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Formulation And *In Vitro* Evaluation Of Floating Tablets Of Itopride Hydrochloride

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ABSTRACT
Itopride Hydrochloride is a gastroprokinetic agent primarily effective in the abdomen. Due to its optimal pH ranges of 3.5-5.5, floating tablets of Itopride Hydrochloride are designed to prolong gastrointestinal residence time at specific sites, thereby enhancing plasma bioavailability. The floating tablets were formulated using the direct compression technique, incorporating hydrophilic polymers such as HPMC K4M, Carbopol 934P, and Xanthan gum to act as release-retarding agents. Effervescent agents, including sodium bicarbonate and citric acid, were used in varying ratios to optimize their impact on the drug release profile. The prepared formulations underwent a series of evaluations, including physical characterization, assay, hardness, friability, weight variation, and in vitro drug release studies. The results indicated that formulation batch F2 demonstrated an optimal drug release profile, achieving 98.20% release over 12 hours.

Keywords: Itopride Hydrochloride, gastroprokinetic agent, floating tablets, gastrointestinal residence time, hydrophilic polymers, drug release profile

INTRODUCTION

Gastro-Retentive Drug Delivery System: An Overview

The oral route is the most common and convenient method for drug administration, where the drug enters the gastrointestinal tract after ingestion. However, in the development of gastro-retentive drug delivery systems (GRDDS), the primary objective is to maintain the drug in the stomach for a prolonged period, allowing for enhanced drug absorption, increased bioavailability, and controlled release of the therapeutic agent. One such system is the floating drug delivery system (FDDS), which is designed to achieve buoyancy in the gastric fluid. The buoyant properties are achieved by reducing the density of the dosage form to be less than that of the gastric fluid. This is typically accomplished by incorporating low-density excipients or fillers into the formulation. However, maintaining the dosage form in the stomach is a challenge due to the variability in gastric emptying time, which typically ranges from 2-3 hours in humans, and the potential for low drug solubility in a high pH environment as the drug passes into the intestines. These factors can lead to incomplete drug release and reduced therapeutic efficacy.

To address these challenges, GRDDS aims to retain the drug in the stomach for an extended period, facilitating better absorption in the gastric environment. This is particularly useful for drugs that are more soluble at the acidic pH of the stomach and exhibit poor solubility or stability at higher pH levels found in the intestines. By maintaining the drug in the stomach, gastro-retentive systems help reduce drug waste, enhance bioavailability, and provide more consistent therapeutic outcomes.

Currently, several approaches are used to enhance gastric retention of drugs, including:

- Mucoadhesive systems: These formulations adhere to the gastric mucosa, prolonging the residence time of the drug.
- Raft-forming systems: These systems form a viscous layer or raft on the gastric contents, preventing the drug from leaving the stomach.

- Low-density systems: These systems float on the surface of gastric fluids due to their low density, ensuring prolonged retention in the stomach.
- Swelling and expandable systems: Upon contact with gastric fluids, these formulations swell or expand, making it difficult for them to pass through the pylorus.
- Super porous hydrogels: These materials rapidly swell to a size large enough to prevent passage through the gastric outlet.
- Magnetic systems: These use magnetic materials to hold the drug in the stomach by external magnetic fields.
- Self-unfolding systems: These systems unfold to a larger size after ingestion, preventing their passage through the stomach.
- High-density systems: These systems settle in the lower part of the stomach, where gastric emptying is slower.
- Floating dosage forms: These are typically matrix-based tablets that contain the drug within a buoyant matrix. When in contact with gastric fluids, the matrix slowly erodes, releasing the drug gradually.

Floating tablets are particularly advantageous for drugs that are slowly released, as the matrix system allows the drug to come into contact with gastric fluids and erode over time, releasing the drug in a controlled manner.

Gastro-retentive drug delivery systems offer a significant advantage by prolonging gastric residence time, which in turn enhances the bioavailability of drugs, decreases drug waste, and improves the solubility of drugs that may have limited solubility in higher pH environments like the intestines. This prolonged retention can lead to more effective therapeutic outcomes, especially for drugs that are unstable or poorly absorbed in the intestines.[2]

Basic Physiology of the Gastrointestinal Tract (GIT)

The stomach, a crucial organ in the gastrointestinal tract (GIT), is anatomically divided into three primary regions: the fundus, body, and antrum (pylorus). Each of these regions plays a distinct role in the digestive process.

- Fundus and Body: These form the proximal part of the stomach, primarily acting as a reservoir for undigested food. The body and fundus allow for the storage and gradual breakdown of ingested materials before they are processed further.
- Antrum (Pylorus): The distal portion of the stomach, the antrum, serves as the main site of mixing and grinding of food. It also functions as a pump to facilitate gastric emptying, pushing the food content into the small intestine through rhythmic contractions.

Gastric emptying occurs in both the fasting and fed states. However, the pattern of motility differs between these two states. In the fasting state, the stomach undergoes a cyclic electrical activity known as the interdigestive myoelectric cycle or migrating myoelectric complex (MMC). This cycle repeats every 2-3 hours, and is responsible for sweeping undigested food and secretions from the stomach and intestines to prepare the digestive tract for the next meal.

The MMC is divided into four distinct phases:

1. Phase I (Quiescent Period): This phase is characterized by the absence of contractions. It is a period of inactivity lasting for 30-60 minutes.
2. Phase II (Irregular Contractions): In this phase, intermittent and irregular contractions begin, gradually increasing in intensity. This phase lasts for 20-40 minutes.
3. Phase III (Burst of Activity): This phase is marked by regular, intense contractions, also known as the "housekeeper wave." These contractions help clear out any residual food particles or secretions from the stomach and small intestine. It lasts for 5-10 minutes.
4. Phase IV (Transition): This is the short transitional phase between the intense activity of phase III and the quiescent period of phase I.

In the fed state, the presence of food in the stomach alters the motility pattern. The MMC is replaced by continuous, irregular contractions that facilitate the digestion and processing of ingested material. These

contractions ensure thorough mixing of food with gastric secretions and promote gradual emptying of the stomach contents into the small intestine.

Understanding the basic physiology of the stomach and its motility patterns is essential for the design of gastro-retentive drug delivery systems, as these systems aim to prolong the residence time of drugs in the stomach by taking advantage of these physiological processes.[3]

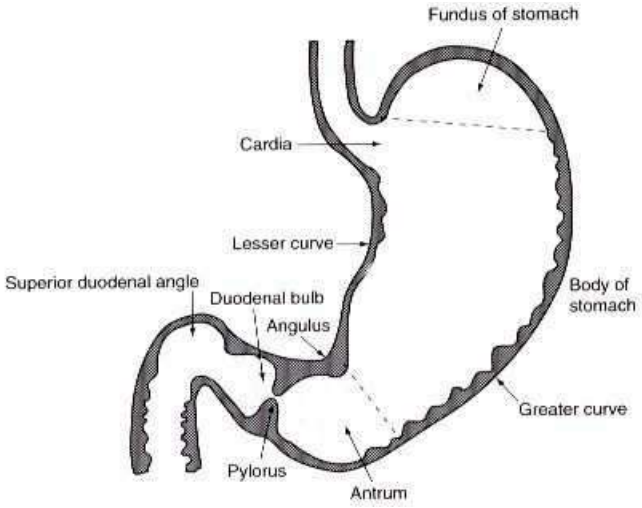

Fig 1: Basic Physiology of the Gastrointestinal Tract

Migrating Myoelectric Complex (MMC), also known as the interdigestive myoelectric cycle, is divided into four distinct phases, each playing a critical role in the regulation of gastric motility during the fasting state. These phases are essential for clearing the stomach and intestines between meals:

1. Phase I (Basic Phase):
   - Duration: 30-60 minutes
   - Characterized by uncommon contractions or a quiescent period, during which there is minimal or no electrical or mechanical activity. This phase is a period of rest for the gastrointestinal tract.
2. Phase II (Preburst Phase):
   - Duration: 20-40 minutes
   - Marked by intermittent action potentials and contractions. During this phase, electrical and mechanical activity gradually increases, preparing the stomach and small intestine for the burst of activity that follows.
3. Phase III (Burst Phase):
   - Duration: 10-20 minutes
   - This phase involves intense and regular contractions that occur for a short period. These powerful contractions serve as a "housekeeping wave," sweeping any remaining food, secretions, or debris from the stomach and small intestine into the colon.
4. Phase IV:
   - Duration: 0-5 minutes
   - A brief transitional phase that occurs between Phase II and Phase I of consecutive MMC cycles. It is a short period that leads back to the quiescent state of Phase I.

These four phases repeat every 2-3 hours during the fasting state, helping to ensure that the stomach and intestines remain clear of residual contents in preparation for the next meal. Understanding these phases is crucial for optimizing drug delivery systems, particularly gastro-retentive formulations, which rely on prolonged retention in the stomach.[4]

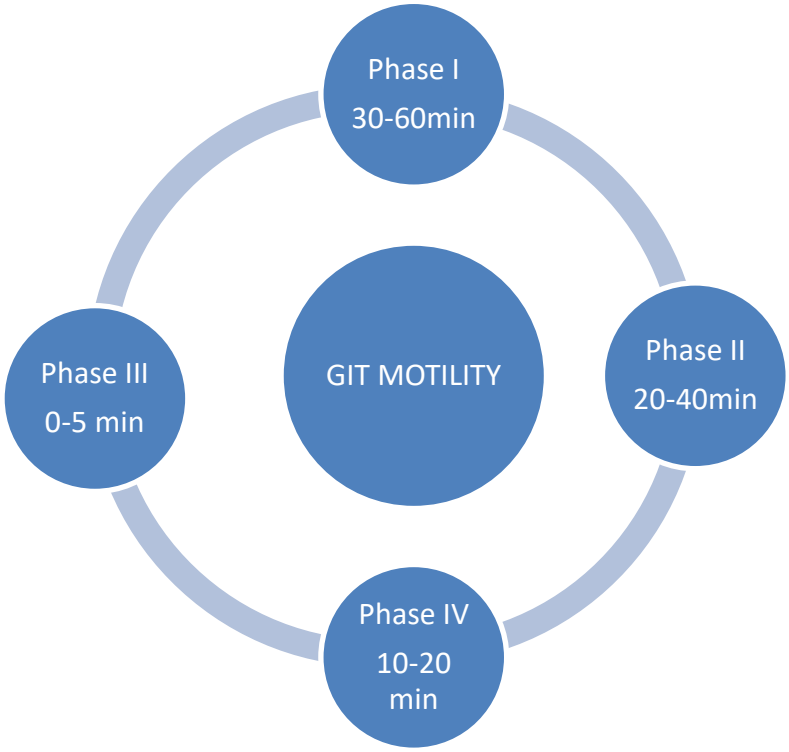

Table 1: Potential candidates of gastroprotective drug delivery system-[5, 6]

S.NO.	DRUGS	EXAMPLES
1.	Narrow absorption window in GIT	L-DOPA, p-aminobenoic acid.
2.	Locally active in the stomach	Misroprostol, antacids.
3.	Unstable in the intestinal or colonic environment.	Captopril, ranitidine, metronidazole.
4.	Disturb normal colonic microbes	Antibiotic used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin.
5.	Exhibit low solubility at high ph values.	Diazepam, chlorrdiazepoxide, verapamil.

Table 2: Factors affecting of gastroprotective drug delivery system- [7, 8, 9, 10, 11, 12]

S.NO.	FACTORS AFFECTING FDDS	
1.	Particle size	Should be range in the 1-2mm.
2.	Density	Should be range of the dosages form 1 g/cm3 to 2.5 g/cm3.
3.	Size & shape of dosages form	Size of dosages form should be greater than 7.5mm in diameter & shape of dosages form should be ring & tetrahedron devices with flexural.
4.	Single unit/multiple unit	Multiple units are preferable because of predictable release profile, co-administration of different units, larger safety margins.
5.	Food intake	Gastric retention times is longer in fed states.
6.	Nature, caloric content	Indigestible polymers, fatty acid salts, increase caloric content, increase acidity increases gastric retention time, fat & protein meal increases GRT.
7.	Frequency of intake	Gastric retention time increases 400 times & due to low frequency of MMC.
8.	Posture	Varies between spine & upright ambulatory states.
9.	Gender	Males have greator GRT than females.
10.	Age	70 shows longer GRT

11.	Nature of drug	Drug with impaction GIT eg. Codeine & pharmokinetic agents
12.	Other factors	Body mass index, physical activity, molecular weight, lipophilicity of the drug.

Floating Drug Delivery System (FDDS)

The Floating Drug Delivery System (FDDS), also known as the Hydrodynamically Balanced System (HBS), is designed to remain buoyant in the stomach for an extended period by having a bulk density lower than that of gastric fluids. This buoyancy allows the system to float on the stomach contents without affecting the gastric emptying rate, while slowly releasing the drug at a controlled rate. Once the drug has been fully released, the remaining system is emptied from the stomach.

The prolonged retention of the drug delivery system in the stomach results in an improved gastric retention time (GRT), which enhances drug absorption, bioavailability, and provides better control over fluctuations in plasma drug concentration. This ensures a more consistent therapeutic effect, especially for drugs that have limited solubility in the intestinal environment or are primarily absorbed in the stomach.

Floating Drug Delivery Systems are classified into two categories:

1. Non-effervescent Systems:
   - These systems rely on the swelling of polymers to create a gel-like barrier that traps air and helps the system remain buoyant in gastric fluids.
2. Effervescent (Gas-generating) Systems:
   - These systems generate gas (e.g., carbon dioxide) through a chemical reaction between acids and carbonates or bicarbonates. The gas becomes trapped in the matrix of the delivery system, causing it to float on the stomach contents.[13,14]

Advantages of FDDS-

- Improve patient compliance by reduced dosing frequency.
- Drug that has less half-life to give prolong activity.
- GRT is improved because of buoyancy.
- Drug releases for a prolong period of time in a controlled manner.
- Improved absorption of drugs that only dissolve in the stomach.
- Single unit is better for floating dose forms because such microspheres leave the drug evenly and there is no risk of dose dumping.
- Release of drugs for local action in the abdomen. [15,16]

Limitations of FDDS -

1. Aspirin and NSAID'S can cause gastric lesions and slow release of such medication
stomach is unwanted.
2. Drugs such as isosorbide dinitrate that are evenly absorbed throughout the GIT would not benefit from inclusion in the gastric retention system.
3. The high turnover of bioadhesion and mucus in acidic environments may raise questions on the effectiveness of the technique.
4. Physical integrity of the system is very essential and primary requirement for system success.
5. High variability in gastric emptying time due to variations in emptying process , unpredictable bioavailability.[17]

CLAASIFICATION OF FDDS –

Floating drug delivery system are classified into three types –

1. Single unit floating dosages system -

I. Effervescent system (gas generating system)

ii. non-effervescent system

2. Multiple unit dosages system –

I. effervescent system

ii. Non – effervescent system
iii. Hollow microsphere
3. Raft forming system
1. Single Unit Floating Dosage Systems -
Single unit dosage forms are easiest to extend but suffers from the risk of losing their effects too early due to their all or none emptying from the stomach and, thus they may reason high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the GIT.[18]
Single unit floating dosages form are two types-
I. Effervescent Systems (Gas-generating Systems)-
These are the matrix type of system

↓

Prepared with the help of swellable polymers such as Methylcellulose & chitosan and various type of compound For ex.-NaHCO3, tartaric acid & citric acid.

↓

And they are formulated in such a way contact with the acidic gastric contents, CO2 is liberated.

↓

And gets entrapped in swolle hydrocolloids, which provide buoyancy to the dosage forms.[19]
ii. Non-effervescent Systems-
Non-effervescent floating dosages systems are gel forming or swellable cellulose type hydrocolloids polymers such as polycarbonate, polyacrylate & polystyrene

↓

This formulation is prepared by the mixing of drug + gel or drug + hydrocolloid

↓

They are contact with gastric fluids they make a swell dosage form and formed gel-like structure

↓

commonly excipients are used in HPMC, carpool, agar, polyacrylate.[20]

2. Multiple Unit Floating Dosage Systems-
Single unit formulations are connected with issues including sticking jointly or being obstructed in gastrointestinal tract, which may also have a ability danger of producing irritation. Multiple unit systems keep away from the „all-or-none" gastric emptying nature of single unit systems. It reduces the inter difficulty variability in absorption and the chance for dose dumping is lower.

Multiple unit dosages systems are three types-
I. Effervescent system –
In these systems are calcium alginate core & calcium alginate/ PVA membrane, both are prepared separated air compartment.

↓

The presence of water increase leaches out the PVA & increase the membrane permeability, maintaining the integrity of air compartment.
Freeze- drying technique also prepared the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise aqueous solution of calcium chloride & obtained beads are freeze- dried.

↓

Prolonged gastric residence time more than 5.5h was observed for floating beads, the non-floating beads had a shorter residence time with a mean onset emptying time of 1hr.

↓

ii. non-effervescent system –
In this effervescent multiple unit systems compared to the effervescent systems non-effervescent systems containing indomethacin using chitosan polymeric excipient.
The multiple unit HBS containing indomethacin as model drug prepared by extrusion process the mixture of drug + chitosan + acetic acid extruded through needle.

↓

The extrudate is cut & dried chitosan hydrates & floats in the acidic media, release required drug and obtained the modified drug polymer ratio.[21]

↓

iii. Hollow microspheres-

Hollow microspheres drug loaded with their outer polymer shelf prepared by a novel emulsion solvent emulsion solvent diffusion method.

↓

The ethanol/dichloromethane solution + drug + enteric polymer was poured into agitated solution of PVA (poly vinyl alcohol) & thermally controlled at 400c

↓

The gas stage is generated in the dispersed polymer droplet by the evaporation of dichloromethane created and internal cavity in the microsphere of the polymer with drug.[22]

3. Raft forming system-

Here, a gel-forming solution (e.g., Sodium alginate solution contain carbonate) swells and forms a sticky cohesive gel contain entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to decrease gastric acidity. Because raft forming systems create a layer on the top of gastric fluids, they are regularly used for gastro-oesophageal reflux remedy.[23]

MECHANISM OF FLOATING DRUG DELIVERY SYSTEM –

Various strategies have been developed to increase the retention time of dosage forms in the stomach in order to enhance drug absorption. These strategies include the introduction of floating dosage forms (gas-generating and swelling/expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delay devices, and the co-administration of gastric-emptying delay drugs. Among these, floating dosage forms are the most widely used.

Floating Drug Delivery Systems (FDDS) work by having a bulk density lower than that of gastric fluids, allowing them to remain buoyant in the stomach for an extended period of time without affecting the gastric emptying rate. Even while floating on the gastric contents, the drug is slowly released at the desired rate from the system. Once the drug is fully released, the remaining system is naturally emptied from the stomach. This prolonged gastric retention time (GRT) ensures better control of drug release and helps maintain more stable plasma drug concentrations, reducing fluctuations.

For the floating mechanism to function properly, it is essential to maintain a minimal amount of gastric content. Additionally, a minimum level of floating force (F) is required to keep the dosage form constantly buoyant on the surface of the gastric fluids. A novel apparatus has been reported in the literature to measure the floating force kinetics, specifically the force (F) needed to keep a submerged object floating as a function of time.

The apparatus continuously measures the force equivalent to F, which determines how well the system remains afloat. The dosage form floats more effectively when F is on the higher positive side. This tool aids in optimizing floating drug delivery systems in terms of stability and durability of floating forces, which is critical to prevent issues like variations in the intra-gastric buoyancy capability that could affect the drug's therapeutic efficacy.

$$F = F_{buoyancy} - F_{gravity}$$
$$= (Df - Ds)\, gv$$

Where, F= sum vertical force, Df = fluid densit ,Ds = object density, v = volume and g = acceleration due to gravity.

Floating systems are firstly described by Davis in 1968, have bulk density lower than that of the gastric fluid, and therefore remain buoyant in stomach for prolong period. [24, 25,]

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM –

1. Size and Shape Evaluation:

Particle size and shape the stage a main role in determining the solubility rate of drugs and therefore potentially its bioavailability. [26]

2. Drug-excipient interaction:

Drug-excipient interaction is done via using FTIR and HPLC. The occurrence of a new peak and/or disappearance of novel drug or excipient peaks be a sign of the drug excipient interaction.[27]

3.Angle of repose – The angle of repose determined by the funnel method and check the flow property of powder.

$$\text{Tan } \theta = h/rs$$

Where, h = height & r = radius of powder

4. weight variation test –

Twenty tablets are selected randomly from every batch and weighed individually to check for weight variation.[28]

Weight variation = Final weight- initial weight / Final weight

5. Bulk density – Bulk density refers to the total density of the material. It contains interparticles spaces and the correct amount of intraparticle pores. The packing of particles is mostly accountable for bulk. Bulk density is defined as: When particles are packed, it is achievable that a large amount of gaps may be present between the particles.

Bulk density = weight of powder blend/ untapped volume of the packing [29]

6.Tapped density- Tapped density is the relation of the total mass of the powder to the tapped volume of the powder.

Tapped density =weight of powder blend/ tapped volume of the packing [30]

7. Hausner's ratio –

Hausner's ratio is calculated by the tapped density/ bulk density.

8.Carr's compressibility index –

Compressibility index determine the tapped density – bulk density/ tapped density*100.[31]

9. Friability test – friability test is determined by the friabilator apparatus. The friabilator is operated at 25rpm for 4 min or run up to 100 revolutions. It is expressed in percentage %.

$$F(\%) = (1-Wo/W) *100$$

Where, Wo = weight of the tablets by the test.

W = weight of the tablets after test.

10. Hardness – hardness test is determined by Monsanto hardness tester & it is expressed is kg/cm.[32]

11. Floating Lag Time / Total Floating Time -

The time between the beginning of the tablet into the medium and its rise to upper one third of the dissolution vessel is term as floating lag time and the time for which the dosage form floats is term as the floating / flotation time/ Total floating time. These tests are generally performed in Simulated Gastric Fluid (SGF) or 0.1 N HCl (900ml) maintained at 37o C, by using USP dissolution apparatus as the dissolution medium.

12. Tablet swelling indices -

Tablet are weighed (W1) and located in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5° C. At usual time intervals, the tablet are removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet are then reweighed (W2). The swelling index (SI) is calculated by the formula:

S1= (W2-W1/W1)

Where,

W2 = Final Weight, W1 = Initial Weight

13. In vivo evaluation for gastro-retention-

This is passed out through the means of X-ray or Gamma scintigraphy monitoring of the dosage form transition in the GIT.

14. Percentage drug entrapment-

Percentage entrapment efficiency was consistent for quantifying the phase distribution of drug in the pre-pared formulations. The drug is extracted by a proper method, analyzed and is calculated from:

PDF = practical drug loading / theoretical drug loading *100

15. In vitro floating ability (Buoyancy %): -
The known quantity of microspheres is swell over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a dissector and weighed.
Buoyancy (%) = (Wf/ Wf + Ws)*100
Where, Wf and Ws are the weights of floating and total microspheres respectively. [33]
16. In vitro drug release -
In vitro release test is determined by using USP II apparatus (paddle) moving at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. New 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. A small, loose piece of non-reactive material such as not further than a few turns of wire helix can be attach to these dosage units that would otherwise float. [34]

CONCLUSION –

Based on the literature reviewed, it can be concluded that drug absorption in the gastrointestinal tract is a highly variable process. Prolonging the gastric retention of a dosage form increases the time available for drug absorption, leading to improved therapeutic outcomes. Various gastro-retentive drug delivery systems—including high-density systems, floating systems, expandable or unfoldable systems, swelling super porous systems, bio adhesive systems, and magnetic systems—have been developed to address this challenge.
Each system offers distinct advantages and disadvantages, depending on the drug's properties and the desired therapeutic effect. However, all of these gastro-retentive dosage forms share the common benefit of enhancing the absolute bioavailability of the drug, ensuring more efficient and prolonged absorption in the gastrointestinal tract

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