

**Review Article****RECENT NEW DEVELOPMENTS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM: A
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Abstract: The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Gastroretentive systems can remain in the gastric region for several hours for significantly prolong residence time of drugs by which improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment

Key words: Floating systems, Gastroretentive systems, Mechanism of floating, evaluation in vitro and in vivo.

INTRODUCTION

Drugs which are easily absorbed from the gastrointestinal tract and have a short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problem, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. To prolong gastric retention, it is important to achieve control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner¹. Oral delivery is the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. Many difficulties are faced during designing controlled release systems for better absorption and enhanced bioavailability. There are several method are used to control release of drug. One such method is the preparation floating system in the stomach contents due to its lower density than that of the gastric fluids. A floating system made of multiple unit forms has relative merits compared to a single unit preparation as compared to other formulation.

The successful development of oral controlled drug delivery systems requires the three aspects of the system, which is.

1. The physiochemical characteristics of the drug²
2. Anatomy and physiology of GIT and Characteristics of Dosage forms³

Stomach anatomy

The basic function of the stomach is to process and transport food in small intestine. The residence time of food is small and mostly proteins are digested. Structurally the stomach is divided into three regions: fundus, body, and pylorus. The proximal part fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions⁴. The mean value of pH in fasted healthy person is 1.1 ± 0.15 . after intake of food the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, gastric secretion in women is slightly lower than that of men⁵.

Mechanism of floating systems

Various methods are used to increase the retention time of content in stomach. It includes introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Floating drug delivery systems (FDDS) have always bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The system is floating on the gastric contents the drug is released slowly at the desired rate from the system⁶. The apparatus operates by measuring continuously the force equivalent to F (function of time) that is required to maintain the submerged object. This apparatus helps in optimizing Floating

drug delivery system with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations⁷

$$F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) gv \dots (1)$$

Where, F = total vertical force, D_f = fluid density, D_s = object density, v = volume and g = acceleration due to gravity.

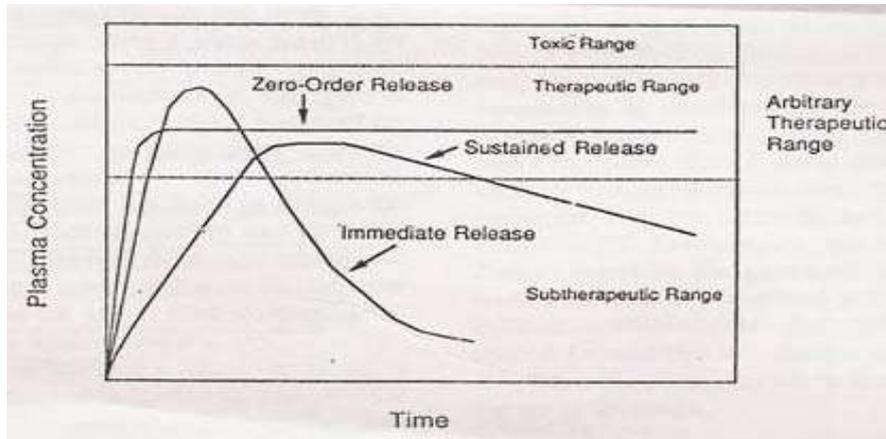


Figure 1: Drug level versus time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional table

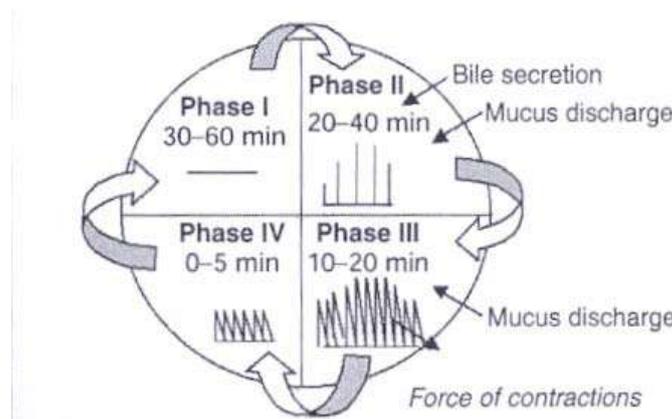


Figure 2 : Motility pattern in gastrointestinal tract

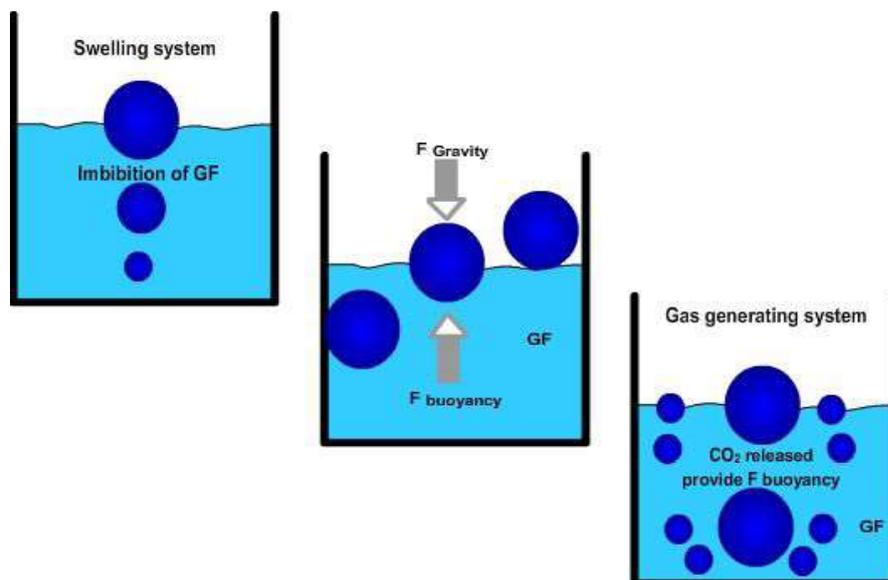


Figure 3: Mechanism of floating systems, GF= Gastric fluid

Based on the mechanism of buoyancy FDDS can be classified into

A. Single Unit Floating Dosage Systems

- a) Effervescent Systems (Gas-generating Systems)
- b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems

- a) Non-effervescent Systems
- b) Effervescent Systems (Gas-generating Systems)
- c) Hollow Microspheres

C. Raft Forming Systems

A. Single Unit Floating Dosage Systems

- a) Effervescent Systems (Gas-generating Systems):

The matrices which are prepared using swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimum stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Thus, carbon dioxide is released which cause the beads to float in the stomach^[8]. Mostly Excipients include HPMC, polyvinyl acetate, Carbopol, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

- b) Non-effervescent Systems:

This type of system, after swallowing, swells in gastric fluid which prevents their exit from the stomach. One of the formulation methods involves the mixing of drug with a gel, which swells in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. Examples of this type of floating drug delivery system include colloidal gel barrier, microporous compartment system, alginate beads, and hollow microspheres. Another type is a Fluid-filled floating chamber⁹ which includes incorporation of a gas-filled floatation chamber into a microporous component that causes a drug reservoir. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. After this drug is swell and start floating.

A newer Self-correcting floatable asymmetric configuration drug delivery system¹⁰. The formulation of ciprofloxacin was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked polymer PVP initially and the gel forming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach. The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug¹¹.

B. Multiple Unit Floating Systems:

In order to overcome problem, multiple unit floating systems were developed, which reduce the intersubject variability and prevent dose-dumping. The development of both non-effervescent and effervescent multiple unit systems¹². Much research has been focussed and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.

a) Non-effervescent Systems:

A few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported¹³. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio¹⁴.

b) Effervescent Systems (Gas-generating Systems):

The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 part of HPMC¹⁷, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h.

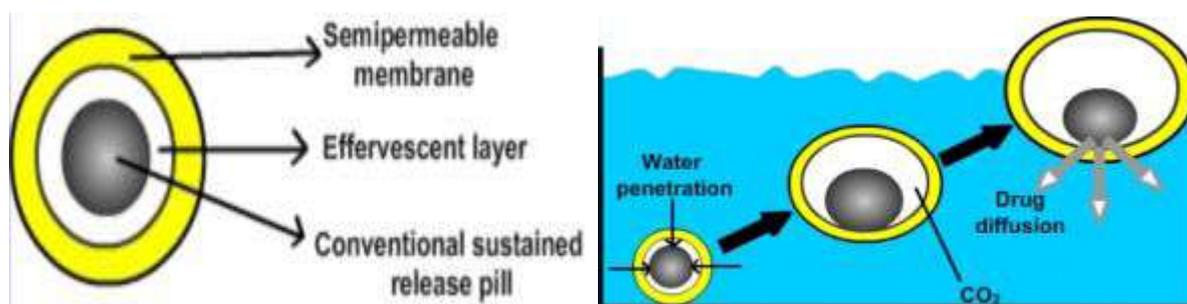


Figure 4: a) Different layers (i) Semi-permeable membrane, (ii) Effervescent Layer (iii) Core pill layer b) Mechanism of floatation via CO₂ generation.

c) Hollow Microspheres:

The most floating system is hollow microspheres. The general techniques in their preparation include simple solvent evaporation¹⁶, and solvent diffusion and evaporation. The drug release and better floating properties mostly depend on the type of polymer, plasticizer and the solvents. Polymers such as polycarbonate, Eudragit® and cellulose acetate were used in the preparation of hollow microspheres. Sustained release floating microspheres using polycarbonate¹⁷, employing solvent evaporation technique. Aspirin, griseofulvin were used as model drugs. Dispersed phase containing polycarbonate in dichloromethane and micronized drug was added to the dispersion medium containing sodium chloride, polyvinyl alcohol and methanol. The dispersion was stirred for 3-4 hours to assure the complete solvent evaporation, and the microspheres formed were filtered, washed with cold water and dried. The spherical and hollow nature of the microspheres was confirmed by Scanning electron microscopic studies¹⁸. It prepared by a novel emulsion solvent diffusion method.

A solution of drug and enteric acrylic polymer (Eudragit® S) in a mixture of ethanol and dichloromethane is added to the aqueous phase containing polyvinyl alcohol (0.75% w/v) and stirred continuously to obtain o/w emulsion. The microspheres obtained are filtered, water washed and dried. After collection the microspheres showed good flow and packing properties, and a floating time of more than 12 h on acidic medium containing surfactant^{19,20}.

C. Raft Forming Systems:

Raft forming systems have received much attention about the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation include that the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of

low bulk density created by the formation of CO₂. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids²¹. The system contains a gel forming agent, sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel when in contact with gastric fluids. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori infection in the GIT. The composition has drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener then the citric acid added which float in fluid.

Factors affecting gastric retention

Several factors include like density, size and shape of dosage form, concomitant intake of food and drugs such as anticholinergic agents (eg. atropine, propantheline), opiates (eg. codeine) and prokinetic agents (eg. metoclopramide) and biological factors such as gender, posture, age, body mass index and disease state (eg. diabetes). The floating force kinetics of such dosage forms has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy. This is because the magnitude of floating strength may vary as a function of time and usually decreases after immersion and its hydrodynamical equilibrium. The prolongation of gastric residence time by food is expected to maximize drug absorption from floating drug delivery system due to increased dissolution of drug and longer residence at the most favorable sites of absorption.

Drugs Used In the Formulations of Stomach Specific Floating Dosage Forms

Floating microspheres – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen²⁴,

Piroxicam, Verapamil, Theophylline, Nifedipine, Nicardipine, Tranilast²⁵ and Terfenadine²⁶

Floating granules - Diclofenac sodium, Indomethacin and Prednisolone

Films – Cinnarizine²⁴, Albendazole

Floating tablets and Pills - Acetaminophen, Acetylsalicylic acid, Ampicillin, Atenolol, Fluorouracil, Isosorbide mononitrate²⁸, Piretanide, Theophylline²³, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol,

Floating Capsules - Chlordiazepoxide hydrogen chloride, Diazepam²⁴, Furosemide, Misoprostol, L-Dopa, Ursodeoxycholic acid, Pepstatin, and Propranolol.

APPROACHES TO GASTRORETENTION

Several techniques are reported in the literature to increase the gastric retention of drugs.

1) High density systems

These systems, which have a density of $\sim 3\text{g/cm}^3$, are retained in the stomach and capable of withstanding its peristaltic movements. The major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm³. Diluents such as barium sulphate (density= 4.9), zinc oxide and titanium oxide must be used to manufacture such high-density formulation³¹.

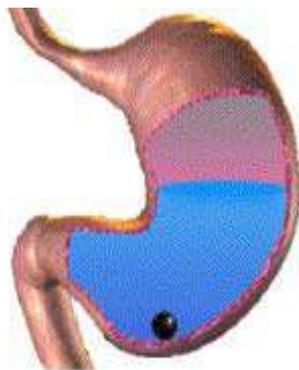


Figure 5: High density systems

2) Swelling and expanding systems

This system is also called as “Plug type system”, since they exhibit tendency to remain lodged in the pyloric sphincters. The polymeric matrices remain in the gastric cavity for several hours. The polymer of molecular weight and swelling properties controlled and sustained drug release can be achieved the polymer absorb water and swells. These cross link prevents the dissolution of

polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer²⁵.

3) Incorporating delaying excipient

Delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and prolongation of the drug release with the help of delivery system incorporating delaying excipient like trietanolamine myristate in a delivery system²⁶.

4) Modified systems

The non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.

5) Mucoadhesive & Bioadhesive systems

The Bioadhesive delivery systems are used to localize a delivery device within the lumen to increase the drug absorption in a site specific manner. Some of the most promising excipient that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin²⁸, etc.

6) Floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids though the system is floating on the gastric contents. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

Evaluation parameters of Gastroretentive system

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo.

1) Hardness, friability, assay, content uniformity (Tablets)

These tests are performed as per described in specified monographs.

2) Floating lag time and total floating time determination

It is noted by the time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in gastric fluid or 0.1 mole.lit⁻¹ HCl maintained at 37^o C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium.

3) Drug release

It is important test for in vitro drug release study and carried out in gastric fluids and intestinal fluids maintained at 37^o C. Dissolution tests are performed using the USP dissolution apparatus. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started and standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors.

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads)

Drug loading by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium and centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated in beads or microspheres and the size and shape calculate by optical microscopy method. The external and cross-sectional morphology which is surface characterization is done by scanning electron microscope (SEM). The measured weight of prepared microspheres was divided by total amount of all non-volatile components used for the preparation of microspheres, which will give the total percentage yield of floating microspheres²⁶.

5) Resultant weight determination Bulk density and floating duration have been the main parameters of a dosage form's buoyancy. Although single density determination does not predict the floating force evolution the dosage forms. It operates by force equivalent to the force F required to keep the object totally submerged in the fluid. The magnitude, direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (Fbuoy) and gravity (Fgrav) forces acting on the objects as shown in the equal

$$F = F_{\text{buoy}} - F_{\text{gra}}$$

$$F = d_{\text{fg}}V - d_{\text{sg}}V = (d_{\text{f}} - d_{\text{s}}) gV$$

$$F = (d_{\text{f}} - M/V) gV$$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, d_f if the fluid density, d_s is the object density is the object mass and V is the volume of the object.

7) X Ray/Gamma scintigraphy

For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating system. In each experiment, the animals are allowed to fast overnight with free access to water, in a formulation allows indirect external observation using a γ -camera or scintiscanner. But the main drawback of γ -scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical²⁶.

8) Pharmacokinetic studies

Pharmacokinetic studies include AUC (Area under Curve), C max, and time to reach maximum and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 mL of water. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. The inclusion of a γ -emitting radionuclide plasma concentration (T max) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance.

9) Specific Gravity

The displacement method is used to determine the specific gravity of floating system using compound benzene as a displacing medium²⁷.

Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications on poor bioavailability drugs because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Some of these are;

Sustained Drug Delivery

In this systems dose large in size and passing from the pyloric opening is prohibited. New sustained release floating capsules of nicardipine

hydrochloride were developed and were evaluated in vivo. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly a comparative study²⁸ between the Madopar HBS and Madopar standard formulation was done it shown the drug was released up to 8 hours in vitro in the former case and the release completed in less than 30 minutes in the latter case.

Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs²⁸.

Absorption Enhancement

Drugs which have poor bioavailability at the site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, In some cases increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%).²⁹

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure. The prolong gastric retention of the dosage form extends the time for drug absorption is now available in floating drug delivery system. Floating controlled drug delivery systems are employed to solve this problem. It also provide intimate contact between a dosage form and the absorbing tissue which may result in high drug concentration in a local area and hence, high drug flux through the absorbing tissue, producing the pharmacological effect for extended period of time with maximum bioavailability and less side effects for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. The increasing delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism

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