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A REVIEW ARTICLE ON GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Gastrorentative drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper gastrointestinal track (GIT) for local or systemic effects. Gastroretentive dose forms can remain in the gastric region for long period and hence significance prolong the gastric retention tine of drug. GRDDS provide efficient means of enhancing the bioavailability and controlled drug delivery. Innovative pharmaceutical formulations known as gastroretentive drug delivery systems (GRDDS) are intended to increase the bioavailability and therapeutic effectiveness of medications that have poor absorption or solubility in the lower gastrointestinal tract. These systems are designed to keep medications in the stomach or upper gastrointestinal tract for longer, enabling regulated absorption and sustained release over time. GRDDS can be especially helpful for medications that are unstable in the intestines or that need a certain window of time to be absorbed. To accomplish gastric retention, a number of technologies have been developed, including floating, bio adhesive, swellable, and magnetically controlled systems. These methods optimize the drug's release profile, lengthen its residence time, and increase patient adherence. The concepts, design approaches, benefits, difficulties, and potential applications of gastroretentive technology are highlighted in this abstract.

KEYWORDS: Gastro-retentive; Gastric residence time; Stomach; Drug.

INTRODUCTION

Oral administration is the most popular and ideal method for administering medication. This could be as a result of the formulation's flexibility, patient compliance, and convenience of administration.[1] Nevertheless, this mode of administration has certain physiological constraints, such as a restricted gastrointestinal transit duration, a variable degree of stomach emptying that differs among individuals, and the existence of an absorption window for multiple medications in the upper section of the gastrointestinal tract (GIT). Due to these challenges, scientists created the gastro-retentive drug delivery system (GRDDS), a delivery method that enables the medication to remain in the stomach for an extended and consistent amount of time.[2] Numerous gastroretentive devices have been developed to be kept in the stomach area for extended periods of time in order to get around these restrictions. Gupta and Garg.[3]

Different GRDDS approaches, namely

a) co-administration of the drug delivery system with pharmacological agents that slow gastric motility

b) bioadhesive systems

c) size increasing systems which are either due to expansion or swelling and shape modification

d) density-controlled systems which are either, high density systems or floating systems

e) magnetic systems have been reported.[4]

Gastroretentive floating drug delivery systems are innovative formulations designed to enhance the bioavailability of certain drugs by prolonging their residence time in the stomach. This technology is particularly useful for drugs that are better absorbed in the stomach or upper gastrointestinal tract.[5] It is also reported that oral treatment of gastric disorders with an H2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion.[6] Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.[7] Since the drug is freely soluble in water (1 g in 25 mL) and has a short

elimination half-life of about 4 h due to which a regimen of 150 mg four times a day is required leads to poor patient compliance.[8] Moreover, ranitidine HCl has a narrow absorption window and is mainly absorbed in the proximal areas of GIT.[9] Hence, when a conventional sustained-release dosage form reaches the colon, where it gets metabolized[10], resulting in low absorption and poor bioavailability (52%). These factors favor the development of a gastroretentive type of drug delivery system9. Technologies used in oral drug delivery of the controlled-release dosage forms are one of the leading areas of science participating in health care of human beings. The main task involved in the developing the oral controlled release dosage form is not only to maintain the drug release in the sustain manner, but prolonging of the gastric residence of the administered dosage forms is equally important until the entire drug is released in the desired duration.[11] Prolonging of gastric residence time enhances drug release duration, and lessens waste of drug along with /better bioavailability.[12] Since the past 3 decades, many approaches to gastroretentive drug delivery systems have been developed, including floating,[13,14] magnetic systems,[15] unfoldable, expandable or swellable systems,[16] muco-adhesive,[17] sedimentation,[18] superporous hydrogel systems.[19] The applications of floating systems are greatly employed for delivery of drugs with reduced bioavailability due to low absorption in the upper gastrointestinal tract. The floating systems improves the bioavailability by keeping the dosage form at the absorption site.[20] Per-oral gastroretentive drug-delivery systems (GRDDS) are designed to deliver drugs in such a manner to the GIT in order to overcome the drawbacks associated with conventional dosage forms. However, these delivery systems are not suitable for drugs that are unstable in the strongly acidic gastric environment or those that may cause gastric lesions, such as nonsteroidal anti-inflammatory agents. In addition, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the GIT.[21] Because several factors affect a drug's bioavailability and suitability for the gastro retentive system, a thorough understanding of the various physiological, biological, and formulation factors affecting GIT transit and emptying pattern is imperative to ensure rational design and improved clinical efficacy. Several technological approaches to improving the gastric retention of a dosage form, including GRDDS, have been reported in the literature. This includes mucoadhesive, high-density, expandable, and floating drug-delivery systems (FDDS).[22-24] FDDS in particular are extensively researched because they do not adversely affect the motility of the GIT. Such a system aims to prolong the gastric retention of dosage forms in the GIT and consequently result in improved local bioavailability, therapeutic efficacy, and a possible reduction in dose size and dosing

frequency.[25-26] Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 min and 2 h. In the fasted state the electrical activity in the stomach, the inter digestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and, hence, the transit of dosage forms. It is characterized by four phases.

Phase I–period of no contraction (40–60 min).

Phase II–period of intermittent contractions (20–40 min).

Phase III–period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave (10–20 min).

Phase IV–period of transition between phase III and phase I (0–5 min)[27]

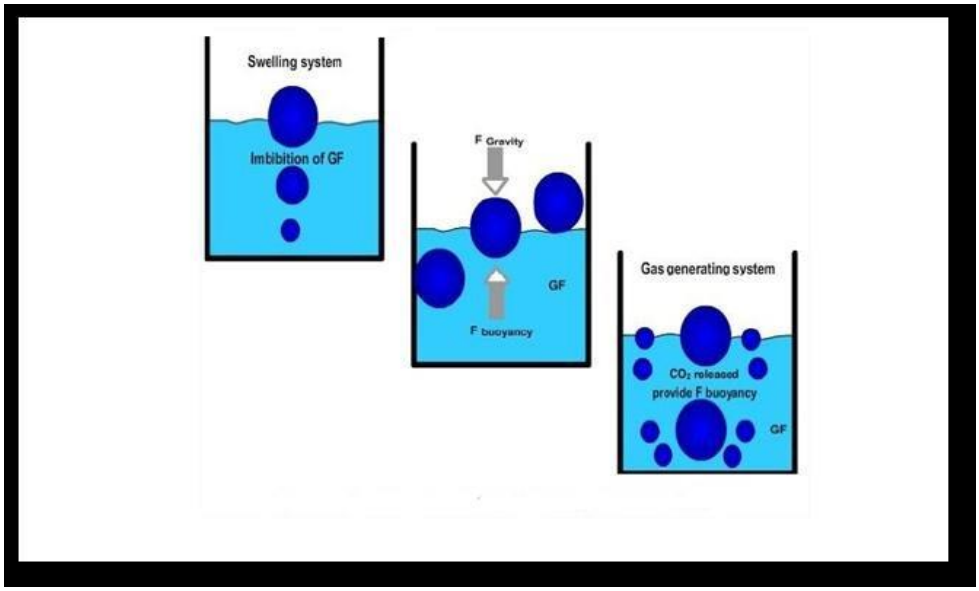


Fig.1.

Floating drug delivery

FDDS have a 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 medicine is delivered gradually at the desired pace while the system is floating on the contents of the stomach. The system is removed from the stomach when the medicine is released. As a result, the GRT rises and variations in plasma medication concentrations are better managed. Because the floating sustained release dosage forms can maintain their low apparent density while the polymer hydrates and forms a gel-like barrier at the outer surface, they are referred to as "hydrodynamically balanced systems" (HBS) and show most of the properties of hydrophilic matrices. As with traditional hydrophilic matrices, the medication is gradually

released from the swelling matrix. It is anticipated that these forms will stay afloat in the stomach contents for three to four hours without compromising the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. The results also showed that the buoyancy retention effect cannot be properly achieved without the presence of gastric contents. Cellulose ether polymers, particularly hydroxypropyl methyl cellulose (HPMC), are the most often used hydrocolloids among those suggested for floating form formulations. To improve buoyancy and reduce the rate at which water is absorbed, fatty materials with a bulk density less than one can be used into the formulation.[28] Investigations on the intragastric retention performance of floating forms have been conducted in both people and animals concurrently with formulation research. These evaluations were conducted directly using X-ray and gamma graphic monitoring of the transit through the GI system, or indirectly using pharmacokinetic investigations using a drug tracer. when subjects with residence time are given a floating capsule. When eating a meal high in fat and protein, it stays afloat at the top of the stomach's gastric contents and gradually descends as the food passes out of the stomach. The range of reported stomach retention times is 4–10 hours. Evaluations of pharmacokinetics and bioavailability validate the beneficial impact of this extended.[29]

The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy.[30]

$F = F_{buoyancy} – F_{gravity} = (Df – Ds)\ g\ v$

Where,

F = total vertical force,

Df = fluid density,

Ds = object density,

v = volume

g = acceleration due to gravity

Advantages

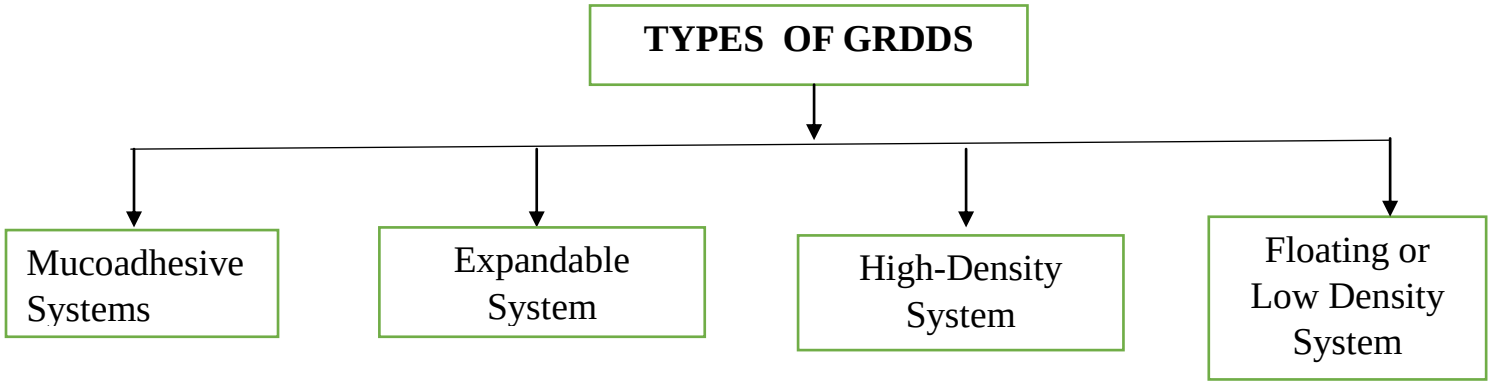
- Better absorption of drugs.
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation.

- Treatment of gastrointestinal disorders.
- Simple and conventional equipment for manufacture.
- Site-specific drug delivery.
- Ease of administration and better patient compliance.

Disadvantages

- They are not suitable candidates for drugs with stability or solubility problem in stomach.
- FDDS require sufficiently high level of fluid in the stomach so that the system can float and thus sufficient amount of water (200–250 ml) of water to be taken together with FDDS.
- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.

TYPES OF GRDDS



A. Mucoadhesive System

A mucoadhesive polymer found in mucoadhesive drug-delivery systems sticks to the mucosal surface of the stomach, more especially the mucus gel layer, extending the drug's retention in the GIT. Mucoadhesive polymers are highly effective excipients in GRDDS due to their ability to stick to the mucus gel layer. These polymers can be semi-synthetic or synthetic, such sodium carboxymethyl cellulose, Carbopol, and hydroxy-propyl methyl cellulose (HPMC), or natural, like gelatin, sodium alginate, and guar gum. Mucoadhesion can be facilitated by swelling and hydration, chemical or mechanical bonding, and activation of particular stomach cell receptors, depending on the type of polymers utilized.[31,47]

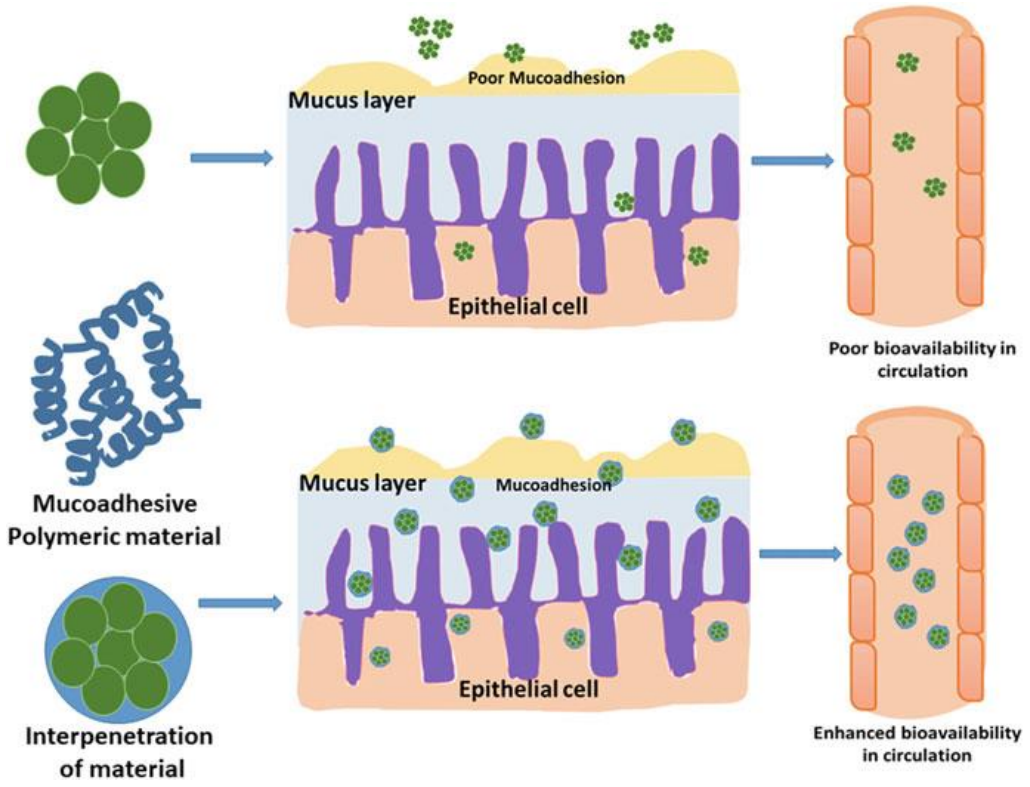


Fig.2.

B. Expandable System

Prolonged gastric retention is the result of the polymers in GRDDS causing swelling to the point where it is impossible to flow through the pyloric sphincter. Because of their propensity to stay stuck at the pyloric sphincter, expandable systems are also known as "plug type systems." The mean diameter of the pylorus in humans is about 12.8 ± 7 mm.[48] The dosage form's size and, thus, its location in the GIT are determined by its ability to withstand the stomach's peristaltic motions. Longer retention times in the stomach are achieved via a non-disintegrating expandable system that is small enough for convenient administration but grows to a size larger than the pylorus aperture. To get the most benefits and prevent undesirable side effects, it is essential to strike a balance between the rate and degree of swelling and the rate at which the polymer erodes. Generally speaking, the expandable GRDDS's effectiveness depends on its capacity to withstand the strong mechanical contractions seen in the stomach while retaining its strength and integrity. However, a major advantage of these systems is their ability to prolong gastric retention independently of the fed or fasted state of the stomach.[49]

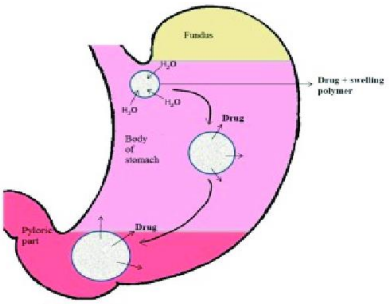


Fig 3.

C. High-Density Systems

Because of their larger density (about 1.004 g/cm3) than the stomach contents, GRDDS are more likely to be retained in the stomach. Strong gastric propulsions prevent early emptying, and higher densities (>1.3g/cm3) cause the dose form to settle in the rugae of the stomach folds close to the pyloric region—the area of the organ with the lowest position when standing upright. Dosage form density in the range of 2.5 to 3.0 g/cm3 is required to withstand the peristaltic movements of the stomach wall for extended periods of time, with the exception of considerable gastric retention that may develop.[50] Coating the medicine with a heavy inert substance, like iron powder, zinc oxide, titanium dioxide, or barium sulfate, is often how higher densities are achieved. If high densities are to be maintained, the high-density system is technically exceedingly challenging to construct, particularly when drug loading exceed 50%. Despite the fact that these systems have shown promising outcomes in veterinary applications.[51,52] Because of variations in retention brought on by posture and movement (e.g., upright vs. supine), their efficacy in human subjects has not been shown.[53]

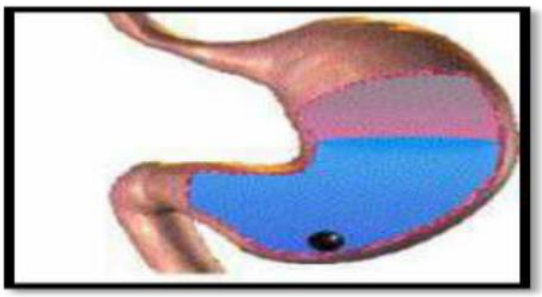


Fig 4

D. Floating or Low-Density System

FDDS enable continuous release of the medicine and stay floated above the stomach contents for extended periods of time due to their low densities (<1.004g/cm2). Specifically, these

systems have been thoroughly investigated since they do not negatively impact GIT motility.[54,57] Their superiority over other types of GRDDS is further evidenced by the large number of floating dosage forms that are being developed and sold worldwide. The many patents awarded for the different systems are listed, along with a description of the drugs that have been generally studied as possible FDDS candidates.[58,59,60]

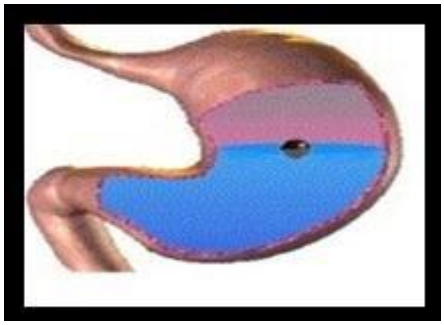


Fig 4

PHYSIOLOGICAL CONSIDERATIONS FOR THE DEVELOPMENT OF GRDDS

.A. Basic GIT Physiology

The stomach is made up of three parts: the fundus, the body, and the antrum. It is anatomically located in the upper left portion of the abdominal cavity, directly behind the diaphragm. Comprising goblet cells, parietal cells, and chief cells, it secretes 2 to 3 L of gastric juice every day in the form of mucus, hydrochloric acid, and pepsinogen, respectively. The stomach's contraction forces mix the digesting gastric juices with the chyme, which is a milky mixture of food. The fundus and body, which make up the proximal portion of the stomach, serve as a holding area for undigested food and propel chyme to the antrum. The primary location for triturating and crushing the food particles is the antrum. Through its propulsive movements, the antrum serves as a pump to control stomach emptying and is the primary location for trituration and grinding of food particles through mixing motions. They may be able to endure the peristaltic waves of the stomach wall and provide prolonged gastric retention if they are sedimented into particles or pellets small enough (density of 1.3 g/cm3 or higher) to become stuck in the rugae or folds of the antrum. The stomach's apparent absorbing surface area is around 0.1 mm2, and its average length is 0.2 mm.[61,62] Anatomically, the pylorus acts as a sphincter between the duodenum and the antrum. The diameter of the human pylorus is 12.8 ± 7 mm.,[63] and serves as a mechanical barrier to the passage of big particles as well as a sieve. For particles to enter the small intestine through the pyloric valve, they must be between 1 and 2 mm in size.[64]

B. Gastric pH

Human physiologic stomach pH fluctuates and differs depending on the GIT's various region.[65] Due to variations in the stomach's condition during measurement (fed or fasted), as well as other physiological and biological parameters, it also shows significant intra- and inter-subject variability. According to reports, the average stomach pH in healthy individuals who fast is 1.1 ± 0.15.[66] The pH in the fed state first drops below 5.0 before progressively rising to the fasting state levels over a few hours. In healthy guys, the typical fed-state pH is 3.6 ± 0.4.[67]

The basal pH of elderly individuals rises to more than 5 due to physiological changes that impact gastric acid secretion, resulting in hypochlorhydria or achlorhydria.[68] Drugs like proton-pump inhibitors and H2-receptor antagonists, as well as pathological situations like AIDS and pernicious anemia, dramatically lower stomach acid output and raise stomach pH. Clinical trials employing GRDDS should have stringent screening procedures to detect such characteristics and modify suitable controls to lessen bias and produce more trustworthy results because of the wide variations in gastric pH.

C. Gastric Emptying

The process of the dose form being emptied from the stomach into the small intestine is called gastric emptying, and it is driven by motility. Gastric emptying controls how long the dosage form stays in the stomach during drug delivery. Because the stomach and proximal small intestine are the main sites of absorption for medications with a narrow absorption window, this process is important.

Oral bioavailability will be impacted by any factors that impact gastric emptying because they will also affect how long the medicine stays in contact with the target site. Controlling or regulating gastric emptying, which is a highly variable process, might increase the stomach's capacity as a drug-absorbing organ and open up new design possibilities.

The stomach's primarily contractile motility pattern helps it ground food into smaller pieces, combine them with gastric fluids to make "chyme," and then empty into the small intestine.[69]

The stomach's motility changes depending on whether it is fasting or fed. Every two to three hours during the fasting state, the stomach and intestines go through an inter-digestive

sequence of electrical processes. The goal of this process, known as the inter-digestive migrating myoelectric cycle (MMC), is to remove all undigested food from the stomach and intestine. This cycle is upset by feeding, which can cause erratic contractile activity for three to four hours. The lag time for the commencement of stomach emptying causes the initiation of MMC to be delayed in the fed condition, which slows down the gas tri-emptying rate.[70]

Factors That Influence Gastric Retention of FDDS

1. Formulation Factors:- Formulation parameters such as shape and size can affect the GRT of gastroretentive FDDS.

a. Shape

Cadwill et al. examined how shape affected the gastric-retention capability of FDDS in an in vivo investigation of healthy human participants. Because of their capacity to grow to a size that allows them to be retained in the stomach and their adaptability to withstand premature emptying by the powerful propulsive forces of the stomach, their findings demonstrated that the tetrahedron- and ring-shaped devices provided longer GRTs and greater retention than the other shapes (i.e., cloverleaf, string, pellet, and disk).[71,72]

b. Size

As was previously mentioned, the length of time that gastric retention lasts can also be influenced by the size of a dose form. With a diameter of 12.8 ± 7 mm when at rest, the human pylorus serves as a sieve to filter the contents of the stomach. Its diameter should therefore be regarded as a significant value for the stomach emptying of various sized dose forms. For non-disintegrating pills of various sizes, varying gastric-emp tying times have been documented.[73] Larger tablets are often discharged during the "housekeeping" waves, whereas smaller ones are emptied during the digesting phase.

2. Patient Posture

Timmermans et al. found that patients who received floating units while lying down retained the dosage form for a longer period of time. However, the size of the dose form had the biggest impact on this extended retention, and buoyancy was no longer a benefit for gastric retention.[75] This was caused by the floating dose form being placed near the pyloric sphincter in the supine posture, which selectively empties the particles according to their size. Wilson and others.[76] have also shown how posture affects stomach emptying in patients who take floating dose forms and then lie on their backs to sleep.

3. Effect of Food

Multiparticulate systems freely disperse throughout the GIT and empty more consistently when food is present in vivo. Single-unit systems, on the other hand, experience an emptying that is "all-or-nothing." As a result, using multi-unit formulations rather than single-unit ones frequently produces consistent gastric-emptying patterns, less intersubject variability in absorption, and a decreased likelihood of dose dumping.[77]

Optimization Studies of FDDS

The variety of designs and the impact of different formulation variables on performance highlight the necessity of FDDS optimization. Floating dosage forms can be as basic as a tablet or capsule or as sophisticated as multilayered, multiparticulate microspheres, depending on the kind of system. The floating kinetics and gastrointestinal retention of the floating dosage forms have been found to be significantly impacted by formulation factors, including the amounts of gas-generating agents, release-modifying polymers, manufacturing aids like lubricants or glidants, and low-density excipients.[78-81] The time needed for the development work can be decreased by optimizing these formulation variables utilizing experimental designs, which enable the evaluation of different processing and formulation parameters influencing the chosen answers with the fewest number of experiments.[82]

Characterization parameter

- **Size and shape evaluation: -**The size and shape of the particles have a big impact on how soluble the medication is and, consequently, how bioavailable it is. Sieve analysis, air elutriation analysis, picture analysis, optical magnifier, electro resistance numeration methods (Coulter counter), geological phenomenon techniques, optical maser optical phenomenon methods, ultrasound attenuation spectrographic analysis, pollution emissions measurements, etc. were used to determine the formulation's particle size.[83]
- **Surface topography: -** Utilizing a scanning microscope (SEM, JEOL JSM – 6701 F, Japan) equipped with an acceleration voltage of 10k.v, a contact angle meter, atomic force research (AFM), and a contact profiliometer, the surface topography and structures were identified.[84]
- **Determination of moisture content**:- Rarely is the water content intrinsically interesting. Instead, it shows whether a result presumed for production and commerce has typical characteristics such as

- The ability to store.

- Agglomeration in powdered materials
- Stability of microbes
- The stability of bacteria
- Content of dry substances
- Purity or concentration
- Business grade (adherence to quality standards).[85]

➢ **Swelling studies:-** In order to determine the molecular variable of swelled polymers, swelling studies were developed. Swelling studies were identified by the use of dissolution equipment, optical research, and other delicate approaches that include imaging, such as light-weight scattering imaging (LSI), refrigerant scanning microscopy (Cryo-SEM), confocal optical maser scanning research (CLSM), etc. The following formula was used to calculate the swelling studies conducted using exploitation Dissolution Equipment (USP dissolution equipment (usp-24) lab India dissolution 2000).[86]

➢ **Drug content: -**The amount of the drug that was present in the formulation is indicated by the percentage drug content. It shouldn't go beyond the limits that the excellent monographs don't inherit. Inductively Coupled Plasma Atomic Emission Spectroscope (ICPAES), close to infrared spectrographic analysis (NIRS), micro titrimetric methods, HPLC, HPTLC methods, and spectrographic analysis techniques were used to determine the drug concentration**.**[87-113]

➢ **Percentage entrapment efficiency: -** Defense by percentage Potency was a dependable way to measure the drug's portion distribution in the ready formulations. Three methods, such as tiny qualitative analysis methodology, immoderate activity, and pressure immoderate filtering, are used to determine defense potency.[53]

➢ **Floating time and dissolution: -** The take a look at for floating time measure is sometimes performed in stirred stomachic fluid or zero.1 mole/ lit HCl maintained at 37°C. It's determined by exploitation USP dissolution equipment containing 900 milli-liter of zero.1mole/lit HCl because the dissolution medium at 37°C. The time taken by the dose type to float is termed as floating lag time and therefore the time that the dose type floats is termed because the floating or flotation time.[54-90] An additional relevant in-vitro dissolution methodology pro-posed to gauge a floating drug delivery system (for pill dose form).[91-100]

CONCLUSION

The most practical and widely used drug delivery mechanism is oral consumption. Patients best take conventional dosage forms however there are certain restrictions of these dosage forms such frequent dosing, greater possibilities of skipping dose of drug etc. Because of these restrictions, controlled- and sustained-release dose formulations received more attention.

One method for sustained-release is gastroretention. Research and development of gastroretentive medication delivery systems has advanced scientifically and technologically in recent years. The most effective method for achieving gastroretention is the Floating Drug Delivery System (FDDS). FDDS stay afloat in the stomach because they have a lower bulk density than gastric fluids. Although there isn't yet a perfect system that will stay in the stomach for a longer period of time, some formulations exhibit higher bioavailability than the current ones. For medications with delayed and insufficient intestinal absorption, the FDDS are helpful. Despite several challenges in the production of FDDS, many businesses are concentrating on commercializing this method.

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