

GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

In recent years, gastro retentive drug delivery systems have gained research interest in the field of oral drug delivery. The purpose of reviewing gastro-retentive drug delivery systems (GRDDS) is to accumulate the current literature with a special emphasis on several gastro-retentive approaches that have recently become important methodologies in the field of site-specific orally administered sustained or controlled-release drug delivery. Gastro-retentive drug delivery systems can be used to overcome challenges associated with conventional oral dosage forms and to release the drug at a specific absorption site to improve the bioavailability of a particular drug substance. Conventional oral dosage forms pose low bioavailability problems. Several efforts have been made to extend the drug delivery system to reduce the frequency of dose administration. GRDDS not only prolongs dosing intervals but also increases patient compliance beyond the level of existing controlled-release dosage forms.

KEYWORDS: Gastro retentive, patient compliance, site-specific, challenges.

INTRODUCTION:

The oral route is the most appropriate and preferred route for systemic or local delivery of any drug. The goal; of any delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Oral dosage forms are intended for systemic effects resulting from drug absorption through the gastrointestinal tract. Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include floating systems, bioadhesive systems, swelling systems, expanding systems, delayed gastric emptying systems, and low-density super porous systems. The oral drug delivery system is the most preferable route of drug delivery due to the ease of administration, patient compliance, non-evasive in nature, and flexibility of formulation. From immediate release to site-specific delivery, oral dosage forms have progressed. Many orally administered drugs display poor bioavailability when administered in a conventional dosage form, that is the rate and extent to which the drugs are absorbed are less than desirable. With several drugs, absorption may be as little as 30% or less of the orally administered dose. To compensate for this effect, a very large dose is often administered so that absorption of a therapeutically required quantity of drug can occur. This technique may be costly with expensive drugs, and the absorbed drug may also have undesirable side effects within the gastrointestinal tract. In addition, poorly absorbing drugs display large inter and intra variability in bioavailability. This problem can be overcome by a modified-release drug delivery system with prolonged residence time in the stomach. After oral administration drug delivery would be retained in the stomach and released the drug in a controlled manner so that the drug could be supplied continuously to its absorption site in the gastrointestinal tract [1]. Gastro-retentive drug delivery is an approach to prolong gastric residence time thereby targeting site-specific drug release in the upper gastrointestinal tract for local and systemic effects. Gastro retentive dosage forms can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches have been designed and developed, including high-density systems, mucoadhesive systems, unfoldable, extendable, or swellable systems, super porous hydrogel systems, and magnetic systems.[2] Gastric emptying of dosage forms is an extremely variable process and the ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a prolonged period than conventional dosage forms[3,4]. Several difficulties are faced in designing a controlled delivery system for better absorption and enhance bioavailability. One such difficulty is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from GIT is a complex procedure and is subject to many variables. It has an application also for local drug delivery to the stomach and proximal intestine [5]. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [6]. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floating, sedimentation, expansion, modified shapes, or by the simultaneous administration of pharmacological agents [7,8,9].

PHYSIOLOGY OF STOMACH

Anatomically the stomach is divided into three regions: Fundus, Body, and Antrum. The proximal part made of the fundus and the body acts as a reservoir for undigested materials where as the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling the actions. Gastric emptying occurs during fasting as well as in the fed state. During the fasting state, an inter-digestive series of electrical events take place, which cycles both through the stomach and intestine every 2 to 3 hours [10]. This is called the inter-digestive migrating myoelectric cycle (MMC) [11].

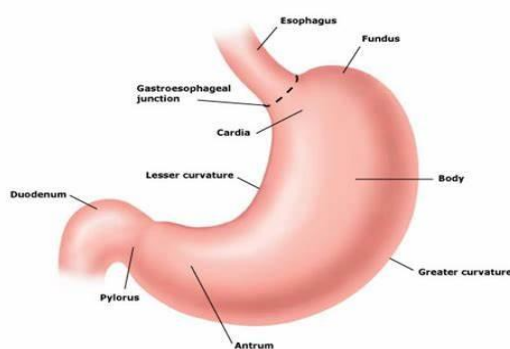


Figure 1. Diagram of a human stomach

The stomach anatomy and physiology contain parameters to be considered in the development of Gastro retentive dosage forms. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time of oral dosage forms include density, size and shape of the dosage form, food intake and its nature, posture, gender, age, sex, sleep, body mass index, physical activity, and diseased states of the individual and administration of the drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (atropine, propantheline), opiates (codeine) and prokinetic agents (metoclopramide). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.

Phase	Description	Duration(min)
Phase I (basal phase)	Idle state without any contraction	30 to 60
Phase II (pre-burst phase)	Intermittent action	20 to 40
Phase III (burst phase)	Regular contractions	10 to 20
Phase IV	The transition period between phase I and phase II	0 to 5

FACTORS AFFECTING GASTRIC RETENTION TIME:

SIZE: Dosage form units having a diameter of greater than 7.50mm are stated to have an improved gastric residence time [12].

DENSITY: The density of the dosage form must be lower than the gastric contents (1.004g/ml).

retention time related to those having a diameter of 9.90mm.

SHAPE OF THE DOSAGE FORM: Tetrahedron and ring-shaped devices have a better gastric residence time than others.

SINGLE OR MULTIPLE UNIT FORMULATION: Multiple unit formulations show a more expectable release profile and insignificant damage of performance because of the failure of units that have dissimilar release profiles related to single unit dosage forms.[13]

FED OR UNFED STATE: In fasting conditions, gastrointestinal motility is categorized by periods of strong motor activity that occur every 1.5 to 2 hours, and if the timing of administration of the formulation overlaps with that of the migrating myoelectric cycle, the gastric retention time of the unit can be anticipated to be very short. However, in the fed state migrating myoelectric cycle is postponed and gastric retention time is significantly longer.

NATURE OF MEAL: Intake of fatty acid salts or indigestible polymers can modify the motility pattern of the stomach to a fed state, hence reducing the gastric emptying rate.

CALORIC INTAKE: Gastric retention time can be improved by 4 to 10 hours with a meal that is high in proteins and fats.

AGE: Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.

FREQUENCY OF FEED: Gastric retention time can rise by over 400 minutes when consecutive meals are given related to a single meal because of the low frequency of migrating myoelectric cycle.

GENDER: Males have a gastric retention time of 3.4 hours while females have 4.6 hours.

ADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

- Maintenance of constant therapeutic level over a long period.
- Enhanced bioavailability [14].
- Gastro retentive dosage form improves patient compliance by decreasing dosing frequency.
- Minimizing mucosal irritation of drugs by releasing drugs slowly at a controlled rate.
- Treatment of gastrointestinal disorders like GERD, Helicobacter pylori infection, etc. [15].
- Floating drug delivery system is a feasible approach for drugs that have limited absorption in the intestine.
- Floating drug delivery systems can reduce the counter activity of the body, leading to higher drug efficacy.
- Improved drug absorption because of increased gastric residence time.
- Controlled drug delivery.
- Ease of administration.
- Targeted therapy for local ailments in the upper gastrointestinal tract.
- Reduced fluctuations of drug concentration.
- Delivery of drugs with a narrow absorption window in the small intestine.

- The controlled, slow delivery of drug from gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects or side effects.
- Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

DISADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

- The drug substances are unstable in the stomach's acidic environment.
- Not suitable for drugs that have solubility or stability problems in the gastrointestinal tract.
- Unsuitable for drugs with limited acid stability [14].
- Not suitable for drugs that irritate or cause gastric lesions on slow release.
- Drugs that absorb selectively in the colon cannot be formulated.
- Floating drug delivery systems require high fluid levels in the stomach to float and work effectively.
- In the swelling system the dosage form must maintain a size larger than the pyloric sphincter.
- The dosage form must resist premature gastric emptying [15].
- High-density approach requires a higher amount of drug.
- The dosage form must withstand peristaltic movements of the stomach.
- Drugs that are absorbed along the entire gastrointestinal tract and which undergo first-pass metabolism may not be desirable.
- Violent gas generation, the disintegration of dosage forms, burst release, dose dumping, and alkaline microenvironment are the limitations.

TYPES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

Gastro retentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enabling sustained and prolonged input of the drug to the upper part of the gastrointestinal tract [16]. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper gastrointestinal tract can greatly improve their bioavailability and their therapeutic outcomes. Gastro retentive delivery system can be classified as follows.

- Bio-adhesive drug delivery system
- Expandable drug delivery system
- Floating drug delivery system
- High-density system
- Low-density system
- Super porous hydrogels

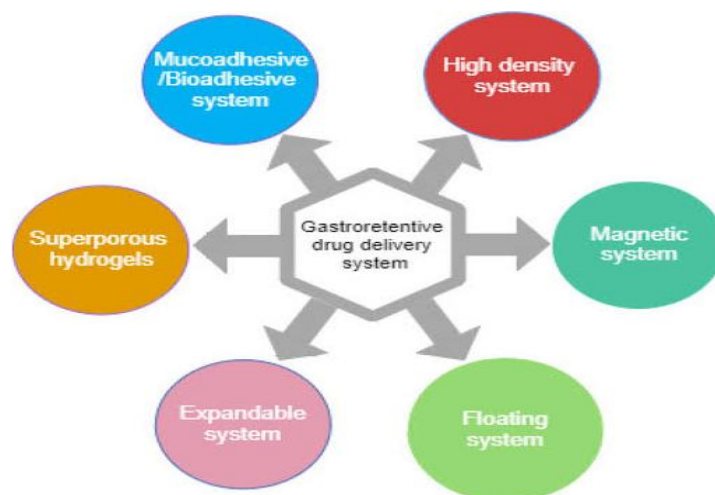


Figure 2. Types of gastro retentive drug delivery systems

BIOADHESIVE OR MUCOADHESIVE SYSTEM

Bio-adhesive or mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastric residence time of the drug delivery system. The basis of adhesion in a dosage form can stick to the mucosal surface by different mechanisms [17]. These mechanisms are:

- Wetting theory
- Diffusion theory
- Adsorption theory
- Electron theory

WETTING THEORY: The ability of bioadhesive polymers to spread and develop intimate contact with the mucous membrane.

DIFFUSION THEORY: Physical entanglement of mucin strands and flexible polymer chains.

ADSORPTION THEORY: Surface forces such as covalent bonds, ionic bonds, hydrogen bonds, and Van der Waals forces result in chemical bonding.

ELECTRONIC THEORY: Attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.

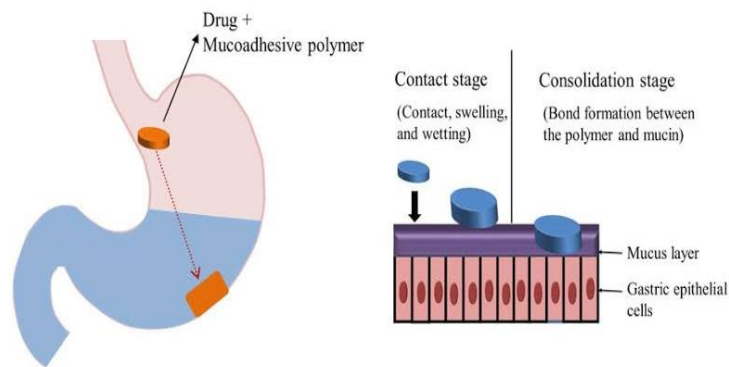


Figure 3. Mucoadhesive gastro retentive drug delivery system, the process of mucoadhesion

EXPANDABLE DRUG DELIVERY SYSTEM

These are dosage forms that swell to an extent that prevents their exit from the pylorus after swallowing.

As a result, the dosage form is retained in the stomach for a long period. These systems may be named plug-type systems since they tend to remain lodged at the pyloric sphincter. Controlled and sustained drug delivery is achieved using an appropriate excipient. The swelling ability of the polymer mainly depends upon the degree of cross-linking of the hydrophilic polymer network. A high degree of cross-linking maintains the integrity of the system, while a low degree of cross-linking causes extensive swelling resulting in the rapid dissolution of the polymer [18].

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems have a bulk density lower than the gastric fluids and thus remain buoyancy in the stomach for a prolonged period, without affecting the gastric emptying rate [19]. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. This type is also called a hydrodynamically balanced system. Types of floating systems are as follows:

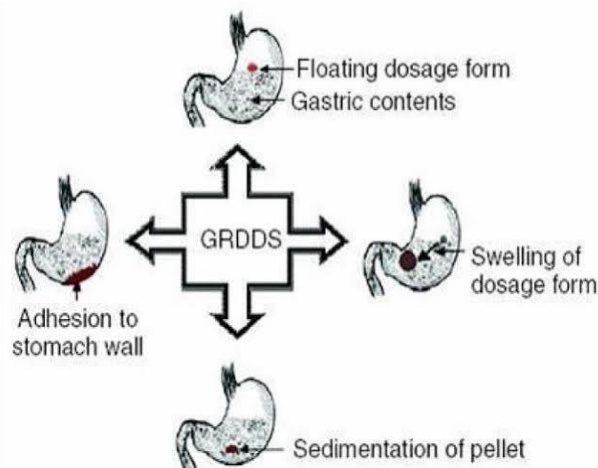


Figure 4. Floating system

1) Non effervescent systems

- Hydrodynamically balanced systems
- Microporous compartment system
- Alginate beads
- Hollow microspheres

2) Effervescent systems

- Gas generating systems
- Volatile liquid or vacuum-containing systems.

NON-EFFERVESCENT SYSTEMS

Non-effervescent systems are prepared from gel-forming or highly swellable cellulose-type hydrocolloids, polysaccharides, or matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate. In these systems, the floating of

dosage forms involves the intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by swollen polymer confers buoyancy to these dosage forms [20]. These systems can be further classified into the following types:

HYDRODYNAMICALLY BALANCED SYSTEMS

These are single-unit dosage forms that contain one or more gel-forming hydrophilic polymers such as hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarboxiphil, polyacrylate, polystyrene, agar [21]. These polymers are mixed with drugs and administered in hydrodynamically balanced system capsules. The capsule shell dissolves in contact with water and the mixture swells to form a gelatinous barrier, which imparts buoyancy to a dosage form for a long period in gastric juice.

MICROPOROUS COMPARTMENT SYSTEM

This system involves the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to prevent any direct contact of the undissolved drug with the gastric surface. The floating chamber in the stomach containing entrapped air causes the delivery system to float in the gastric fluid. The gastric fluid that enters through the aperture dissolves the drug and causes continuous transport of the dissolved drug across the intestine.

ALGINATE BEADS

A multi-unit gastroretentive sustained release dosage form of a water-soluble drug is prepared by emulsion gelation technique [22]. The beads are made using sodium alginate as the polymer and oil was entrapped in the beads by gently mixing or homogenizing the oil and water phase containing sodium alginate which was then extruded into a calcium chloride solution.

HOLLOW MICROSPHERES

Hollow microspheres are considered one of the promising buoyant systems because they combine the advantages of multiple unit systems and floating systems. These are prepared by using the solvent diffusion technique.

EFFERVESCENT SYSTEMS

Effervescent systems include the use of gas-generating agents, carbonates, and other organic acids. Mostly carbon dioxide is used as a gas-generating agent. An alternative is incorporating a matrix containing a portion of the liquid that produces gas that evaporates at body temperature. These are further classified as follows:

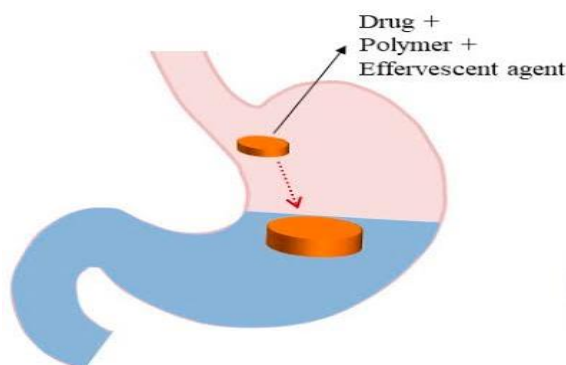


Figure 5. Effervescent system

GAS GENERATING SYSTEMS

The mechanism involved in this system is the production of carbon dioxide gas due to the reaction between sodium bicarbonate, citric acid, and tartaric acid [23]. The gas produced gets entrapped in the jellified hydrocolloid layer of the system which decreases the specific gravity and makes it float over gastric contents. The system consists of a sustained-release drug surrounded by double layers. The outer layer is a swellable membrane layer.

These can be further classified into:

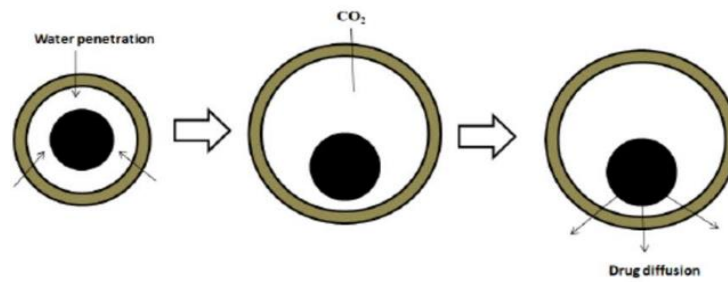


Figure 6. Gas generating system

1. FLOATING CAPSULE

These are prepared by formulating a mixture of sodium bicarbonate and sodium alginate. On exposure to an acidic environment, carbon dioxide gas is generated which is trapped in the hydrating gel network and makes the system float [24].

2. FLOATING PILLS

These are a type of sustained release formulations which are multiple types of unit dosage forms. The sustained-release pill is surrounded by two layers [25]. The outer layer consists of a swellable membrane and the inner layer consists of effervescent agents. The systems swell due to swellable membranes and then sink. Due to the presence of an effervescent agent, carbon dioxide is released and the system floats.

3. FLOATING SYSTEM WITH ION EXCHANGE RESIN

The most common approach for formulating these systems involves resin beads loaded with bicarbonates. This is then coated with ethyl cellulose which is usually insoluble but permeable to water, this causes carbon dioxide to release and the system to float [26].

HIGH-DENSITY SYSTEMS

High-density systems involve the formulation of dosage forms with a density that must exceed the density of normal stomach content [27]. These formulations are prepared by coating the drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide, titanium oxide, etc. These materials increase density up to 1.5 to 2.4 gm/cm³.

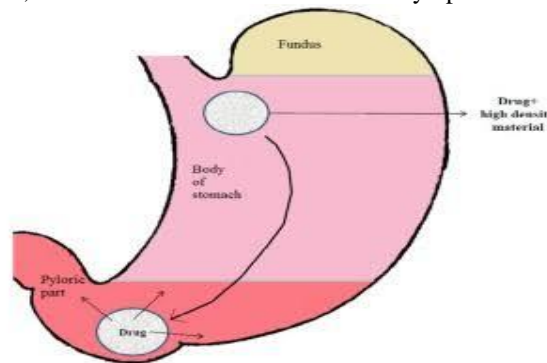


Figure 7. High-density systems

MAGNETIC SYSTEMS

These systems appear as small gastro retentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach [28]. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision.

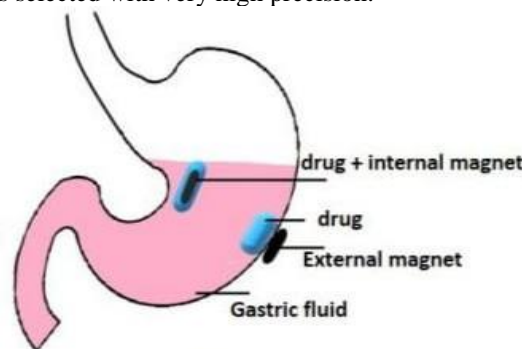


Figure 8. Magnetic systems

RAFT FORMING SYSTEMS

In these systems, the raft floats on gastric fluids because of the low bulk density created by the formation of carbon dioxide. Usually, these have a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of carbon dioxide to make the system less dense and float on the gastric fluids [29].

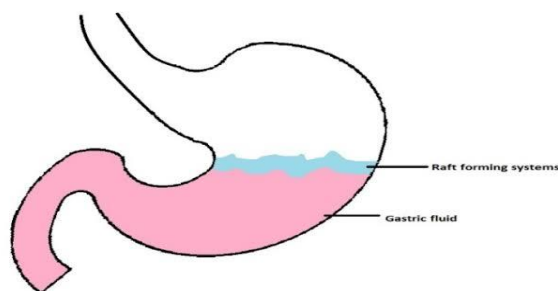


Figure 9. Raft forming system

SUPER POROUS HYDROGEL SYSTEMS

These are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is a very slow process and several hours may be required to reach the equilibrium state during which the premature evacuation of the dosage form may occur [30]. Super porous hydrogel has a pore size of greater than 100 μ m which swells to equilibrium size within minutes, due to the rapid intake of water by capillary wetting through interconnected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure of gastric contraction.

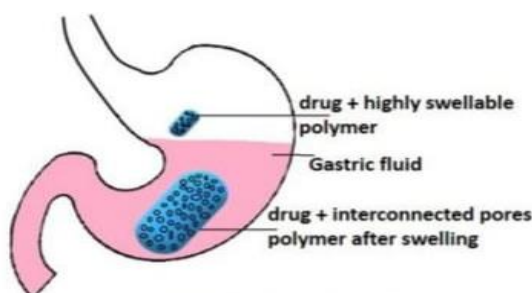


Figure 10. The super porous hydrogel system

EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

BULK DENSITY:

A quantity of drug powder was weighed initially and introduced into a 10ml measuring cylinder [35]. The bulk volume was determined and the apparent bulk density in g/ml was calculated using the formula-

$$\text{BULK DENSITY} = \text{weight of powder} / \text{bulk volume}$$

TAPPED DENSITY:

A quantity of drug powder blend from each batch, previously shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder [37]. After that, the initial volume was noted and the cylinder was allowed to tap under its weight onto a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. Calculated by the formula

$$\text{Tapped density} = \text{weight of powder} / \text{tapped volume}$$

HAUSNER'S RATIO:

This was calculated as the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \text{Tapped density} / \text{bulk density}$$

CARR'S COMPRESSIBILITY INDEX:

The compressibility index of the powder blend was determined by the formula

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

ANGLE OF REPOSE:

The angle of repose of the powder blend was determined by the funnel method [38]. The accurately weighed powder blend was taken in a funnel, and the height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to freely flow through the funnel onto the surface. The diameter and angle of repose were calculated by using the following equation

$$\text{Tan } \phi = h/r$$

HARDNESS:

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet of a hardness of about 2-4kg/cm² is considered adequate for mechanical stability.

THICKNESS:

The thickness of all the tablet formulations was measured using vernier calipers by placing tablets between two arms of the vernier calipers.

FRIABILITY:

The friability of the tablet was measured in a Roche Friabilator, 20 tablets were taken, weighed and initial weight was noted (w_0). Percentage friability was calculated from the loss in weight by using the following equation. The weight loss should not be more than 1%.

$$\text{Friability (\%)} = \{(\text{Initial Weight} - \text{Final weight}) / (\text{Initial weight})\} \times 100$$

CONTENT UNIFORMITY:

In this test, 20 tablets were randomly selected and the percentage drug content was determined, the tablets containing not less than 85% or not more than 115% of the labeled drug content can be considered as the test was passed.

PERCENTAGE OF DRUG ENTRAPMENT:

Percentage entrapment efficiency was reliable for quantifying the phase distribution of the drug in the pre-formulation. The drug is extracted by a suitable method, analyzed, and calculated by the formula

$$\text{PDE} = \text{Practical drug Loading} / \text{Theoretical Drug Loading} \times 100$$

BUOYANCY LAG TIME/ LAG TIME FOR FLOATING TABLETS:

A buoyancy lag time test was performed to check the floating behavior. The tablets were dropped in the dissolution medium, i.e., 0.1N HCl, and the time taken by them to come to the surface of the dissolution medium, i.e., time taken for floating on the surface was reported.

MATRIX INTEGRITY:

The swollen mass of the tablets remained intact or not was checked. Matrix integrity was observed throughout in-vitro dissolution studies.

SWELLING INDEX:

Weight gain and water uptake:

The swelling behavior of dosage units can be measured either by studying its dimensional changes, weight gain, or water uptake. The study is done by immersing the tablets in 0.1N HCl at 37°C and determining these factors at regular intervals.

Water uptake (WU) is measured in terms of % weight gain as given by the equation below,

$$\text{WU} = (W_t - W_0) \times 100 / W_0$$

Where, W_t = final weight of the tablet at time(t)

W_0 = initial weight of the tablet

Tablets were removed at intervals of 2,4,6, and 8h, excess water was blotted, and tablets were weighed. Water uptake is measured in terms of percent weight gain.

EXAMPLES OF DRUGS MARKETED

Brand name	Drug
Cifran	Ciprofloxacin
Madopar	L-DOPA and Benserazide
Valrelease	Diazepam
Topalian	Aluminium-Magnesium antacid
Almagate flat coat	Aluminium-Magnesium antacid
Liquid gavison	Aluminum hydroxide
Convion	Ferrous sulfate
Liquid gavison	Sodium bicarbonate, Alginate acid

COMMONLY USED FLOATING DRUG DELIVERY SYSTEMS

Dosage forms	Drugs
Floating tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin.
Floating capsules	Diazepam, Furosemide, Misoprostol.
Floating microspheres	Aspirin, Griseofulvin, Ibuprofen.
Floating granules	Diclofenac sodium, Indomethacin, Prednisolone.

APPLICATIONS OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

- Sustained drug: Gastro retentive drug delivery systems float on the gastric contents over a prolonged period, as these systems have a bulk density of less than 1.
- Site-specific drug delivery: This delivery system is very useful for drugs that are absorbed from the stomach or the proximal part of the small intestine, especially with respect to their applications for the treatment of H. pylori infection.
- Fluctuations of drug concentration can be minimized: This feature is important for drugs with a narrow therapeutic index. Fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentration can be prevented.
- Absorption enhancement: This is important in the case of drugs that are absorbed from the inner part of the gastrointestinal tract and formulating this type of drugs as gastro retentive drug delivery systems can improve the poor availability thereby maximizing their absorption.
- Enhanced bioavailability: Increased bioavailability of riboflavin. Increases drug absorption by several processes.
- Targeted therapy for local ailments in the upper gastrointestinal tract: Prolonged and sustained release has many advantages for local therapy in the stomach and small intestine.

CONCLUSION

Gastro retentive drug delivery technologies have been extensively explored in recent years. Gastro-retentive drug delivery systems are the most preferable systems in order to deliver drugs that have a narrow absorption window near the gastric region. Recently many drugs have been formulated as floating drug delivery systems with the objective of sustained release and restricting the region of drug release to the stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non-effervescent and effervescent floating drug delivery system designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery.

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