Gastroretentive drug delivery systems. A review. Int. J. Pharm. World Res. 2011;2:1-24.
40. Chandira RM, Palanisamy P, Jaykar B. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. Int. Res. J. Pharm. 2012;3:257-267.
41. Vinchurkar K, M Sheetal, Sainy J, Khan M. Formulation and evaluation of once a day dual component gastro retentive drug delivery system. Asian J. Sci. Technol. 2019;10:10247-10254.
42. Shep S, Dodiya S, Mayee R. Swelling system. A novel approach towards gastroretentive drug delivery system. Indo glob. J. pharm. Sci. 2011;1:234-242.
43. Rocca DJ, Omidian H, Shah K. Progresses in gastro retentive drug delivery systems. Business Briefing Pharmatech. 2003;152-156.
44. Zate SU. Kothawade PI, Mahale GH, Kapse KP, Anantwar SP. Gastro retentive bioadhesive drug delivery system: a review. Int. J. PharmTech Res. 2010;2:1227-1235.

45. Madgulkar A, Kadam S, Pokharkar V. Studies on formulation development of mucoadhesive sustained release Iitraconazole tablet using response surface methodology. AAPS Pharm Scitech. 2008;9:998-1005.
46. Yeole PG, Khan S, Patel VF. Floating drug delivery systems. Need and development. Ind. J. Pharm. Sci. 2005;67:265-272.
47. Dolas RT, Hosmani A, Bhandari A, Kumar B, Somvanshi S. Novel sustained release gastroretentive drug delivery system: a review. Int. J. Pharm. Res. Dev. 2004;2:26-41.
48. Hardenia SS, Jain A, Patel R, Kaushal A. Floating drug delivery systems. A review. Asian J. pharm. life sci. 2011;1:284-293.
49. Desu P, Paasam V, Kotra V. Formulation and in vitro evaluation of superporous hydrogel based gastroretentive drug delivery system of Vildagliptin. Journal of Research in Pharmacy. 2019;23:873-885.
50. Joshi P, Patel P, Modi H, Patel MR, Patel KR, Patel NM. A review on gastro retentive drug delivery system. J. Pharm. Sci. Bio-Sci Res. 2012;2:123-128.
51. Groning R, Berntgen M, Georgarakis M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit. Eur J Pharm Biopharm. 1998;46:285-291.
52. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. Int J Pharm 1992; 86 Suppl. 1:79-88.
53. Sangekar S, Vadino WA, Chaudhary I, Parr A, Beinh R, Digenis G. Evaluation of the effect of food and specific gravity of tablets, on gastric retention time. Int. J. Pharm. 1987;35:187-191.
54. Patel N, Nagesh C, Chandrashekhar S, Patel J, Devdatt J. Floating drug delivery system: an innovative acceptable approach in gastro retentive drug delivery. Asi. J. Pharm. Res. 2012;2:07-18.
55. Pham AT, Lee PI. Probing the mechanism of drug release from hydroxy propyl-methyl cellulose metrics. Pharm Res. 1994;11:1379-84
56. Sharma N, Agarwal D, Gupta MK, Mahaveer PK. A comprehensive review on floating drug delivery system. Int. Res. J. Pharm. 2011; 2:428-441.
57. Caldwell LJ, Gardner CR, Cargill RC. Drug Delivery Device Which Can Be Retained in the Stomach for a Controlled Period of Time, US Patent No. 4735804. April 05, 1988.
58. Shivkumar HG, Vishakante GD, Pramodkumar TM. Floating controlled drug delivery systems for prolong gastric residence. Ind. J. Pharm. Edu. 2004;38:172-179.
59. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235-259.
60. Burns SJ, Corness D, Hay G. Development and validation of an in vitro dissolution method for a floating dosage form with biphasic release characteristics. Int. J. Pharm. 1995;121:37-34.
61. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J. Pharm. Sci. 1994;83:18-24.
62. Hendee WR. In: Textbook of diagnostic imaging. Fundamentals of diagnostic imaging: Characteristic of radiographic image. WB Saunders Co, Philadelphia. Volume 1, 9-10.
63. Koner P, Saudagar RB, Dharwal SJ. Gastro-retentive drugs: a novel approach towards floating therapy. J Novel Drug Deliv. 2007;1:2211-2215.
64. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi; India. 2006;197-217.
65. Fatema K, Shashi S, Shaikh T, Zaheer Z. Gastroretentive drug delivery system an overview. Asian Pac. J. Health Sci.2016;3:131-144.

66. Devkant S, Anjali S. Gastro retentive drug delivery system. A review. Asian Pac. J. Health Sci. 2014;1:80-89.
67. Biller S, Baumgarten D, Haueisen J. Magnetic marker monitoring: A novel approach for magnetic marker design. MEDICON 2010, Ifmbe Proceedings. 2010;29:260:263.
68. Saisivam S, Shakeel F. Development of floating matrix tablet of losartan potassium: In vitro and in vivo evaluation. J Drug Deliv Sci Technol. 2013;23:611-617.
69. Jain S, Sindu A. Development of floating dosage form of ranitidine hydrochloride by stastical optimization technique. J Young Pharm. 2010;2:342-349.
70. Arza R, Gonugunta C, Veerareddy P. Formulation and evaluation of swellable of floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS Pharmasci Tech. 2009;10:220-226.
71. Parmar K, Gohel M, Parikh R. Sustained release floating microspheres of acyclovir. Formulation, optimization, characterization and in vitro evaluation. Int. J. Drug. Dev. Res. 2011;3:242-251.
72. Suthakaran R, Akkala M. Formulation and evaluation of sustained release floating matrix tablet of an antiretroviral drug. Journal of scientific research in pharmacy. 2016;5:82-83.
73. Yin L, Qin C, Chen K, Zhu C, Cao H, Zhou J. Gastro-floating tablets of cephalexin: preparation and in vitro/in vivo evaluation. Int J Pharm. 2013;16:241-248.
74. Munir R, Massud A, Inam S, Umber A. Development and evaluation of gastroretentive tablet of furesomide. Int J. Adv. Pharm. Res. 2013;4:2362-2370.
75. Wang Y, Gan Y, Zhang X. Novel gastroretentive sustained release tablet of tacrolimus based on self microemulsifying mixture: in vitro evaluation and in vivo bioavailability test. Acta Pharmacol. Sin. 2011;31:1294-1302.
76. Jimenez MI, Quirino BT, Villafuerte RL. Sustained delivery of captopril from floating matrix tablets. Int J Pharm. 2008;362:37-43.
77. Sharma M, Kohli S, Dinda A. Invitro and in vivo evaluation of repaglinide loaded microspheres prepared from different viscosity grades of HPMC polymer. Saudi Pharm J. 2015;23:675-682.
78. Wadher KJ, Kakde RB, Umekar MJ. Formulation and evaluation of sustained release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymers. Indian j Pharm Sci. 2011;73:208-215.
79. Rudraswamy NR, Gupta VR. Formulation and evaluation of gastroretentive controlled release tablets of alfuzosin hydrochloride. Pak J Pharm Sci. 2015; 28:2147-52.
80. Sonali NG, Hiremath SP, Daskankoppa FS, Jamakandi VG, Sreenivas SS. Design and evaluation of gastroretentive mucoadhesive cephalexin tablets. Pharm Dev Technol. 2010;15:178-83.
81. Gangurde HH, Chordiya MA, Sivakumar T. Formulation and evaluation of sustained release bioadhesive tablets of ofloaxin using 3^2 factorial design. Int. J. Pharm. Investig. 2011;1:148-156.
82. Gattani S, Londhe SG, Chalikwar SS. Formulation and evaluation of gastroretentive drug delivery of verapamil hydrochloride. Eur. J. Parenter. Pharm. Sci. 2010;15:125-129.
83. Saritha D, Sathish D, Rao YR. Formulation and evaluation of gastroretentive floating tablets of Domeperidone maleate. J. Appl. Pharm. Sci. 2012;2:68-73.
84. Jahagirdar HA, Kulkarni R, Kulkarni S. Pharmaceutical composition of rifaximin. U.S.Patent 8383151. June 23. 2008.
85. Mandal UK, Chatterjee B, Senjoti FG. Gastro□retentive drug delivery systems and their in vivo success: A recent update. Asian J. Pharm. Sci. 2016;11:575–584.

86. Gautam CS, Lekha S, Pradip KS, Kavita S. Iron deficiency in pregnancy and the rationality of iron supplements prescribed during pregnancy. Medscape J Med. 2008;10:283-305.
87. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019;11:1-22.
88. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Durg Deliv. 2011;18:97-110.
89. Lopes CM, 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.
90. Prinderre P, Sauzet C, Fuxen C. Advances in gastro retentive drug□delivery systems. Expert Opin. Drug Deliv. 2011;8:1189-1203.
91. Achi AA, Gupta MR, Stagner WC. Integrated Pharmaceutics: Applied preformulation, Product design, and Regulatory science (1st ed). John Wiley & Sons: New York, 2013:1;1024.
92. Mishra A, Shahiwala A. In-Vitro and In-Vivo Tools in Drug Delivery Research for Optimum Clinical Outcomes (1st ed). CRC Press,New York, 2018:1;350.
93. Kotreka U, Adeyeye MC. Gastroretentive floating drug□delivery systems: A critical review. Crit. Rev. Ther. Drug. 2011;28.
94. Waterman KC. A critical review of gastric retentive controlled drug delivery system. Pharm Dev Technol. 2008;07:1-10.

Table 1: Showing some recent trends in GRDDS.

Drug	Requirement for development	Dosage forms	References
Verpamil HCL	a) Low bioavailability	CR floating tablet	21
	b) Short elimination half-life		
Fenofibrate	a) Low solubility	Osmotic tablet	24
	b) Short half-life	(pump)	
	c) Low bioavailability(40-50%)		
Nicardipine HCl	a) Short half life	Floating capsule	26
	b) Low bioavailability		
Pantoprazole	a) Short half life	Beads	35
	b) Low bioavailability		
	c) Acidic in nature		
Losartan	a) Short half-life Tablet	Tablet	68
	b) Low bioavailability (33%) due to first pass metabolism		
Ranitidine HCl	a) Short half-life	Floating (pulsatile)	69
	b) Absorption window in a part of GIT	DDS	
	c) Poor Bioavailability		
Ciprofloxacin HCl	a) Short elimination half-life (about 4 h)	Floating tablet (matrix)	70
	b) Narrow absorption window & absorbed in proximal SI		
	c) Freely soluble in water		

Acyclovir	a) Short half-life	SR Floating microsphere	71
	b) Oral bioavailability is poor (15-30%) due to poor water solubility		
	c) Degrade at high pH		
Ziduvudine	a) Dose dependant solubility	Tablet	72
	b) Short biological half-life		
	c) Poor bioavailability		
Ciphalexin	a) Acidic drug	Floating Tablet	73
	b) Short half-life		
	c) Poor bioavailability		

Table 2: Some of the Drug Candidates for GRDDS.

Drug	**Pharmacological and/or therapeutic class**	**Solubility**	**Stability in gastric & intestinal**	**Absorption & Oral bioavailability**	**Half-life (h)**	**References**
Trimetazine dihydrochloride	Antifungal	Freely soluble in water	—	Rapidly absorbed	6.0 ±1.4	36
Itraconazole	Antifungal	Low water solubility	—	Variable in individual	2.1	45
Ranitidine	Histamine H2-receptor anatagonist	Low solubility at alkaline Ph	Colonic metabolism	50% absolute bioavailability	2.5-3	69
Ciprofloxacin	Fluoroquinoline	Freely soluble in water	—	Mainly absorbed in proximal areas	4	70
Furosemide	Loop diuretic	Poor water solubility	—	Absorbs mainly from stomach	1.3± 0.8	74
Tacrolimus	Immunosuppressant	Poor water solubility	—	Low Oral availability	—	75
Captopril	Angiotensin Converting enzyme inhibitor	Freely soluble in water	Stable at gastric pH but unstable in intestine	—	2	76

Repaglinide	Oral hypoglycemic agent	Poorly soluble in water	—	Low bioavailability	1	77
Metformin hydrochloride	Antidiabetic	Freely soluble in water	—	Absolute bioavailability (50-60%)	1.5-1.6	78
Alfuzocin HCL	Alpha adrenergic receptor blocker	Highly water soluble	—	Absorbed from upper GIT	5	79
Cephalexin	Cephalosporin antibiotic	—	Degrade in alkaline Ph	—	1	80
Ofloxacin	Fluoroquinoline	—	—	Highly soluble in Absorption occurs	9	81
	Antidiabetic			Acidic media and precipitate in upper GIT alkaline media		
Verapamil hydrochloride	Calcium channel blocker	Soluble in water	—	Low bioavailability (10-20%) due to first pass effect	4	82
Domperidone	Prokinetic agent	Good solubility in acidic pH but reduced	—	Rapidly absorbed from the stomach & upper part of GIT	7	83

Table 3: Gastroretentive technologies adopted by various pharmaceutical companies.

Technology	Company	Product	API	References
Bioadhesive tablets	Lupin,	Xifaxan	Rifaximin	84
	India		Ofloxacin	
Effervescent floating system	Ranbaxy,	Zanocin OD	Metformine HCL	
	India	Riomet OD	Ciprofloxacin	85
		Cifran OD		
Colloidal gel forming floating system	Ranbaxy, India	Conviron	Ferrous sulphate	86
Foam based floating system	Sato Pharma, Japan	Inon ace tablets	Simethicone	87
			Gabapentin	
Polymer based Swelling technology: AcuFormTM	Depomed, USA	Gabapentin GR	Ciprofloxacin	88
		ProQuin XR	Metformin HCL	
Effervescent and swelling based floating system	Sun Pharma,	Prazopress XL	Prazosin Hcl	89
Swelling based floating system	Japan	Metformin Hcl	Metformin Hcl	90
	Galenix, France	Cafeclor LP	Cefaclor	
		Tramadol LP	Tramadol	
Floating CR capsule	Roche, UK	Madopar	Levodopa & benserzide	90
		Valrelease	Diazepam	
Expandable system (Unfloading)	Intec Pharma, Israel	Accordion PillTM	Carbidopa/levodopa	90
Erodible matrix based system	Bayer, USA	Cipro XR	Ciprofloxacin Hcl and betaines	91
Coated multi-layer and swelling system	Sun Pharma, India	Baclofen GRS	Baclofen	92
Gastro retention with osmotic system	Glaxosmithkline, UK	Coreg CR	Carvedilol	93
Effervescent floating	Reckitt	Liquid	Alginic acid and	93

liquid alginate preparation	Benckiser Healthcare,UK	Gaviscon	sodium bicarbonate	
Bilayer floating capsule	Pfizer, UK	Cytotec	Misoprostol	94
Raft forming system	Pierre Fabre	Topalkan	Aluminium magnesium	94
	Medicament, France	Almagate flatcoat	Aluminium magnesium antacid	

Table 4. List of commonly used drugs for various floating system [85,87,90,91,92,93,94].

Type of system	Drugs used
Microspheres tablets/ pills	Rosiglitazone maleate, Verapamil, Orlistat, Aspirin, Griseofulvin, Acetyl salicylic acid, Ibuprofen, Ampicillin, Captopril, Sotalol, Isosorbide dinitrate, Terfanadine
Tablets	Losartan, Furesomide, Ciprofloxacin, Captopril, Cinnarazine, Sotalol, Ampicillin, Florouracil, Metformin hydrochloride, Atenolol, Baclofen
Films	Cinnarizine, Peritanide, Quinidine gluconate, Albendazole, P-aminobenzoic acid, Prednisolone
Granules	Ranitidine HCl, Diclofenac sodium, Cinnarizine, Indomethacin, Fluorouracil, Diltiazem, Isosorbide dinitrate
Powders	Riboflavin, Sotalol, Theophylline
Capsules	Verapamil HCL, Chlordizepoxide, Diazepam, Misoprostol, Furosemide, L - dopa, Pepstatin, Nicardipine

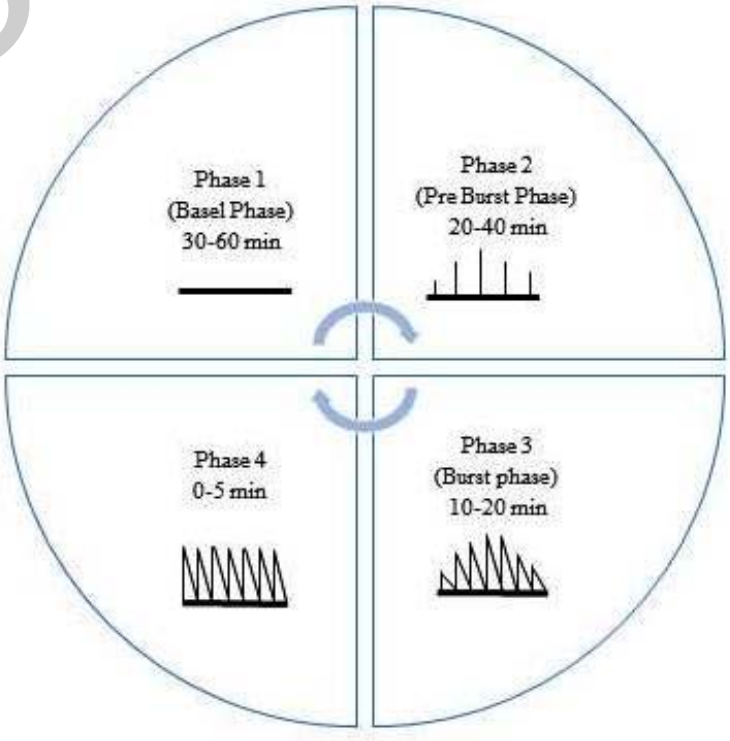


Fig.1 Motility pattern in gastrointestinal tract

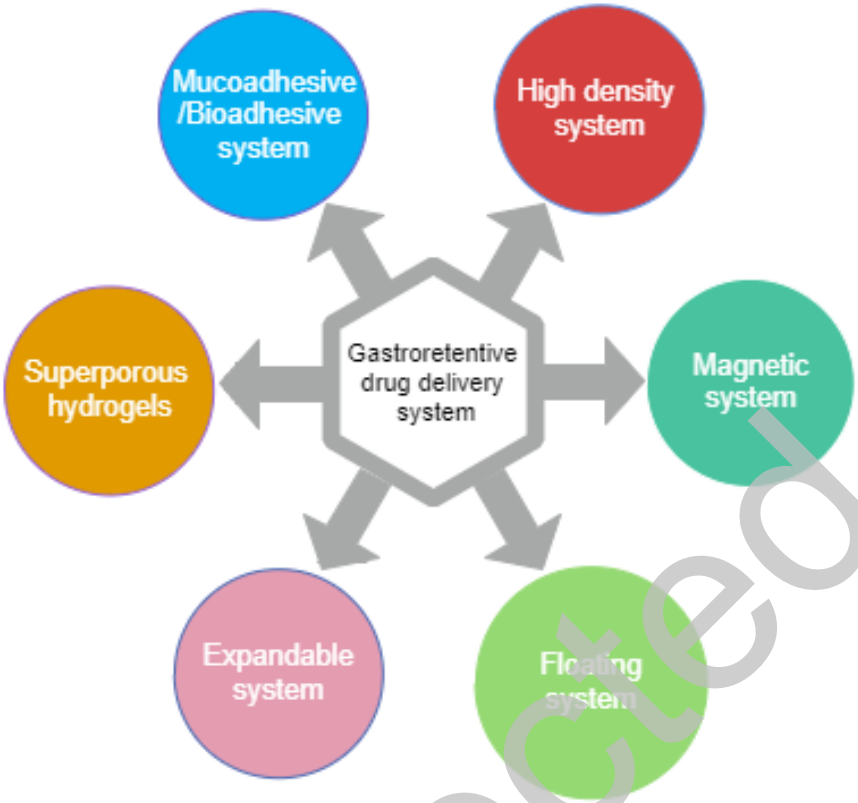


Fig.2 Approaches of gastroretentive drug delivery system

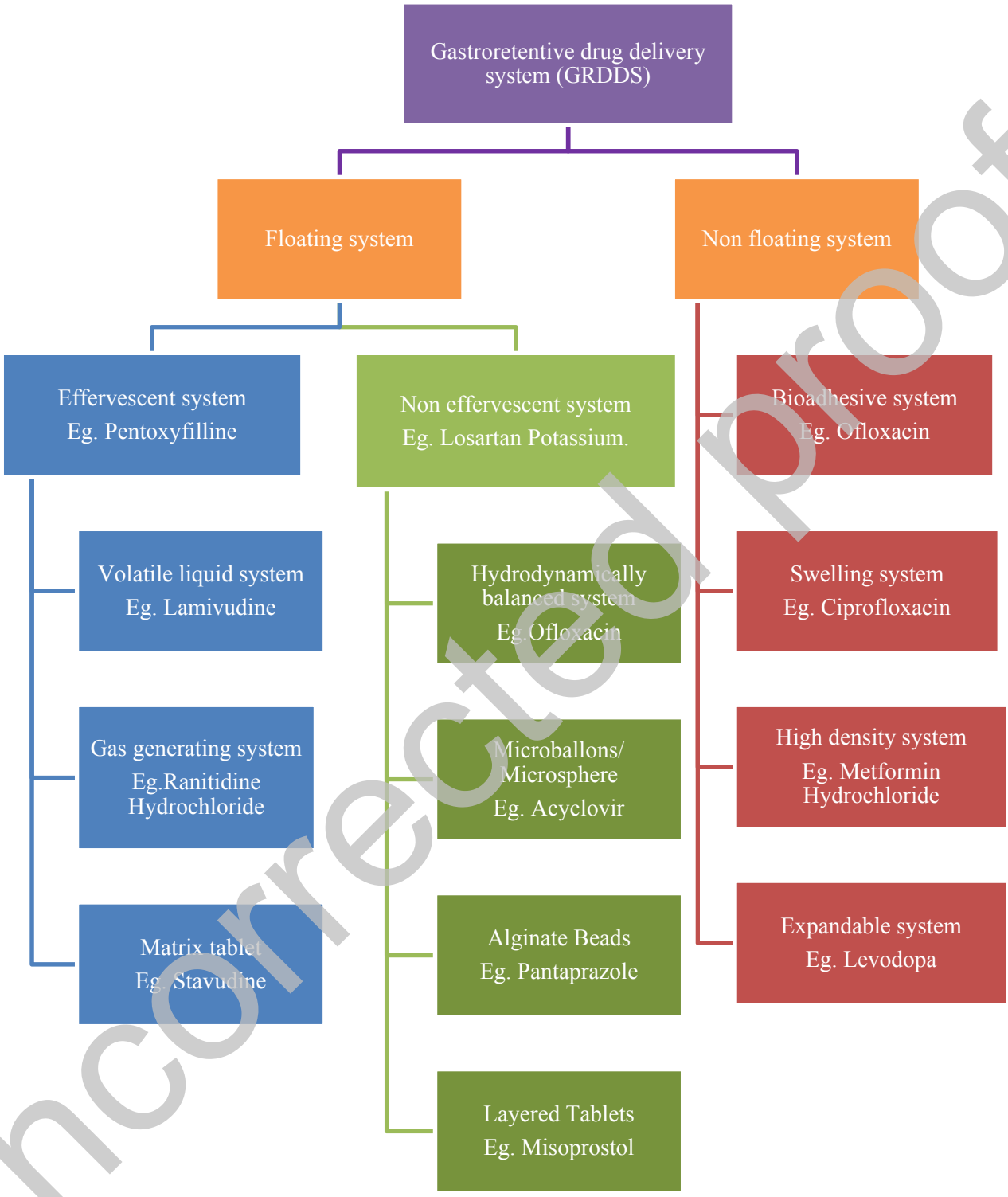


Fig. 3 Classification of gastroretentive drug delivery system.

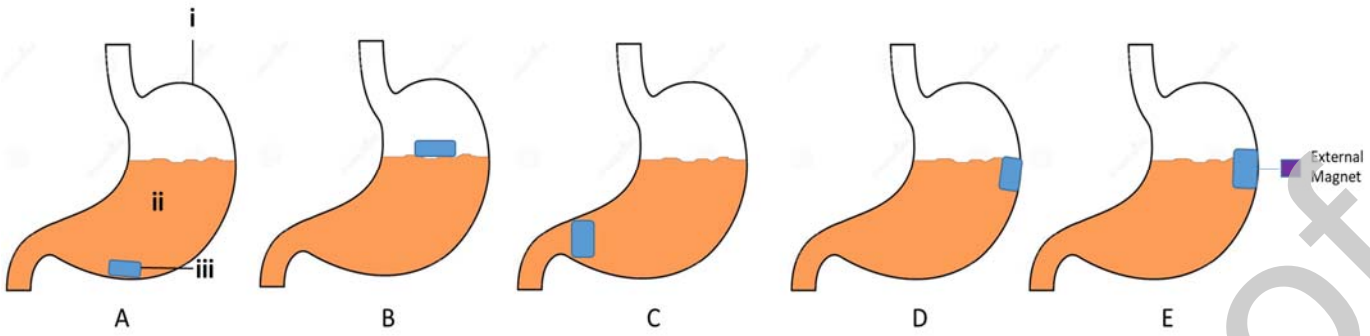


Fig. 4 Different types of gastroretentive drug delivery system. A- High density system, B- Floating/low denisty system, C- Inflatable system D- Mucoadhesive system, E- Magnetic system. (i- Stomach, ii- Gastric fluid, iii- Dosage form)

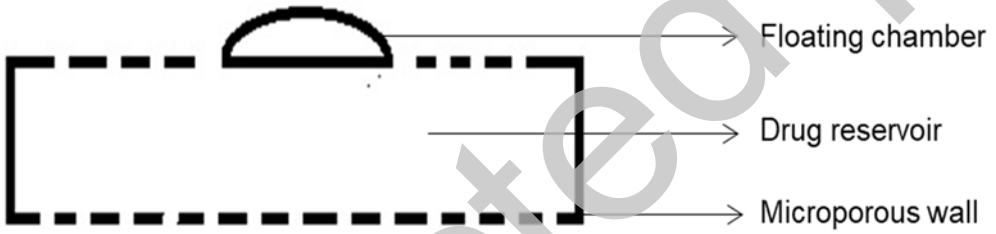
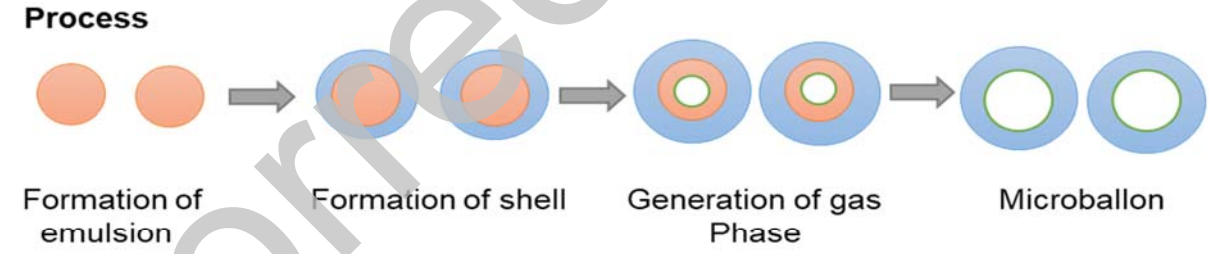


Fig. 5 Intragastric floating gastrointestinal drug delivery system.



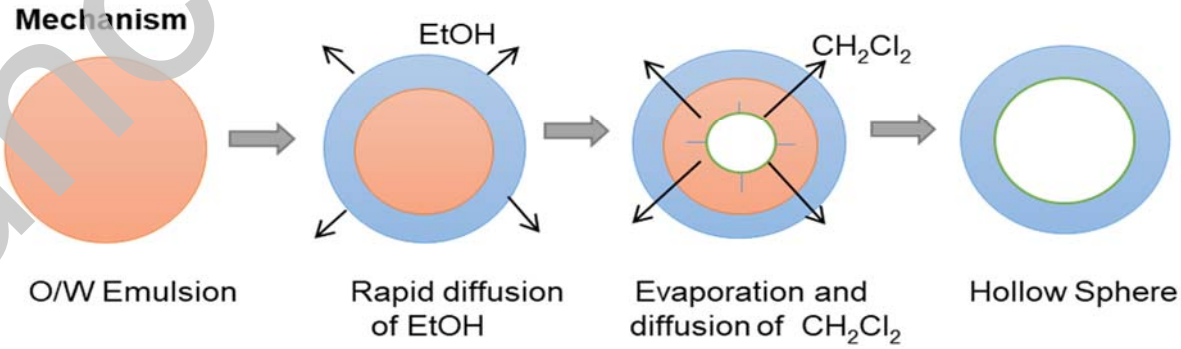
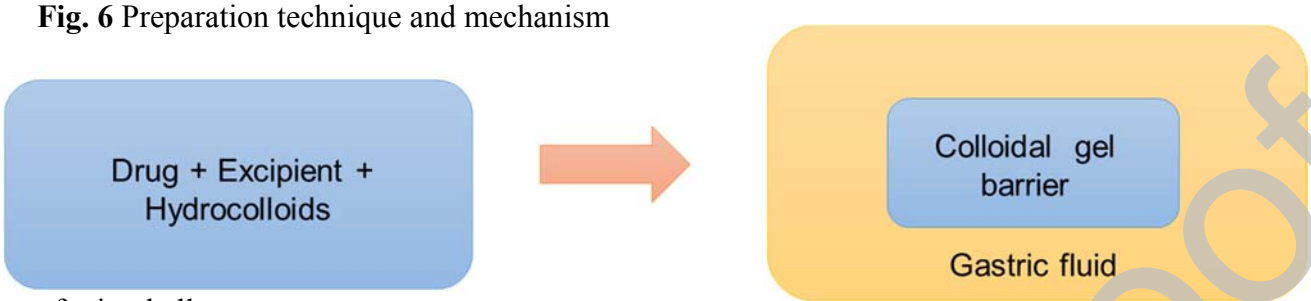


Fig. 6 Preparation technique and mechanism



of microballoons formation

Fig. 7 Mechanism of single layer tablet

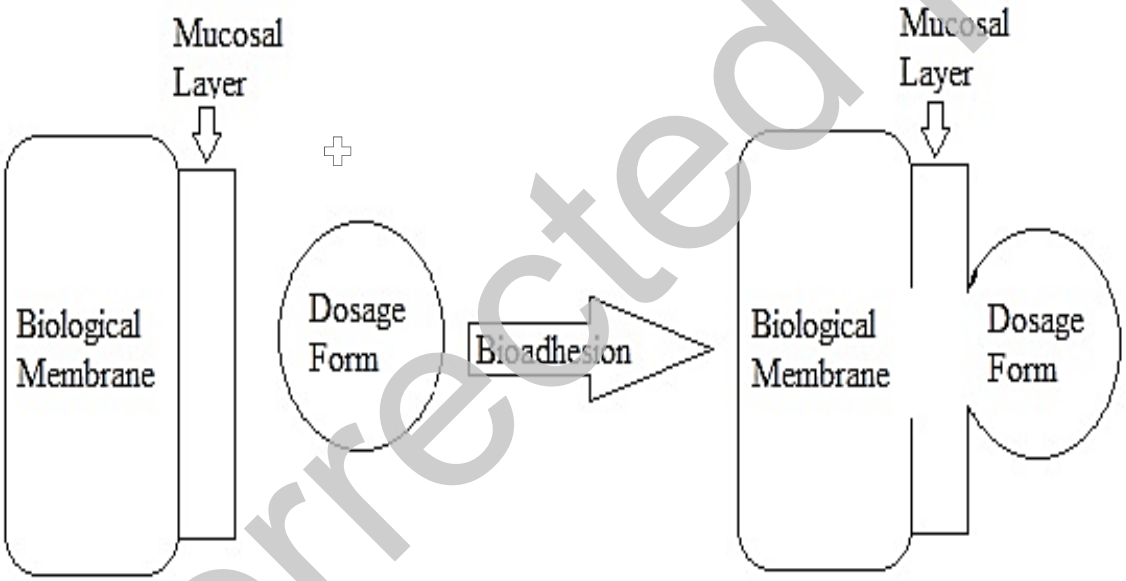


Fig. 8 Principle of mucoadhesive drug delivery system