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FLOATING *IN SITU* GEL: AN APPROACH FOR IMPROVED BIOAVAILABILITY

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ABSTRACT

The development of *in situ* gelling systems that are gastro retentive has sparked renewed interest in academia and industry. This is because the *in situ* gelling system has many benefits, such as ease of administration and lower administration frequency, which promote patient compliance. A method called gastric retentive drug delivery can achieve site-specific drug release in the upper gastrointestinal tract for either a local or systemic effect by prolonging the gastric residence period. When floating drug delivery devices come into contact with stomach fluid, they float quickly. They have a low bulk density (1.00 g/cm3) and are buoyant enough to float above stomach fluid for a lengthy period of time while the medicine releases at the desired pace at a particular location. Such gel transformations are caused by one or more mechanisms, including physiological stimuli (for example, temperature and pH), physical changes in biomaterials (for example, solvent transport and swelling), and chemical reactions (for example, enzymatic, ionic, and photo initiated polymerization). *In situ* gelling systems can be formulated via different routes such as oral, nasal, ophthalmic, etc. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DLlactide-co-glycolide), and poly-caprolactone are used for formulation development of *in situ* forming drug delivery systems. Traditional oral dosage forms exhibit low bioavailability as a result of the stomach's quick emptying. The goal of this study is to conduct a review on a novel in-situ gel. The gastroretentive *in situ* gelling system helps to increase the bioavailability of the drug compared to conventional liquid dosage forms.

KEYWORDS: Gastroretentive *in situ* gel, floating drug delivery system, Gastroretentive *in situ* gelling system.

INTRODUCTION

The oral route is thought to be the most convenient for administering drugs because it is the least complicated. Since many traditional oral medication administration methods have some restrictions regarding quick stomach emptying times, gastric retention has drawn interest in recent years. With the ability to stay in the stomach region for several hours, the gastro retentive drug delivery system (GRDDS) greatly extends the duration that medications spend in the stomach. Extended stomach retention increases drug solubility, decreases drug waste, and increases bioavailability of medications that are less soluble in high pH environments.[1] Floating systems, bioadhesive systems, high-density systems, swelling and expanding systems, and other methods have been developed to accomplish gastric retention.[1-3]

Gastroretentive Drug Delivery System (GRDDS)

Nowadays, controlled and sustained drug delivery is expected in pharmaceutical design, and extensive study has been done to improve the effectiveness, safety, and dependability of therapeutic products. The fact that oral dosage forms are simple to handle and administer accounts for the high degree of patient compliance with these forms. Changing the GI transit time is a major difficulty in the development of oral controlled medication delivery systems. Pharmaceuticals' gastric emptying varies greatly and is influenced by the dosage form as well as the stomach's fed or fasted condition. Between five minutes and two hours is the typical range for stomach residence periods. Within There are four stages to the dosage form transition.

1. **Phase I:** Period of no contraction (40-60 minutes),
2. **Phase II:** Period of intermittent contractions (20-40 minutes),
3. **Phase III:** Period of regular contractions at the maximal frequency that travel distally. (10-20 minutes) and
4. **Phase IV:** Period of transition between phase III and phase I (0-5 minutes).

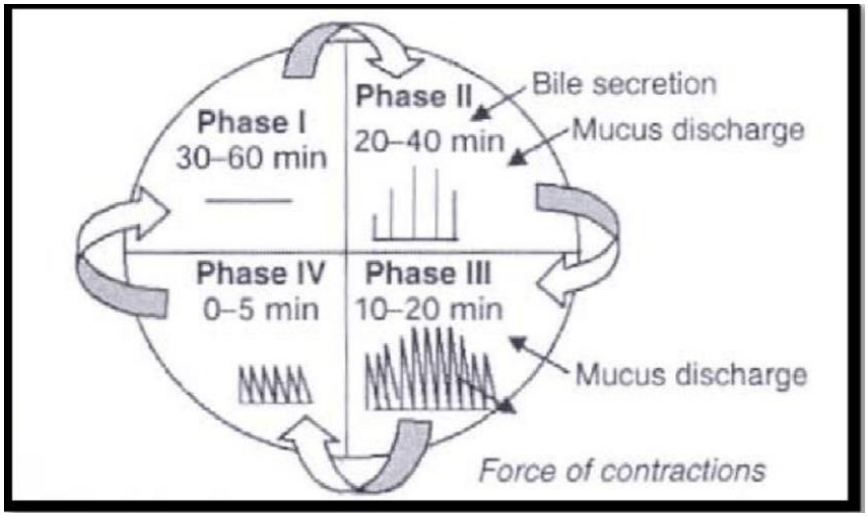


Figure 1: Dosage form Transition.

Various Methods of Gastroretention

Several methods were employed to promote stomach retention of an oral dose form, including:

• Hydro dynamically balanced systems (HBS).

• Effervescent system.

• Low-density systems.

• Raft systems incorporate alginate gels.

• Bioadhesive or mucoadhesive systems.[4-5]

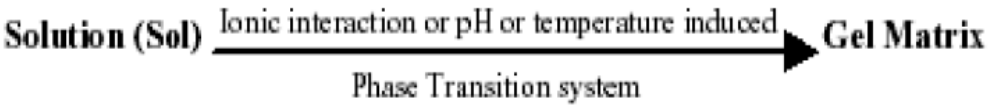
A) FLOATING DRUG DELIVERY SYSTEM

A novel approach in FDDS is the in-situ gelling mechanism. The *In-Situ* Gelling System can be administered through several channels, including the oral, nasal, ocular, peroral, rectal, vaginal, and parenteral routes. Because gastro retentive FDDS have a smaller bulk density than gastric fluid, they float in the stomach for a longer amount of time without slowing down the rate at which the stomach empties. When exposed to bodily fluids or a pH shift, *in situ* gelling systems, which are liquid at room temperature, gel. Due to the bioadhesive nature of the polymer, the gel created by the *in situ* gelling system sticks to the gastric mucosa or floats over the contents of the stomach, resulting in prolonged drug delivery in the gastrointestinal tract. Additionally, the gel produces gastric retention of the dosage form and lengthens the gastric residence time.

ADVANTAGES

- Administration simplicity and high compliance with patience.

- Delayed medication release combined with increased stomach retention.
- Reduces the frequency of dose.
- By acting directly onto the specified spot, it demonstrates a local action and site specificity.
- Effects are less severe than with other pharmaceutical dosage forms.
- Formulation flexibility.
- Production is simple.[6]



Floating drug delivery system(FDDS) can be divided into.

a) Effervescent system,
b) Non-effervescent system,
c) Microbaloons or hollow microspheres,
d) Hydrodynamically balanced system,
e) Alginate beads, and
f) Microporous compartment

B) NON FLOATING DRUG DELIVERY SYSTEM

Different processes allow these gastro retentive drug delivery systems to remain retained in the stomach while not floating. The non-floating system is further subdivided into.

a) High-density medication delivery device that sinks
b) Magnetic system;
c) Bio-adhesive or muco-adhesive system
d) Unfoldable system

A) FLOATING DRUG DELIVERY SYSTEM

a) Effervescent system

This system is composed of effervescent substances such as sodium bicarbonate, disodium glycine carbonate, cyto-glycine, citric acid, and tartaric acid, as well as swellable polymers like chitosan. The formulation floats in the stomach because the system produces carbon dioxide when it comes into touch with gastric juice.[7] Multiple unit pills and single unit matrix tablets are further divisions of this method. A single unit matrix tablet could have one or more layers. Additionally, floating systems using ion exchange resins have been

documented. Figures 2 and 3 depict an effervescent system and the medication release from it, respectively.

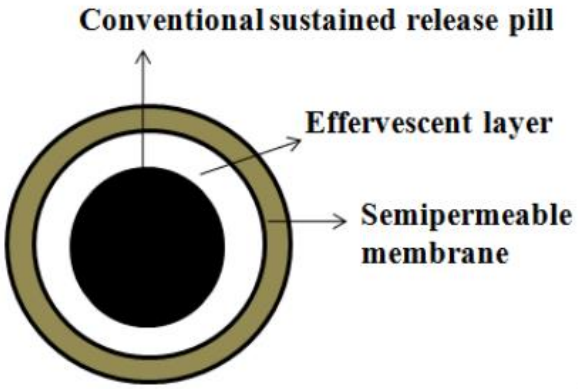


Figure 2: Effervescent system.

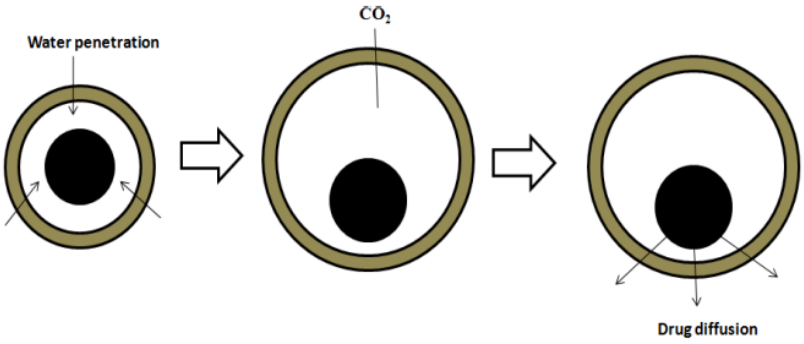


Figure 3: Drug Release From Effervescent System.

Non-effervescent system

Gel-forming or highly swellable hydrocolloids of the cellulose type, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene are employed in this system. This dosage form swells when it comes into touch with stomach juices after oral administration and achieves a bulk density of less than 1. The dose form is buoyant due to the trapped air inside the inflated matrix. Through the gelatinous mass, the so-formed swelling gel-like structure serves as a reservoir for the drug's continuous release. Superporous hydrogels are a prime illustration of this method in action. When the dose form comes into touch with stomach fluid, it swells dramatically to multiple times its initial volume. The dosage form is then forced into the pylorus by the stomach contraction, but because of the dosage form's bigger size, the contractions cause it to slide over the system's surface and push back into the stomach.[8]

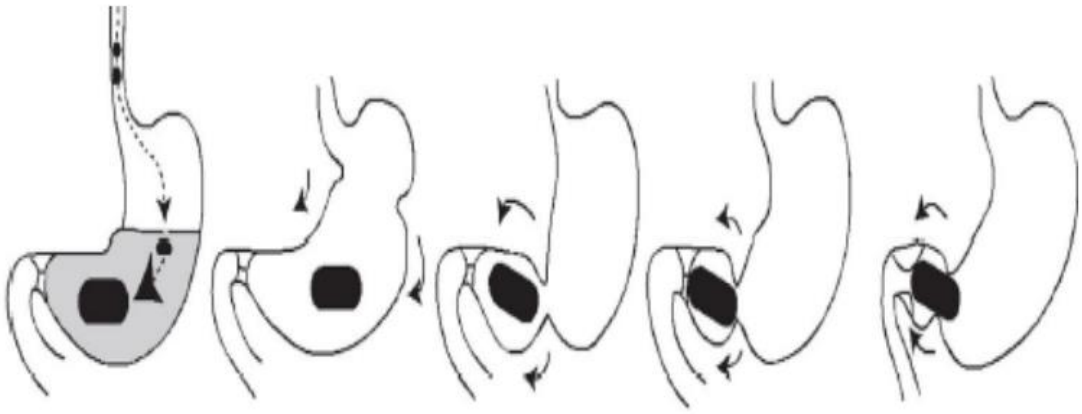


Figure 4: Gastric retention of highly swellable gastro retentive drug delivery system.

Alginate beads, microbaloons, microporous compartments, and a hydrodynamically balanced system are further categories for the non-effervescent system.

1. Hydrodynamically balanced system

First to design the hydrodynamically balanced system were Sheth and Tossounian. Medication containing gel-forming hydrocolloids designed to stay buoyant on stomach contents is part of a hydrodynamically balanced system.[9] One or more gel-forming cellulose-type hydrocolloids, such as agar, carrageen, hydroxypropyl methylcellulose, hydroxypropyl cellulose, or alginic acid, are present in this system. Additionally, matrix-forming polymers such polyacrylate, polystyrene, and polycarbophil are present. Such a system hydrates its hydrocolloid and produces a colloid gel barrier around its surface when it comes into touch with gastric fluid.

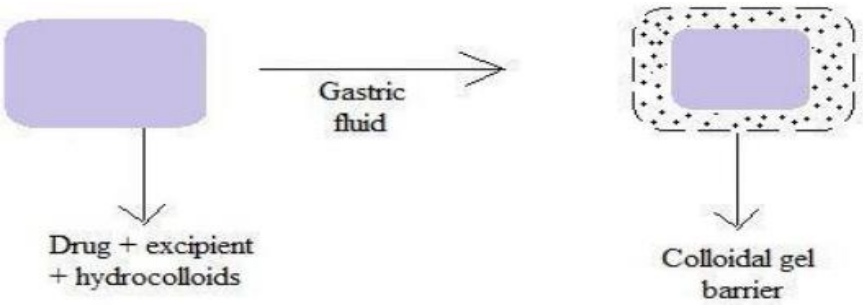


Figure 5: Hydrodynamically Balanced System.

2 Microbaloons or hollow microspheres

The emulsion-solvent diffusion method is used to create hollow microspheres, or microbaloons, that are loaded with the medicine within their outer polymer shells. Figure 6 provides an overview of the processes in this process. A 40°C agitated polyvinyl alcohol

aqueous solution is filled with an acrylic polymer and a 1:1 ethanol: dichloromethane solution. The interior cavity in the polymer microsphere containing the medicine is formed by the gas-phase that is produced in the dispersed polymer droplet by the evaporation of dichloromethane. For nearly 12 hours, the microballoons remain suspended above the surface of surfactant-containing acidic dissolving media.[10]

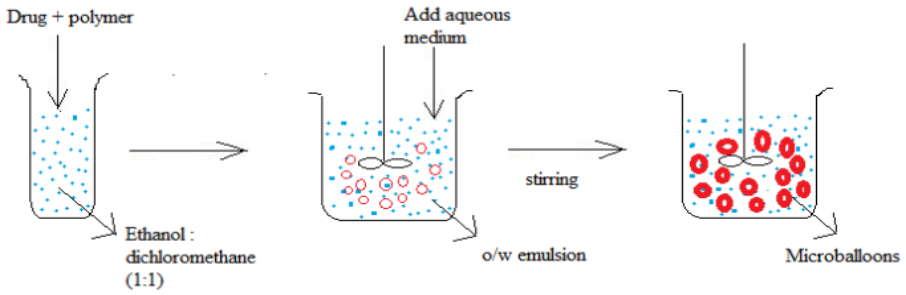


Figure 6: Preparation of Microballoons.

3 Alginate beads

Multi-unit floating dose forms have been developed using freeze-dried calcium alginates.[11] Aqueous calcium chloride solutions can be used to create spherical beads with a diameter of approximately 2.5 mm by dropping sodium alginate solution into them. We separate and let air dry these beads. As a result, the stomach develops a porous system that stays buoyant.

4 Microporous compartment

The drug reservoir in this system is enclosed inside a microporous compartment with pores running the length of its top and bottom walls (Fig. 7). The entrapped air in the flotation chamber causes the delivery system to float above the stomach content. Through the opening, gastric fluid enters the stomach, dissolves the medication, and transports it to the stomach and the first section of the small intestine for absorption.

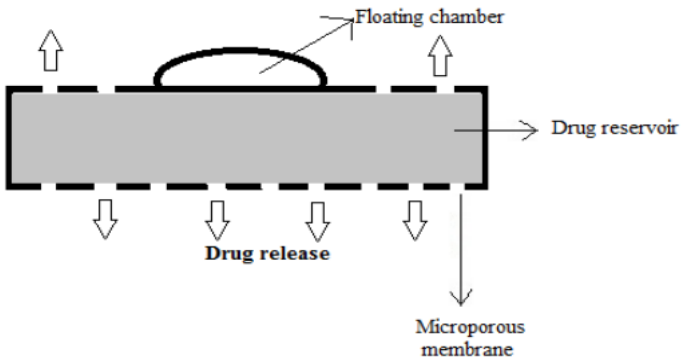


Figure 1: Microporous Compartment.

B NON FLOATING

SYSTEM

1 High-density medication delivery device that sinks

This method involves creating formulations that are denser than the typical gastric content by either coating the medication on a hefty core or combining it with inert substances including iron powder, barium sulphate, zinc oxide, and titanium oxide.[12] The density can be increased by these materials to 1.5–2.4 gm/cm3. They can prolong pellets' GI transit time, which ranges from an average of 5.8 to 25 hours, depending on density. However, they failed to note the system's efficacy in people, and no commercial formulation has been released.[13]

2 Bio-adhesive or muco-adhesive system

The stomach retention duration is extended to the gastric mucosal barrier by the bioadhesive system's adherence (Fig. 8). The delivery system's adhesion to the stomach wall lengthens its residence period, which boosts bioavailability. Polycarbophil, carbopol, lectin, chitosan, carboxymethylcellulose, gliadin, and other substances are utilised in macroadhesion.[14] The stomach wall's propulsive force, however, is typically too great for the gastric mucoadhesive force to withstand. Another drawback of such a system is the constant generation of mucus and dilution of the stomach content. A synergistic approach involving floating and bioadhesion systems has been tested by numerous researchers.

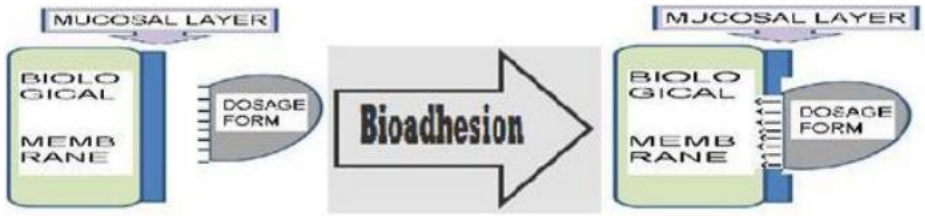


Figure 8: Bio-Adhesive System.

3 Magnetic system

A small magnet is contained in the dosage form, and an additional magnet is applied to the abdomen over the stomach position. This arrangement should reduce patient compliance by applying the external magnet precisely.

4 Unfoldable system

The medication delivery mechanism expands and unfurls, staying anchored at the sphincter to prevent it from leaving the stomach (Fig. 3 and 4). To do this, the system needs to be small

enough to be ingested, but it also needs to unfold itself when it comes into touch with stomach juices. Finally, it needs to get smaller over time so that it can be swiftly removed.[15]

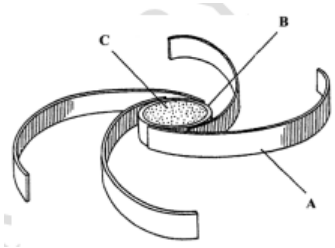


Figure 9: Partially unfolded dosage form.

METHODS[16]

The *in situ* gel formation is triggered by a variety of mechanisms, including physical changes in biomaterials (such as swelling and solvent diffusion), chemical reactions (such as enzymatic, chemical, and photo-initiated polymerization), and physiological stimuli (such as temperature and pH).

BASED ON PHYSICAL CHANGES

- **SWELLING**

The process of in-situ gel production involves the absorption of water by polymeric lipid, which then expands to occupy the appropriate space. One such material is myverol 18-99, also known as glycerol mono-oleate, a polar lipid that expands in the presence of water to produce liquid crystal phase structures. It can be broken down in vivo by the stomach's enzymatic action and possesses certain bioadhesive qualities**.**

- **DIFFUSION OF SOLVENT**

This technique causes the polymer matrix to precipitate or solidify as a result of the solvent from the polymer solution diffusing into the surrounding tissue. For such a system, N-methyl pyrrolidone (NMP) solvent is helpful.

BASED ON CHEMICAL REACTION

Enzymatic, photo-initiated, and precipitation of inorganic particles from supersaturated ionic solutions are examples of chemical reactions that lead to insitu gelation.

- **IONIC CROSSLINKING**

Phase transitions in polymers can occur in response to different ions. Certain polysaccharides, like sodium alginate, rotacarrageenan, gellan gum (Gelrite®), and pectin, are classified as

ion-sensitive polymers because they change phases when different ions like K+, Ca2+, Mg2+, and Na+ are present. For example, when divalent or polyvalent cations, such as Ca2+, are present, alginic acid gels because of its interaction with the guluronic acid block in alginate chains.

- **ENZYMATIC CROSSLINKING**

In situ gelling system creation is best achieved via enzymatic cross-linking. Using this technique, gel is created by creating cross links with the enzymes found in bodily fluids. Although they haven't been studied extensively, *in situ* creation caused by natural enzymes seems to have certain benefits over chemical and photochemical processes. An enzymatic process, for instance, manages efficacy under physiological conditions and eliminates the requirement for potentially harmful substances like initiators and monomers. Insulin-releasing hydrogel-based intelligent stimuli-responsive delivery systems have been studied. Adjust the enzyme concentration while keeping up a functional mechanism that admits the mixes were introduced prior to gel formation, hence regulating the rate of gel formation.

- **PHOTOPOLYMERISATION**

Electromagnetic radiations are utilised in the photo-polymerization approach to generate the *in situ* gelling system. An invading and reactive macromere or monomer solution can be injected into a tissue location, and gel can be formed by applying electromagnetic radiation. The best polymers for photopolymerization are those that can be broken down by a polymerisable functional group when exposed to a photoinitiator such as acrylate or a similar monomer. Long wavelength ultraviolet and visible macromers are usually employed in photopolymerization. Because short wavelength ultraviolet light has a limited tissue penetration and is biologically hazardous, it is rarely employed frequently. This technique uses ketone as the ultraviolet photo-polymerization initiator, such as 2,2 dimethoxy-2-phenyl acetophenone. ethyl eosin initiators and camphorquinone are utilised in visible.

BASED ON PHYSIOLOGICAL STIMULI

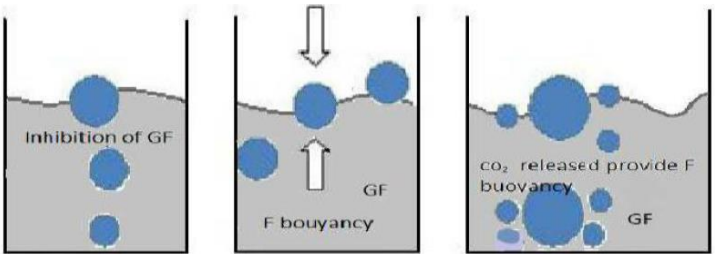
- **TEMPERATURE DEPENDENT *IN SITU* GELLING**

Thermally activated *in situ* gel In the formulation of *in-situ* gelling, temperature is the most frequently utilised stimulus in environmentally responsive polymer systems. The Temperature changes are simple to implement and manage, both *in vitro* and *in vivo*. In this technique, body temperature causes gelation; external heat is not required. When these

hydrogels come into touch with bodily fluids, their liquid state changes to a gel state (35–37°C) as a result of a rise in temperature. Temperature-induced systems come in three varieties. They can be classified as thermally reversible (polloxamer, pluronics, Tetronics), positively thermosensitive (poly (Nisopropylacrylamide), or negatively thermosensitive (polyacrylic acid). Thermoresponsive or temperature-responsive polymers—which exhibit abrupt, sharp changes in their physical characteristics with temperature—are employed in this system. There is a miscibility gap between these polymers at high and low temperatures.

- **pH TRIGGERED *IN SITU* GELLATION**

Changes in pH cause gel to develop in this system. This technique uses pH-responsive or pH-sensitive polymers. pH-sensitive polymers contain pendant basic or acidic groups that can take or release protons in response to pH variations in their surroundings. Poly electrolytes are large-scale polymers with ionizable groups. Because the formulation contains poly electrolytes, the external pH rises, which causes the hydrogel to swell and create *in situ* gel. Anionic polymers are among the appropriate polymers for this strategy. Among them are polyethylene glycol (PEG), pseudo latexes, carbomer and its derivatives, cellulose acetate phthalate (CAP), poly methacrilic acid (PMC), etc.



F= F buoyancy- F gravity = (Df – Ds) gv

Where, F = total vertical force,

Df = fluid density,

Ds = object density, V = volume, and

g = gravitational acceleration.

EVALUATION

A. *IN VITRO* EVALUATION

1) GENERAL TEST

These assessments cover appearance, consistency of content, drug content, hardness, friability, and weight variation.

2) FLOATING SYSTEMS

a) Buoyancy Lag Time

Lag in buoyancy After the dosage form is inserted into the dissolution media, the amount of time it takes for it to float on top of the medium is measured. The dissolving test may include measurements of these factors**.**

b) Floating Time

Floating time is the amount of time that the dose form remains constantly afloat on the dissolving medium. Typically, it is carried out in 370°C Simulated Gastric Fluid.

c) Specific Gravity/Density

Benzenes displacement medium can be used in the displacement method to measure density.

3) SWELLING SYSTEMS

a) Swelling Index

The dosage form is extracted at regular intervals after being submerged in 370C Simulated Gastric Fluid to cause swelling. Dimensional changes are then quantified in terms of the increase in tablet thickness/diameter over time.

B) *IN VIVO* EVALUATION

a) Radiology

A common radio opaque marker is barium sulphate. Internal bodily systems are examined using X-rays. In order to observe stomach retention, BaSO4 is integrated into the dose form and X-ray images are obtained at different intervals.

b) Gastroscopy

Using a gastroscopy, one can physically examine the impact of stomach lengthening.

c) Scintigraphy

Emitting elements are integrated into the dose form, much like in X-rays, and scintigraphy is used to capture images. One common emitting substance is technetium, or 99mTc pertechnetate.

d) Ultrasonography

Because it cannot be traced back to the gut, it is not commonly employed.

e) Magnetic Marker Monitoring

This method is safe because it doesn't use radiation. Using this method, iron powder is added to the dosage form to magnetically mark it, and sensitive bio-magnetic measuring apparatus can capture photos.[15,17,18]

C) WATER UPTAKE BY THE GEL

The release of the medication from the polymer matrix is significantly influenced by the water content of the drug delivery system. The primary mechanism of drug release is water seeping into the matrix, which is followed by the drug's simultaneous release via breakdown or diffusion.

D) MEASUREMENT OF DENSITY OF THE GEL

When assessing the buoyant ability of the gastroretentive dose form, density is a crucial criterion. The formulation's density must be less than or equal to the gastric contents (~1.004 gcm−3) in order for it to float on top of the contents of the stomach.

E) MEASUREMENT OF GEL STRENGTH

The gelled mass's tensile strength can be inferred from the gel strength. It shows that the gelled mass can tolerate peristaltic movement in an *in vivo* setting.[19]

F) STABILITY STUDIES

The parameters for accelerated stability studies were 40±2˚C at 75±5% relative humidity, while the room temperature storage condition was 25±5˚C and 65% RH. The test for stability will last for 30 days.[20]

APPLICATION OF THE FLOATING *IN SITU* GELLING SYSTEM:

1) Increased Absorption

Medications that are mostly absorbed from the upper portion of the stomach have longer contact times at the location of greatest absorption. As a result, the degree of absorption increases.[21]

2) Improved Bioavailability

The drug's bioavailability significantly increases as its absorption from the stomach increases. A longer stomach transit time also results in a higher medication bioavailability.[22]

3) Less Adverse Effect Of Drug

The frequency of the bad effect on the colon reduces to a greater extent as the medicine stays in the stomach until it is completely released.[23]

4) Site Specific Drug Delivery

The absorption rate increases when drugs received from the stomach have sufficient residence time for absorption. Furthermore, a lower dose is needed because the drug's local activity in the stomach is sustained.[24,25]

CONCLUSION

The development of an efficient gastroretentive dosage form for targeted stomach-specific drug delivery poses a significant challenge. Among various strategies employed to achieve the desired gastroretention, the floating drug delivery system has emerged as a highly promising technique. Within this approach, the floating *in situ* gelling system stands out, as it undergoes a transition from sol to gel in the acidic conditions of the stomach. This transition allows for prolonged drug release specifically in the stomach, while the system remains buoyant on the gastric fluid surface. These systems offer advantages such as enhanced absorption of drugs that are absorbed from the upper part of the stomach. The prolonged contact time with gastric mucosa leads to increased local action of the drug, resulting in less frequent dosing and improved treatment efficiency. Understanding the floating and gel-forming behavior of polymers is crucial for enhancing gastric retention and improving the bioavailability of various pharmacologically active agents. Compared to traditional oral dosage forms, the floating oral *in situ* gelling system boasts several benefits in terms of formulation and assessment. A highly effective drug delivery system can be achieved by combining natural and synthetic polymers in the *in situ* gel formulation process. Gaining insights into the behavior of polymers that exhibit both floating and gelling properties is essential for optimizing stomach retention and, consequently, enhancing the bioavailability of different medications.

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