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Original Article

FDDS: A Novel Approach to Hydrodynamically Controlled System

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ABSTRACT

The majority of people prefer to take their medications orally. Numerous factors are crucial to the advancement of the medication distribution system. The drug delivery system has developed over time, and one component that has evolved is polymers. Molecules that consist of several monomer units connected by bonds are known as polymers. As an added bonus, floating drug delivery systems (FDDS) work well with medications that are mainly absorbed in the upper parts of the GI tract, which includes the stomach, duodenum, and jejunum. The goal of this review was to provide a comprehensive overview of floating drug delivery systems (FDDS), including the various forms of FDDS, the principles and mechanisms of floating to achieve gastric retention, and the polymers utilised in these systems. The origin of the polymers utilised in the medication delivery system determines whether they are synthetic or natural. The two varieties of polymers each have their own set of benefits and drawbacks. A variety of natural and synthetic polymers are detailed in this article, each with their own unique role in the drug delivery system. The article makes note of natural polymers such as guar gum, chitosan, xanthan gum, Gellan gum, and sodium alginate. Ethylcellulose, HPMC, and Eudragit are the synthetic polymers that were suggested.

Keywords: Oral drug delivery system, floating drug delivery systems (FDDS), Synthetic polymers, Natural polymers.

INTRODUCTION

Hydrodynamically controlled systems, also known as floating drug delivery systems, are low-density devices that float on top of the stomach contents and don't slow the stomach's emptying pace for an extended length of time.[1] Medications that do not dissolve well or become unstable in the digestive tract fluids can benefit from these. An improved gastric retention time, control over fluctuations in plasma drug concentration, and increased therapeutic benefit of the drug substance are all outcomes of a system that floats on gastric contents and releases the drug at a controlled rate before being emptied from the stomach. Drugs absorbed in the proximal gastrointestinal tract (GIT) or those insoluble or hydrolysed by the stomach's acidic pH may find relief through extended gastric retention. Plus, when treating specific conditions with local and sustained drug delivery to the stomach and proximal small intestine, there are a lot of potential benefits to prolonged gastric retention of the therapeutic moiety, such as increased bioavailability, better therapeutic efficacy, and maybe even a smaller dose.To achieve proper floating, a minimum stomach content is required [2]. Additionally, the dose form must have a minimum floating force (F) in order to remain buoyant on the meal's surface. A new method for finding the net weight was employed to gauge the floating force; this method involves continually measuring the force F (as a function of time) needed to hold the submerged object in place. A greater positive value for F makes the object float more effectively.

Oral controlled-release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as:

1. Easily administrations.
2. Low cost of therapy.
3. Patient compliance and flexibility in formulation

Effective disease problem treatment with minimal side effects and increased patient compliance at a cost-effective method is the ultimate goal of any drug delivery system. Among the many medication delivery methods on the market, those for oral administration account for over half.[3] Meds are released at a regulated, predictable, and predetermined rate by controlled release drug delivery systems (CRDDS). Some of the advantages that can be achieved with a controlled release drug delivery system include ensuring optimal Improved therapeutic drug concentration in the bloodstream with consistent and repeatable release rates over a long period of time; abolition of side effects; a decrease in dosing frequency and drug waste; optimisation of therapy; and improved patient compliances. Various delayed gastric emptying devices, such as floating systems, swelling and expanding systems, high-density systems, modified-shape systems, and mucoadhesive systems that induce bio-adhesion to the stomach mucosa, can be used to manage the gastric retention of solid dosage forms. Drugs in gastro retentive dose forms have a much longer gastric residence duration since they can stay in the stomach for several hours. Some medications are less soluble at high pH environments, yet prolonged stomach retention increases bioavailability, decreases drug waste, and makes them more soluble overall. Improved patient access to novel therapeutically effective drugs is one of the many benefits of gastro retention.[4]

Fig 1: Floating drug delivery system (FDDS)

Advantages of Floating Drug Delivery System:

- It is very useful for drugs that are particularly absorbed from the stomach or the proximal part of the small intestine, e.g., Riboflavin and Furosemide
- It minimizes the fluctuations in plasma drug concentration and prevents concentration-dependent adverse effects associated with peak concentrations of drugs found useful for drugs with a narrow therapeutic index
- It is advantageous for drugs with poor bioavailability because of site-specific absorption from the upper part of the GIT thereby maximizing their absorption.
- It is useful for drugs with short half-life to get an appreciable therapeutic activity
- Enhancement of the bioavailability for drugs that can metabolized in the upper GIT
- It is used to overcome the adversities of gastric retention time as well as the gastric emptying time The duration of treatment through a single dose is efficient and releases the drug over an extended period.[5]

Disadvantage of floating tablet:

- It is not feasible for those drugs that suffer from solubility or stability problems in the GI tract.
- It requires a high level of gastric fluid in the stomach for drug delivery to float and work efficiently in fluid. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- GRT is influenced by many factors like gastric motility, pH, and the presence of food which are never constant and could not predict the buoyancy
- It offers high variability in gastric emptying time.[6]

- The dosage form should be administered with a minimum of glass full of water (200-250 ml)
- The drugs, which are absorbed throughout GIT, undergo first-pass metabolism (Nifedipine, Propranolol, etc.), are not a desirable candidate
- The ability of a drug to remain in the stomach depends upon the subject being positioned upright. [7-8]

CLASSIFICATION OF FLOATING TABLET:

Non-effervescent system: The non-effervescent FDDS is based on the polymer's swelling mechanism or bio-adhesion to the GI tract's mucosal layer. In non-effervescent FDDS, gel-forming or highly swellable cellulose-type hydrocolloids, polysaccharides, matrix-forming materials including polycarbonate, polyacrylate, polymethacrylate, and polystyrene, as well as bio-adhesive polymers like chitosan and carbopol, are the most often employed excipients.

Effervescent system: Gas-producing agents, such as sodium bicarbonate, and other organic acids, such as citric and tartaric acid, included in the formulation, are used in effervescent systems to create carbon dioxide (CO2) gas, which lowers the system's density and causes it to float on the stomach contents. Alternatively, a matrix containing a percentage of liquid can be included to generate gas that evaporates at body temperature.

Colloidal Gel Barrier System: Sheth and Tossounian were the ones who initially created a hydrodynamically balanced system. Gel-forming hydrocolloids help them stay buoyant in the stomach, which improves GRT and increases the quantity of medication at the absorption site. This technique uses a variety of gel-forming agents, including matrix-forming polymers like polystyrene and polycarbophil, as well as highly soluble cellulose-type hydrocolloids like hydroxyethyl, hydroxypropyl, and hydroxypropyl methylcellulose**.**

Bilayer floating tablet: A bilayer tablet contains two layers immediate release layer which releases the initial dose from the system while the other sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintaining a bulk density of less than unity and thereby it remains buoyant in the stomach.

Micro porous Compartment System: In this inside the micro porous compartment which has pores in the top and bottom walls contains an encapsulated drug reservoir. In the drug reservoir peripheral walls are completely sealed due to this sealing direct contact of the undissolved drug with the gastric surface is prevented. Entrapped air in the floating chamber stimulates the system to float over gastric content. Through an aperture, the gastric fluid enters which dissolves the drug for absorption across the intestine.

Volatile liquid-containing systems: It is possible to include an inflatable chamber filled with fluids to offer a medication delivery device with sustained gastric retention. This system contains liquids like cyclopentane and ether, which gasify at body temperature and cause the stomach chamber to expand. They are made up of osmotically regulated floating structures called hollow deformable units. The system is split into two halves. There is a medicine in the first compartment and a volatile liquid in the second.

Raft forming systems: Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats. because the buoyancy created by the formation of CO_2 acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus. Usually, the system contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation to make the system less dense and float on the gastric fluid.

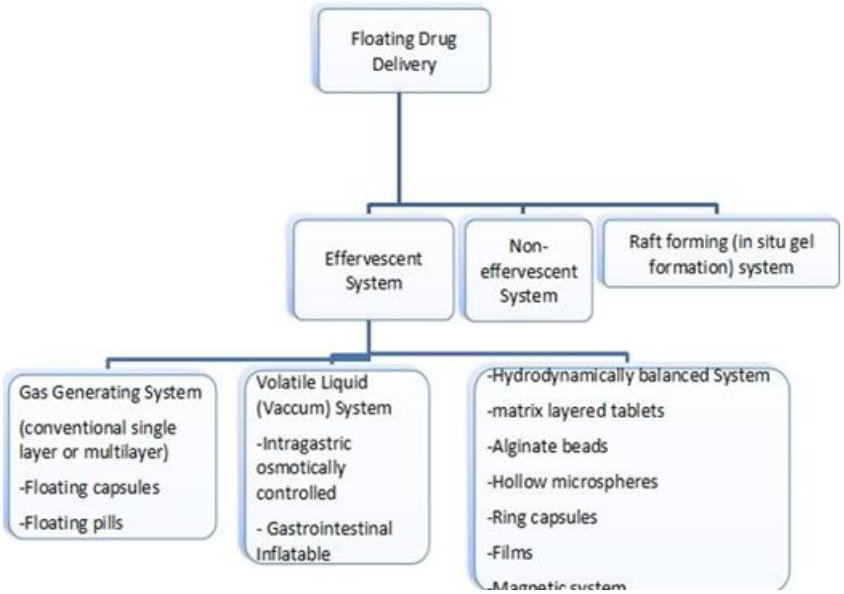

Fig 2: Classification of floating drug delivery system

METHODS OF PREPARATION

Methodology for single-layer floating tablets: Basically, single-layer floating tablets are prepared by compression methods. For this normally three basic compression methods are used. They are as follows:

- Direct compression,
- Dry granulation,
- Wet granulation

Direct compression: The practice of compressing tablets straight from powdered ingredients without changing the materials' physical composition is known as direct compression. This technique is applied to crystalline substances with good compressibility and flow characteristics, such as ammonium chloride, sodium chloride, methenamine, and potassium salts (chloride, chlorate, and bromide). Tablet computers are used to create compressed tablets using a single compression process. The tablet machine's upper and lower punches crush the material under high pressure when a certain amount of powdered tablet material flows into a die.

Dry granulation method: It is defined as the formation of granules by slugging if the tablet ingredients are sensitive to moisture and/or unable to withstand elevated temperature during drying.

Wet granulation method: In wet granulation, the active ingredient, diluents, and disintegrants are mixed or blended well in a rapid mixer granulator (RMG). The RMG is a multi-purpose chopper that consists of an impeller and a chopper and is used for high-speed dispersion of dry powders and aqueous or solvent granulations. Moist materials from wet milling steps are placed on large trays and placed in drying chambers with a circulating air current and thermo-stable heat controller. Commonly used dryers are tray dryersand fluidized bed dryers. After drying, the granules are reduced in particle size by passing through the smaller mesh screen. After this, the lubricant or glidant is added as a fine powder to promote the flow of granules. These granules are then compressed to get a tablet. Dry granulation when compared with wet granulation has a shorter, more cost-effective manufacturing process. Because it does not entail heat or moisture, dry granulation is especially suitable for active ingredients that are sensitive to solvents, or labile to moisture and elevated temperatures.[9]

METHOD OF EVALUATION

Drug-excipient interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance of the original drug or excipient peak indicate the DE interaction. Apart from the above-mentioned evaluation parameters, for the effect of aging with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy. [10]

Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. Accurately weighed batch (F1–F9) powder was placed in a 10 mL graduated measuring cylinder. The initial volume was observed. The Db was calculated in gm/mL using the following formulae,

Db =M/Vb

Where, Db =Bulk density, M=Mass of the powder, Vb=Bulk volume of powder

Tapped density: Accurately weighed batch (F1-F10) powder was placed in 10 mL graduated measuring cylinder. The cylinder was tapped initially 100 times from a distance of 14+2 mm. The tapped volume was measured to the nearest

graduated unit. Again, the tap volume was measured to the nearest graduated unit. The Dt was calculated in g/mL using the following formulae. [11]
Dt =M/Vt
Where, Dt =Tapped density, Vt =Tapped volume of the powder, Dt =Tapped density, M=Mass of the powder

Angle of repose: Good flow properties are critical for the development of any pharmaceutical tablets, capsules, or powder formulations. The angle of repose is defined as the maximum angle possible between the surface of the pie of powder and the horizontal plane. It is performed to determine the flow property of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on a horizontal surface, giving a heap angle of powder on a paper. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation. [12]
Tan θ=h/r
Where, h and r are the height and radius of the powder cone, respectively.

Hasusner's ratio: Hasusner's ratio is carried out by tapped density divided by bulk density.
Hasusner′s ratio= tapped density/ bulk density

Carr's consolidation index: Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated using the given formula.
Carr's index (%)=[(Dt –Db) × 100]/Dt

Appearance: The tablets were checked for the presence of cracks, pinholes, etc. There should be uniformity in the color and the dimensions of the tablets.

Hardness: A tablet's hardness reveals its capacity to tolerate managing mechanical shocks. The hardness of the tablet was assessed using the Monsanto hardness tester. The unit of measurement is kg/cm^2. Five tablets were chosen at random, and their hardness was assessed.

Friability: Roche Friabilator was used to gauge tablet strength. 20 tablets were weighed, put into the friabilator, turned 100 times, then removed and dusted. Reweighing the tablets allowed for the calculation of the weight reduction percentage. The % friability was calculated by:
$F= [(W_{initial}- W_{final}) \times 100]/ W_{initial})$

Weight variation: From each batch, 20 tablets were chosen at random, and they were all weighed separately and collectively using an electronic balance. The typical weight was recorded.[13]
PD= [(WH-WL) × 100]/ WH
Where, PD= percentage deviation WH= highest weight (mg)
WL= lowest weight (mg)

Drug content: Ten tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed in a 100 ml volumetric flask and dissolved in a suitable quantity of 0.1 N HCl. Then the volume was made up to 100ml with 0.1 N HCl and filtered. 2 ml of filtrate was transferred to a 100 ml volumetric flask and the volume was made with 0.1 N HCl. The absorbance of the resulting solution is measured by UV spectrophotometer at drug-specificnm range.[14]

FloatingTest: The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time between the introduction of the dosage form and its buoyancy on 0.1 N HCl, and the time during which the dosage form remains buoyant were measured. The time taken for the dosage form to emerge on the surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and the total duration of time during which the dosage form remains buoyant is called Total Floating Time (TFT).

Swelling Study: The swelling behavior of a dosage form is measured by studying its weight gain or water uptake (WU). The study was done by immersing the dosage form in 0.1 N HCl at 37°C and determining these factors at regular intervals up to a period of 12 hours. Water uptake was measured in terms of percent weight gain, as given by the equation.
WU = (Wt –Wo) x 100 / Wo
Wt = Weight of the dosage form at time t. Wo = Initial weight of the dosage form.[15]

Disintegration Test (U.S.P.)

The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2 0 C such that the tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.

Table 1: List of drugs formulated of floating tablets

S. No.	Name of Drug	Category of Drug	Short Summary	Reference
1.	Famotidine	Histamine-2 Blocker	The results indicated that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration.	**[17]**
2.	Ranitidine	Histamine H2-receptor Antagonist.	The studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile.	**[18]**
3.	Cefuroxime axetil	Antibacterial	Tablets were prepared by direct compression technique. Kinetic treatment to dissolution profiles revealed drug release ranges from anomalous transport to case 1 transport, which was mainly dependent on both the independent variables.	**[19]**
4.	Levofloxacin hemihydrate	Antimicrobial	The tablets were prepared by melt granulation method to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption.	**[20]**
5.	Atenolol	$Beta_1$-selective (cardio selective)	The floating matrix tablets of Atenolol were prepared by direct compression method. The release kinetics showed first order model and zero order model.	**[21]**
6.	Cefpodoxime Proxetil	beta-lactam antibiotic with bactericidal activity	The tablets were prepared by direct compression technique. The gastric residence time of Cefpodoxime Proxetil containing formulation was prolonged & floated in stomach for longer period, & increased bioavailability.	**[22]**
7.	Bromocriptine Mesilate	Anti Parkinson Agents (dopamine Agonist)	Formulation was Prepared by Direct Compression Method. Showed Good Physical Properties and stability. This dosage form especially caused reduction in dosing frequency and increased bioavailability.	**[23]**
8.	Captopril	Hypertension	Floating tablets were prepared by wet granulation method. Resulted in zero-order sustained release floating formulation of captopril, with enhanced oral bioavailability.	**[24]**
9.	Ramipril	Hypertension	The gastro retentive drug delivery systems were retained in the stomach for a longer period of time and improve the bioavailability.	**[25]**
10.	Ofloxacin	Antibiotic	Ofloxacin floating tablets enhanced the bioavailability and therapeutic efficacy of the drug. All formulations possessed good	**[26]**

			floating properties with total floating time between 8- 12 hrs.	
11.	Losartan Potassium	Antihypertensi ve	Floating tablets were prepared by wet granulation method, resulting in prolonging the gastric emptying time. The floating tablets remained in the stomach for a longer period of time with sustained drug release.	**[27]**

According to the test the tablet must disintegrate and all particles must pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass. Disintegration time: Uncoated tablet: 5-30 minutes coated tablet: 1-2 hours. [16]

***In-vitro* drug release study:**
The USP basket technique was used for the release testing. 900ml of 0.1N HCL was added to the jar, and the medium was allowed to acclimate to a temperature of 37^0C while rotating at 50 rpm. The tablet was placed inside the container and basket, and the machine ran for twelve hours at a speed of fifty rotations per minute. At regular intervals, 10 ml of the fluid was withdrawn, filtered, and then reintroduced. With the use of the dissolving solution, the samples were properly diluted. [28]

Mechanism of action
Low density: Due to the components used in its formulation, the tablet has a lower density than gastric juices, usually less than 1 g/ml. Polymers such as sodium alginate, hydroxypropyle methylcellulose (HPMC), and other gas-generating substances like bicarbonates are examples of common excipients.

Buoyancy: Tablet's contact with the stomach fluid after swallowing causes the gas- generating substances (such as sodium bicarbonate and gastric acid to react to release carbon dioxide it sweels and becomes buoyant, allowing the tablets to "float" on the surface of the stomach contents since the created gas is retained within the tablet matrix.

Extended holding in the stomach: The floating tablet avoids an early evacuation from the stomach through the pyloric sphincter by staying buoyant. By doing this, the tablet's gastric residence duration is extended, enabling the medicine to be released gradually over an extended length of time in the stomach.

Slow medicine release: As the floating tablet stays in the stomach, the medicine is gradually released, guaranteeing a prolonged release profile. This is particularly advantageous for medications that are unstable or poorly soluble in the alkaline environment of the intestines, or those are mostly absorbed in the stomach or upper small intestine.

Erosion or dissolution: The floating tablet progressively erodes or dissolves over time, delivering the medication into the stomach fluid in a regulated way. [29-32]

Important elements:
Citric acid and sodium bicarbonate are effervescent chemicals that produce gas and cause the pill float.
Hydrophilic polymers: xanthan gum and HPMC (to limit drug release and provide the floating mechanism).
Lipid-based materials: For low density, certain formulations employ lipid-base excipients. For medications that require a longer absorption window or are absorbed in the stomach, this mechanism is very helpful because it improves bioavailability **(**Figure 3).

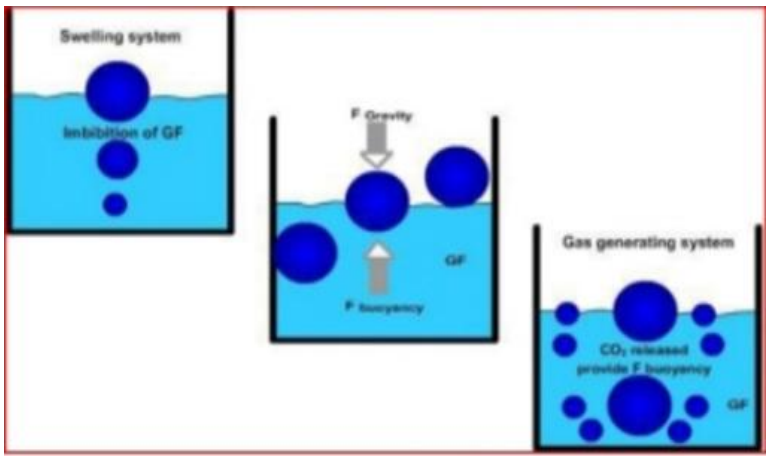

Fig 3: Mechanisms of buoyancy in Floating Drug Delivery Systems.

Proper tablet formulation requires balancing density and buoyancy: If the tablet's density is too high, it will sink rather than float, and if it is too low, it will float but make insufficient contact with the stomach lining, potentially affecting drug release and absorption.

Delayed onset in the fasting state: The stomach may empty more quickly. Floating tablets may not remain in the stomach long enough to full fill their intended purpose. Furthermore, the effervescent mechanism (in the case of gas-generating tablets) may not function properly on an empty stomach due to a lack of gastric contents to support the floating action.

Limited to certain drugs: Floating tablets are only acceptable for medications that are largely absorbed in the stomach or upper small intestine. Maintain a steady profile in acidic settings (stomach). Requires regulated or sustained stomach release. Drugs that are unstable in acidic environments or are largely absorbed in the intestines may not benefit from floating tablet formulations.

Difficulties in large-scale manufacturing: Producing a consistent formulation with exact buoyancy and medication release qualities might be problematic. Variations in tablet size, shape, and substance during manufacture may have an impact on floating ability and drug release profiles.

Effervescent systems: The use of gas-generating substances (such as sodium bicarbonate) that emit carbon dioxide when in contact with gastric acid, resulting in an abuoyant effect.

Non-effervescent systems: The use of swellable polymers (such as hydroxypropyl methylcellulose or sodium alginate) to absorb stomach fluid, swell, and lower tablet density.

Osmotic systems: These systems use osmotic pressure to slowly force the medication out while remaining buoyant **(**Figure 4).[33-34]

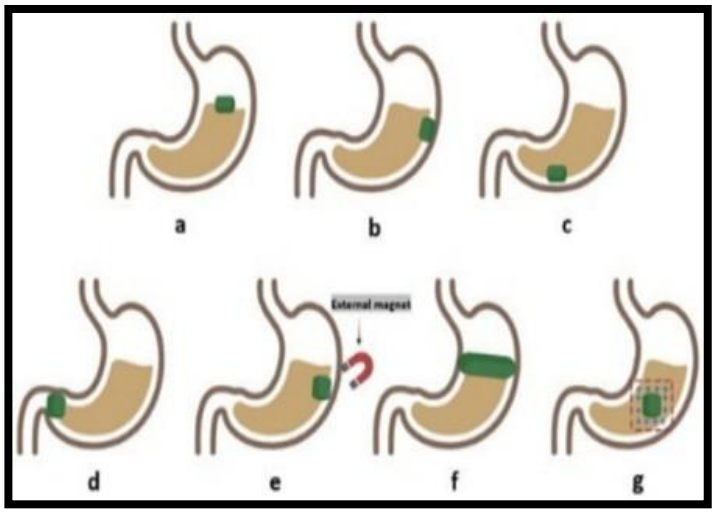

Fig 4: Mechanism of floating tablet in stomach.

Basic GIT Physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus). The design and evaluation of FDDS is based on anatomy and physiology of GIT. The stomach is J shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac regions of abdominal cavity .The Gastrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region (Figure 5). The stomach is an organ with a capacity for storage and mixing.[35]The average length of the stomach is about 0.2 meter and the apparent absorbing surface area is about 0.1 sq. meter.

The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emp-tying by propelling Actions.

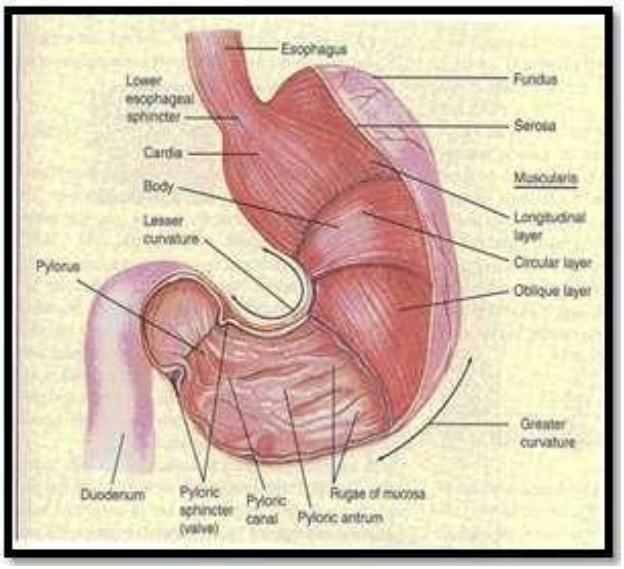

Fig 5: Human Stomach

Process of Gastric Emptying

Gastric emptying occurs in both the fasting and fed states. During the fasting state an inter-digestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided in to four phases. [36-37] After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern (Figure 6). [38]

- Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
- Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contrac-tions.
- Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
- Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.[39]

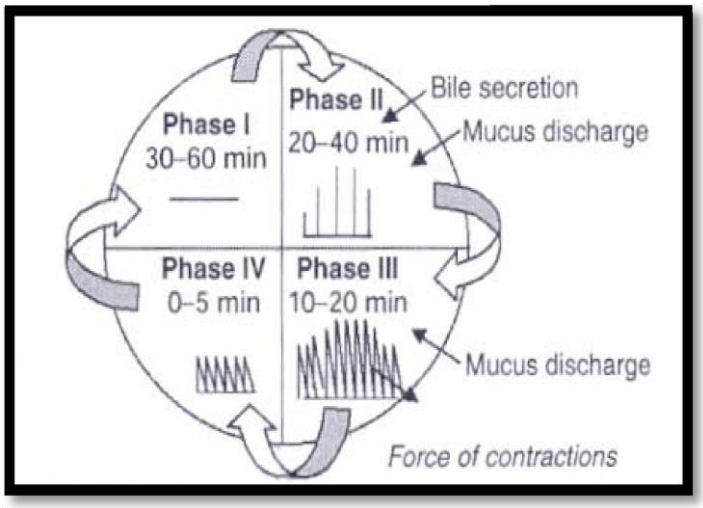

Table 2: Salient Features of Upper Gastrointestinal Tract

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I, E, CM

Factors Affecting the Floating and Floating Time

1. **Density: -** Floating is a function of dosage form buoyancy that is dependent on the density.
2. **Shape of dosage form: -** Tetrahedron and ring-shaped devices with flexural modules of 48 and
3. 22.5 kilo pounds per square inch (KSI) are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes. [40]

4. **Concomitant drug administration: -** Anticholinergics like atropine and propantheline,opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
5. **Fed or unfed state: -** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. [41]
6. **Nature of meal: -** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release. [42]
7. **Caloric content and feeding frequency: -** Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
8. **Age: -** Elderly people, especially those over 70, have a significantly longer; floating.[43] Disease condition such as diabetes and crohn's disease etc. also affect drug delivery.
9. **Posture: -** Floating can vary between supine and upright ambulatory states of the patient. [44]

Marketed overview

Floating tablets have acquired popularity in the pharmaceutical sector, especially for medications that require gastro retentive delivery. Several goods are now available. [45]

Recent innovation and trends

- **Polymer innovations:** Novel biocompatible and biodegradable polymers are being developed to improve buoyancy and medication release properties. These advancements aid in the drug's long-term retention in the stomach.
- **3D printing techniques:** Using 3D printing to create floating tablets allows for exact control over the structure and drug release rates, resulting in individualized treatment.
- **Nano formulations:** Adding nanoparticles to floating tablets improves the solubility and bioavailability of poorly soluble medicines, increasing therapeutic efficacy.
- **Sustainable materials:** Research into sustainable, biodegradable materials for floating tablets seeks to lessen environmental impact while retaining effective drug delivery.[46]
- **Combination drug therapies:** Recent research has focused on creating floating tablets containing various active components, which can increase therapeutic outcomes and patient compliance.
- **Biodegradable polymers:** The usage of ecologically friendly ingredients in the composition of floating tablets is increasing, addressing efficacy and sustainability problems.
- **Metformin SR:** Extended-release versions of Metformin use a floating mechanism to keep therapeutic levels in patients with type 2 diabetes, improving glucose control and patient compliance.
- **Ciprofloxacin extended-release tablets:** Ciprofloxacin floating formulations improve its bioavailability, allowing for less frequent dose and better patient adherence to treatment.
- **Ranitidine and famotidine:** These H2 receptor antagonists used to treat GERD and peptic ulcers benefit from increased stomach retention, which leads to better therapeutic results.
- **Domperidone:** Floating formulations of this antiemetic drug provide improved control of nausea and vomiting by guaranteeing a more consistence's therapeutic impact. [47]
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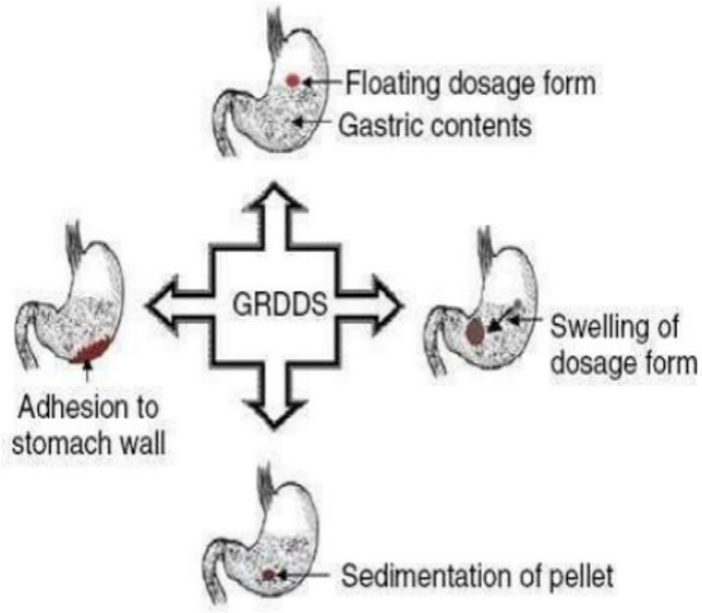

Fig : 7. Mechanisms of gastro retentive drug delivery systems.

Table 3: Examples of commercially available floating drug delivery systems

Name	Company	Type and Drug	Remark
MadoparHBS (PropalHBS)	Roche, USA	Floating Capsule, Levodopa and Benserazide	Floating CR Capsules
Valrelease	Hoffman LaRoche, USA	Floating Capsules, Diazepam	Floating Capsules
Topalkan	Pierre Fabre Drug, France	Floating Antacid, Aluminium and Magnesium mixture	Effervesents Floating liquid Alginate Preparation
Conviron	Ranbaxy, India	Ferrous Sulphate	Colloidal gel Forming FDDS
Cifran	Ranbaxy, India	Ciprofloxacine (1gm)	Gas Generating Floating Form
Cytotech	Pharmacia, USA	Misoprostol (100mcg/200mcg)	Bilayer Floating Capsules

POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

Polymers are used in floating system so as to target the drug delivery at specific region in the GI tract i.e. stomach. Both synthetic and natural polymers are used in the floating drug delivery. Natural polymers used in floating system are Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate, etc. Synthetic polymers used for the floating drug delivery are HPMC, Eudragit, ethyl cellulose, etc. [48]

Natural Polymers

Natural gums (obtained from plants) are hydrophilic carbohydrate polymer of high molecular weight. They are generally insoluble in organic solvents, like hydrocarbon, ether. Gums either water soluble or absorb water and swell up or disperse in cold water to give a viscous solution or jelly. Natural polymer has advantages over synthetic polymer. They are as follows:

- Biodegradable
- Biocompatible and non-toxic.
- Low cost.
- Environment friendly
- Local availability.

Natural polymer has some disadvantages. They are as follows:

- Microbial contamination
- Batch to batch variation
- Uncontrolled rate of hydration.[49]

Guar gum

Guar gum is naturally occurring galactomannan polysaccharide. Guar gum hydrates and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retards the drug release and makes it a flexible carrier for extended-release Dosage forms. In pharmaceutical guar gum is used as disintegrant and as a polymer in floating drug delivery system.

Properties of guar gum:

- It is soluble in water but insoluble in organic solvents.
- Strong hydrogen bond property.
- Excellent thickening, emulsion, film forming property.
- Ability to control rheology.

Advantages of guar gum in floating drug delivery system:

It has been reported that polymer swelling play an important role in the pattern and amount of drug release.
It was found that guar gum formulations were relatively insensitive to stirring speed during in vitro drug dissolution testing and dissolution profile was not affected significantly. [50]

Chitosan

Chitosan is natural polymer obtainer by deacetylation of chitin. It has favorable biological properties such as nontoxic, biodegrable, biocompatible. It is a bioadhesive polymer and has anti-bacterial properties thus make it suitable for site specific delivery. Chitosan is high molecular weight polycationic weak base with pka value of 6.2-7. On addition to acidic pH of 1.2 or neutral media it becomes buoyant in nature and provide control release. By increasing thickness of chitosan film release rate can be decreased.

Advantages of chitosan:

- It forms film that reduces effect of gastrointestinal transit time.
- Hallow microcapsule tend to float on gastric fluid for about 12hrs.
- Release rate of drug followed zero order kinetics. [51]

Xanthan gum
Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of carbohydrate. Xanthan is a long-chained polysaccharide with large number of trisaccharide side chains. Gum also has an excellent solubility and stability under acidic and alkaline conditions and in the presence of salts and resists common enzymes.

Advantages of Xanthan gum:
- It is used to increase or decrease rate of release of drug from formulation.
- Soluble in water.
- High viscosity at low concentration.
- It has potential advantage of drug release at zero order kinetics. Some tablet containing xanthan gum and citric acid show buoyancy for more than 24hrs.

Gellan gum
Gellan gum is an anionic, high molecular weight, deacetylated extracellular, linear polysaccharide. This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics. Gellan gum is produced as a fermentation product from spingomonas elodea.

Advantages of Gellan gum:
- It has excellent flavor release, high gel strength, and excellent stability.
- It forms gel when positively charged ions are added
- It is used in food product as thickening agent or stabilizing agent.

Sodium alginate
Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of d'mannuronic acid and L guluronic acid. The block structure and molecular weight of sodium alginate Samples have been investigated.

Typical Properties: Acidity/alkalinity ph-7.2 (1% w/v aqueous solution).
Solubility: Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic Solvents and aqueous acidic solutions in which the ph is less than 3. Slowly soluble in water, forming a viscous colloidal Solution.

Viscosity (dynamic): Various grades of sodium alginate are commercially available that yield aqueous solutions of varying Viscosity. Typically, a 1% w/v aqueous solution, at 208C, will have a viscosity of 20-400mpa s (20–400cp). Viscosity may vary depending upon concentration, pH, temperature, or the Presence of metal ions. Above pH 10, viscosity decreases. [52]

Synthetic Polymers
Synthetic polymers are becoming increasingly important in pharmaceuticals. Uses of synthetic polymer are as binder, film coating agent, etc. Polymer are macromolecule having very large, contain a variety of group. Synthetic polymers are either purely synthetic or they are modified form of natural polymer know as semi synthetic. List of synthetic polymer used is as follows:
1. Hydroxypropyl methyl cellulose
2. Eudragit
3. Ethyl cellulose

Disadvantages of synthetic polymer are as follows
- High-cost toxicity environmental pollution
- Acute and chronic adverse effect
- Poor biocompatible
- Inflammatory response and local reaction.

Hydroxypropyl methyl cellulose
Hydroxypropyl methylcellulose ethers belong to an extensive family of white to off-white, odorless, water-soluble polymers that bind, retain water, thicken, form films, lubricate. It is a semi synthetic, inert, viscoelastic polymer, used as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

Synonyms:

- Hypromellose,
- Methocel, Metolose,
- Pharmacoat, Benecel MHPC, E464 etc.

Functional category:
Bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended-release agent, film-forming agent, foaming agent, granulation aid, modified-release agent, mucoadhesive, release modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained release agent, tablet binder, thickening agent, viscosity-increasing agent.General properties common to the Hypremellose are listed below. Individual type exhibits these properties to varying degrees and may have additional properties that are desirable for specific applications.

Apparent density: 0.25~0.70g/cm3
The refractive index=1.336
Surface tension: 42 to 56mn/m
Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol. [53]

Applications:
In oral products, HPMC is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher viscosity grades are used with organic solvents. Examples of film coating materials that are commercially available include Any Coat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1% Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Advantages
Water soluble and most abundant polymer in nature
Used as a thickener, film former and water retension agent
Hydrophilic matrix is the simplest sustained release technology for oral dosage form. [54]

2. Eudragit
Nonproprietary names: BP: Acidum methacrylicum et methylis methacrylas polymerisatum 1:2 USPNF: Methacrylic acid copolymer

Synonyms: Polymeric methacrylates.
Functional category: Film former; tablet binder; tablet diluent

Description:
Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. Eudragit S 100 is available as powder and solvents used for this is 95 % Acetone and alcohols which is soluble in intestinal fluid from pH 7 and used as an enteric coating material. Eudragit L and S also referred to as methacrylic acid copolymers in the USPNF 23 monograph, are anionic copolymerization products of methacrylic acid and methylmethacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L (Type A) and approximately 1:2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. Eudragit L- 100 and Eudragit S-100 are white free-flowing powders with at least 95 % of dry polymers.

Incompatibilities:
Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

Applications:
Polymethacrylates (Eudragit) are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit S 100 is soluble in acetone and alcohols and 1N NaOH. In contrast, Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid. Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH >6 whereas, Eudragit S and FS are soluble at pH >7. The S grade is generally used for coating tablets, while the flexible FS 30 D dispersion is preferred for coating particles. Eudragit RL, RS, NE 30D, NE 40D and NM30D are used to form water-insoluble film coats for sustained release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10–50%. Polymethacrylates polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.[55]

Ethyl cellulose
Ethocel (Ethylcellulose polymers) has been widely used in the pharmaceutical industry for over 50 years. Ethylcellulose has been used for choice in pharmaceutical formulations for various purposes, such as taste masking of bitter actives, moisture protection, stabilizer, extended release multiparticulate coating, microencapsulation of actives, extended-release binder in inert matrix systems, solvent and extrusion granulation.

Solubility: Ethylcellulose is a water insoluble cellulose ether, which is prepared from cellulose, it is a partly Oethylated cellulose, its ethoxy content (-OC2H5) is between 44-51 %. It is insoluble at any pH that occurs in organism, but in the presence of the gastric Juice it undergoes swelling. It is then permeable for water and permits extended modified drug release. This makes it suitable for improved patient compliance.

Applications:
The application of EC in wet extrusion processes is limited, since the polymer has considerable elastic properties, but can be successfully used as matrix former in combination with some plasticizing agents. The potential of coarse Ethylcellulose (CPEC) and fine particle Ethylcellulose (FPEC) as diluent with high molecular weight polyethylene oxide (PEO), which was used as an extrusion aid and a binder have shown that water is sufficient to prepare a wet granulation product when using FPEC. MCC was included in formulations to contribute its plasticity to the wetted mass during extrusion and to the extrudate during spheronization.
Ethylcellulose is an ideal polymer for the formation of products allowing modified drug release. A small number of Ethylcellulose polymers have been approved for general pharmaceutical application and are used in extended-release solid dosage formulations. Several types of such Ethylcellulose exist, e.g. Ethocel 4, Ethocel 10 and Ethocel 45, which differ in the length of the polymer chains, the rate of dissolution, and the viscosity of their solution. Ethylcellulose is suitable to prepare MR coatings. [56]

LIMITATIONS/DISADVANTAGES OF FDDS:
1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable
4. Drugs which are irritant to gastric mucosa are also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal Tract. [57.

CONCLUSION
Medication absorption in the upper gastrointestinal tract (gastric, duodenal, and jejunal) is enhanced by the FDDS. For the purpose of regulated medication release from dosage forms, polymers are utilised. There are a variety of uses for polymers in formulations, including as gelling agents, emulsifying agents, agents to increase viscosity, agents to retard rate, and many more. This highlights the significance of polymer understanding in the medication delivery industry. To

develop more effective dose forms, however, much work remains in overcoming the various physiological and pharmacological obstacles. Finding ways to precisely control the drug input rate into the GI tract for optimisation of medicinal agent pharmacokinetic and toxicological profiles should be the focus of future research work in the FDDSs.

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