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POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEMS: AN UPDATED REVIEW

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Abstract - The oral route of drug delivery is widely preferred due to its convenience and patient compliance. In the development of drug delivery systems, various components play crucial roles, among which polymers have gained significant importance. Polymers are macromolecular compounds composed of multiple monomer units linked together by chemical bonds. Floating drug delivery systems (FDDS) offer an additional advantage for drugs primarily absorbed in the upper segments of the gastrointestinal (GI) tract, such as the stomach, duodenum, and jejunum. The focus of this review is to elucidate the types of FDDS, the mechanisms employed for achieving gastric retention, and the polymers utilized in these systems. Polymers used in drug delivery systems can be classified into three categories based on their origin: natural, semi-synthetic, and synthetic. Each type of polymer has its own set of advantages and disadvantages. This article specifically discusses the different types of natural, semi-synthetic, and synthetic polymers employed in drug delivery systems. Natural polymers such as guar gum, chitosan, xanthan gum, gellan gum, and sodium alginate are highlighted in this review. Semi-synthetic polymers including ethyl cellulose ether (EC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and sodium carboxymethyl cellulose (NaCMC) are also discussed. Synthetic polymers mentioned in the review include HPMC and ethyl cellulose.

Index Terms **-:** Polymers, gastroretentive drug delivery systems, floating dosage forms, HPMC, ethyl cellulose.

I.INTRODUCTION

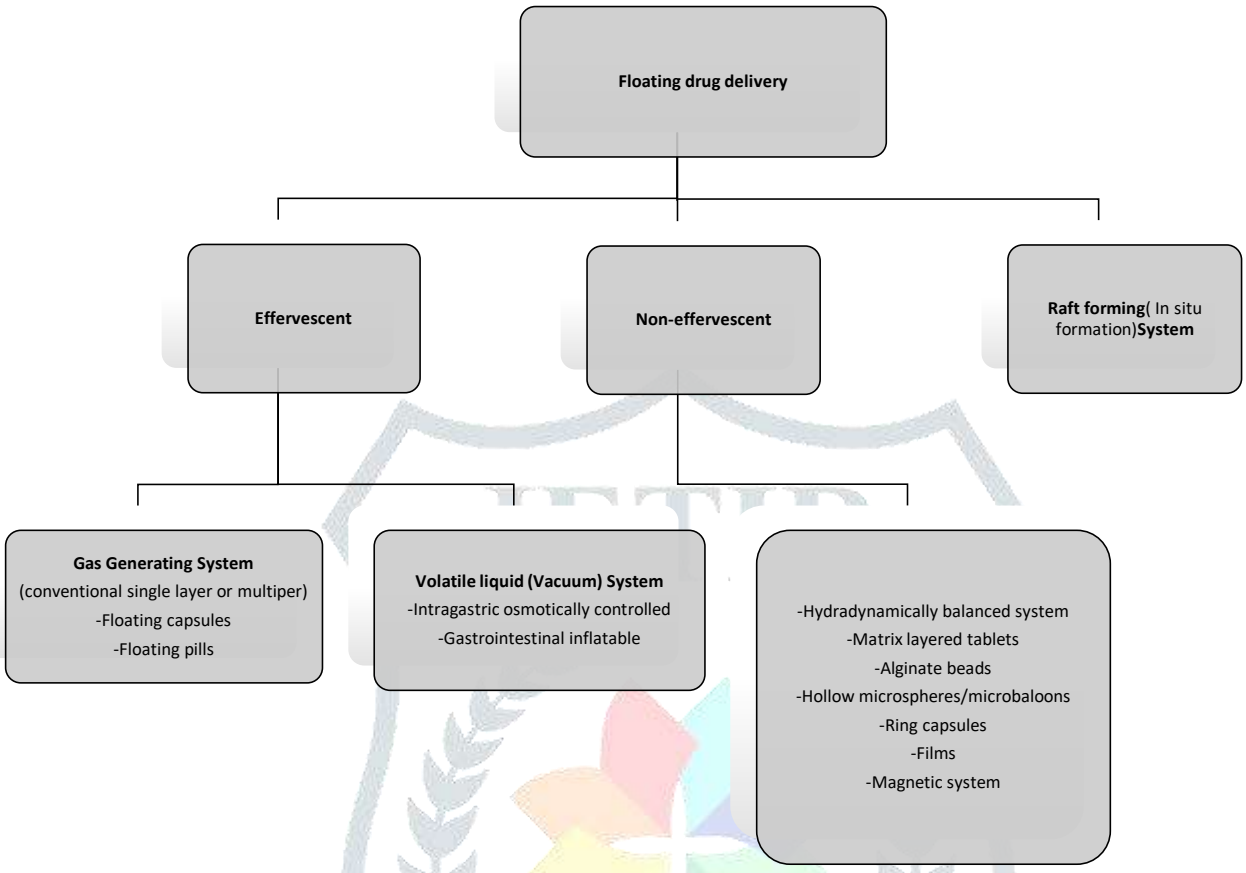
A polymer is a substantial molecule consisting of recurring structural units, often referred to as macromolecules, which are joined by covalent chemical bonds. There is a wide range of both synthetic and naturally occurring polymers. However, the utilization of natural polymers in pharmaceutical contexts holds particular appeal due to their cost-effectiveness, abundant availability, and non-toxic nature. Moreover, natural polymers offer the advantage of being amenable to chemical modifications, potentially biodegradable, and, with few exceptions, biocompatible.[1]

Plant-derived substances present various challenges, including being produced in limited quantities and complex mixtures whose composition can vary depending on factors like plant location and seasonal variations. This complexity often leads to a time-consuming and costly process for isolating and purifying these substances. Additionally, there is a growing concern regarding the protection of intellectual property rights in this context.[2,3] Plant-derived polymers have specific applications in pharmaceutical formulations, including their utilization in the production of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems, and viscous liquid formulations.[4,6] In these dosage forms, polymeric materials serve various functions, including acting as binders, matrix formers, drug release modifiers, film coating agents, thickeners or viscosity enhancers, stabilizers, disintegrants, solubilizers, emulsifiers, suspending agents, gelling agents, and bioadhesives.[7]

II.FLOATING DRUG DELIVERY SYSTEM

The floating drug delivery system, also recognized as a hydrodynamically balanced system (HBS), operates by maintaining buoyancy within the gastric contents, allowing for controlled and gradual release of the drug at the intended rate. Once the drug is dispensed, the remaining system is evacuated from the stomach. This mechanism extends the gastrointestinal residence time (GRT) and enhances the regulation of plasma drug levels, thereby minimizing fluctuations in drug concentration .[8] Floating drug delivery systems (FDDS) have been developed to effectively retain drugs within the stomach, particularly for medications with poor solubility and low stability in intestinal fluids. The fundamental concept of FDDS revolves around creating dosage forms with lower density than gastric fluids, enabling them to float on the stomach contents. These systems, characterized as hydro-dynamically controlled low-density formulations, possess sufficient buoyancy to remain afloat in the stomach for an extended period without significantly altering gastric emptying rates. Upon drug release, the residual system is expelled from the stomach, contributing to prolonged gastric residence time and improved regulation of plasma drug concentrations. Leveraging the principle of buoyancy, FDDS provides a straightforward and practical strategy for achieving prolonged gastric residence time and sustained drug release. [9] (table.1) the classification of Floating Drug Delivery Systems (FDDS) takes into account their physicochemical behaviour and appearance, which can vary based on several factors.

Table. 1: Classification of floating drug delivery system (FDDS)



2.1 Effervescent System: This specialized drug delivery system comprises a matrix-type design incorporating swellable polymers like methylcellulose and chitosan, in combination with effervescent compounds including sodium bicarbonate, tartaric acid, and citric acid. The formulation is meticulously crafted to ensure that upon contact with gastric juice, carbon dioxide is released, which becomes trapped within the swollen hydrocolloid. This process imparts buoyancy to the dosage form.
The foundation of this delivery system lies in the design principle of a swellable asymmetric triple-layer tablet approach. [10,11]

2.1.1 Gas generating system: The low-density Floating Drug Delivery System (FDDS) operates on the principle of CO_2 release upon contact with gastric fluids post-oral ingestion. Formulated materials are designed to trigger CO_2 liberation upon exposure to the acidic environment of the stomach. This liberated CO_2 becomes trapped within a gel-based hydrocolloid (fig.1), inducing an upward movement of the dosage form and maintaining its buoyancy. Consequently, the specific gravity of the dosage form decreases, allowing it to float on the chyme.
The components responsible for CO_2 generation are integrated into the tablet matrix, either in a single-layer or multi-layered configuration. This setup facilitates a gas-generating mechanism within the hydrocolloid layer, while the drug is housed in another layer, ensuring a sustained release effect. [10,12]

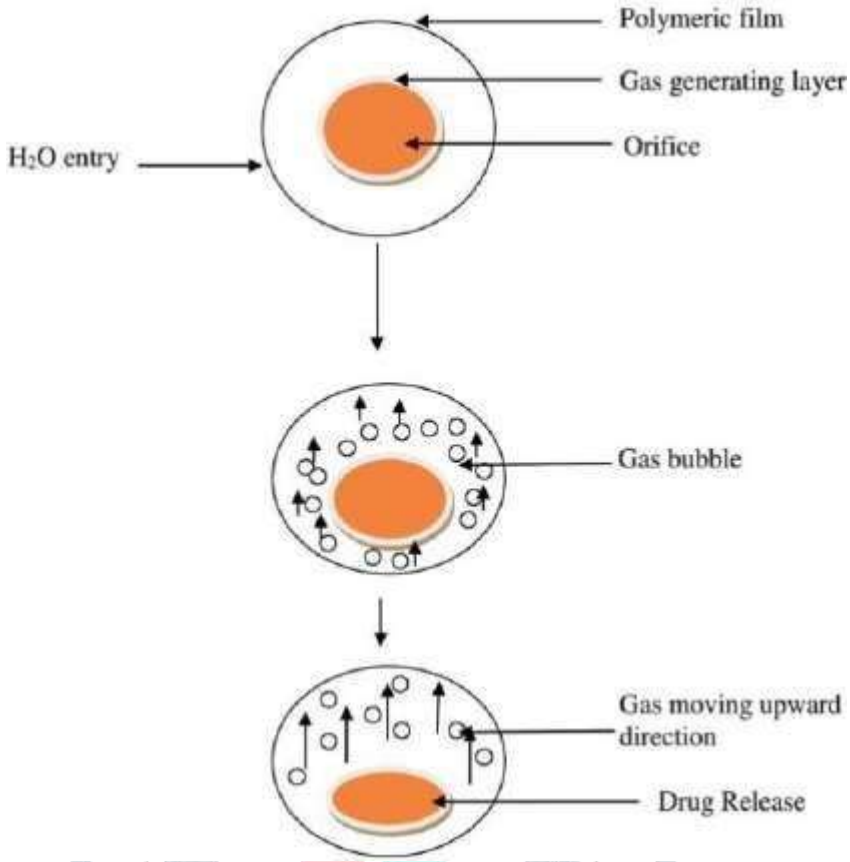


Fig.1: Mechanism of floatation via CO_2 liberation

2.1.2Volatile liquid containing systems (Osmotically controlled drug delivery system): This description outlines an osmotically controlled floating system composed of a flexible, collapsible unit with an attached housing. The housing is internally divided into two chambers by a pressure-sensitive movable barrier that is impermeable. Typically, the first chamber holds an active drug, while the second contains a volatile liquid like cyclopentane or ether. This liquid vaporizes at body temperature, generating gas that causes the device to float, thus facilitating prolonged drug release (fig.2). To aid in the expulsion of the unit from the stomach once drug delivery is complete, a bioerodible plug is included, allowing the vapor to escape. [10,12]

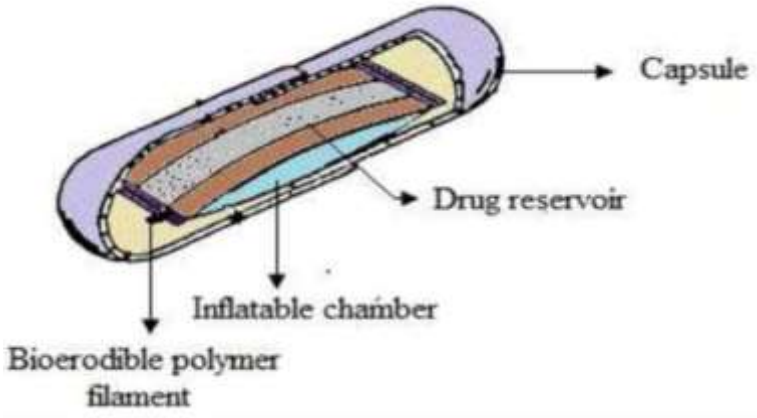


Fig.2: Volatile Liquid Containing System.

2.2 Non-effervescent system: The commonly utilized polymers in the preparation of these systems fall into two main categories: gel-forming or highly swellable types, and matrix-forming types. Examples of highly swellable polymers include polysaccharides and hydrocolloids, while matrix-forming polymers encompass polyacrylate, polymethacrylate, polycarbonate, and polystyrene. In the formulation approach, the drug is typically mixed with a gel-forming hydrocolloid. After oral administration, the hydrocolloid swells upon contact with gastric fluid, reaching a bulk density lower than one. This reduction in density allows the dosage form to achieve buoyancy by trapping air within the swollen polymer matrix.
This system further comprises various subtypes, each tailored to specific drug delivery needs and therapeutic requirements.[13]

2.3 Raft forming system: Raft forming systems have garnered significant attention for their utility in delivering antacids and medications for gastrointestinal infections and disorders. The fundamental mechanism underlying raft formation involves the creation of a viscous cohesive gel upon contact with gastric fluids. In this process, each portion of the liquid swells, giving rise to a continuous layer referred to as a raft. The raft, buoyed by the formation of CO_2, acts as a barrier, effectively preventing the reflux of gastric contents such as HCl and enzymes into the esophagus (fig.3).

Typically, these systems comprise a gel-forming agent along with alkaline bicarbonates or carbonates. These alkaline substances play a crucial role in reducing the density of the system, thereby enabling it to float on the gastric fluids. This change in density facilitates the formation of the protective raft, contributing to its efficacy in mitigating reflux and providing relief from gastrointestinal issues.[14]

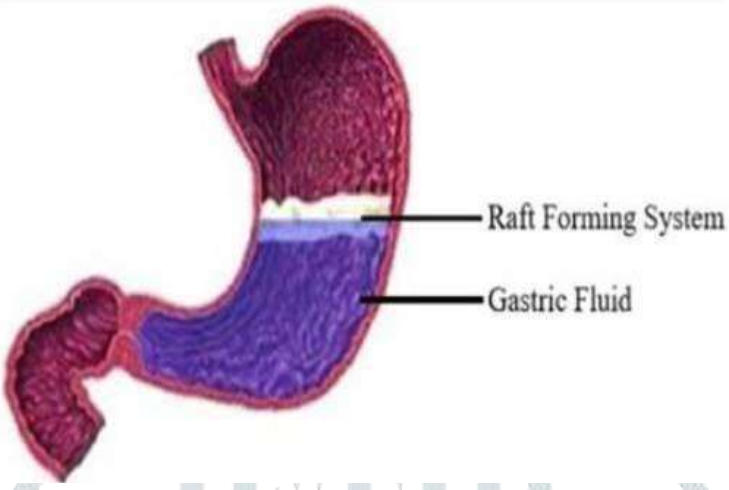


Fig.3: Raft forming system.

III.POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM:

Polymers play a crucial role in floating systems designed to target drug delivery to specific regions in the gastrointestinal (GI) tract, particularly the stomach. Both synthetic and natural polymers find application in floating drug delivery systems.

Natural polymers utilized in floating systems include Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate, among others. These natural polymers offer biocompatibility and often possess mucoadhesive properties, aiding in sustained drug release and improved localization within the stomach.

On the other hand, synthetic polymers such as Hydroxypropyl methylcellulose (HPMC), Eudragit, and ethyl cellulose are also commonly employed in floating drug delivery systems. These synthetic polymers offer precise control over drug release kinetics, enhanced stability, and tailored drug release profiles.

By leveraging the properties of both natural and synthetic polymers, floating drug delivery systems can achieve targeted drug delivery to the stomach, thereby improving therapeutic outcomes while minimizing side effects.[15]

3.1 Natural polymers: Natural gums, derived from plants, represent hydrophilic carbohydrate polymers characterized by their high molecular weight. These gums typically exhibit insolubility in organic solvents such as hydrocarbons and ethers. Instead, they demonstrate properties of water solubility or water absorption, leading to swelling or dispersion in cold water, ultimately yielding a viscous solution or jelly-like consistency.

Natural polymers offer several advantages over synthetic counterparts:

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

Natural polymers, despite their advantages, also come with some disadvantages:

- Microbial contamination
- Batch to batch variation
- Uncontrolled rate of hydration
- Reduced viscosity on storage.[16]

Table:2 List of natural polymers

S.no	Polymers	Source
1.	Guar gum	Endosperm of seed of cynopsis tetragonolobus
2.	Chitosan	Shell of marine invertebrates
3.	Xanthum gum	Fermentation of glucose by Xanthomonas compestris
4.	Gellan gum	Pseudomonas elodea
5.	Sodium alginate	Laminaria hyperboria

3.1.1 Guar gum: Guar gum is a type of polysaccharide composed of a linear chain of D-mannopyranosyl units connected by β-1,4 glycosidic bonds. These mannopyranosyl units are linked to D-galactopyranosyl units through α-1,6 bonds. This structure provides guar gum with its characteristic properties, including its ability to form viscous solutions and act as a thickening agent in various applications.[17,18]

Guar gum is a naturally occurring galactomannan polysaccharide. When exposed to cold water, it hydrates and swells, forming viscous colloidal dispersions or sols. This unique gelling property can delay drug release, making it an adaptable choice for extended-release dosage forms.[19]

Properties of guar gum:

- Guar gum demonstrates solubility in water while remaining insoluble in organic solvents.

- It exhibits a strong propensity for hydrogen bonding.

- This substance possesses outstanding properties for thickening, emulsion formation, and film creation.
- Guar gum also offers the capability to regulate rheology.

3.1.2 Chitosan: Chitosan is a linear aminopolysaccharide, resulting from the copolymerization of glucosamine and N-acetylglucosamine.[17,18] Chitosan is a naturally derived polymer obtained through the deacetylation process of chitin. It possesses advantageous biological characteristics, including non-toxicity, biodegradability, and biocompatibility. This polymer exhibits bioadhesive properties and possesses antibacterial attributes, rendering it suitable for site-specific delivery applications. Chitosan is a high molecular weight polycationic weak base, with a pKa value ranging from 6.2 to 7. When exposed to acidic pH levels around 1.2 or neutral environments, it undergoes buoyancy, thereby facilitating controlled release mechanisms.[19]
Increasing the thickness of a chitosan film can lead to a reduction in the release rate of substances, thereby slowing down the release process.[8]

Advantages of chitosan:
- The substance's film-forming properties are utilized to diminish the impact of gastrointestinal transit time, potentially improving drug absorption within the body.
- Hollow microcapsules exhibit a propensity to remain buoyant in gastric fluid for an extended period of approximately 12 hours, thereby facilitating prolonged drug release and absorption.
- The drug's release rate adheres to zero-order kinetics, indicating a consistent and controlled release pattern independent of concentration, which can be advantageous for maintaining therapeutic drug levels without plagiarizing.[20]

3.1.3 Xanthan gum: Xanthan gum is a type of polysaccharide characterized by a primary chain composed of D-glucose residues connected via β-1,4-glycosidic bonds. It also contains side chains comprised of two combined units of D-mannose and a D-glucuronic acid residue.[17,18] This polymer exhibits solubility in water but remains insoluble in organic solvents. A 1% aqueous solution typically yields a pH range of 6.0 to 8.0 and demonstrates a viscosity between 1200–1600 cP at 25°C. In the field of FDF (Fixed-Dose Combination) technology, xanthan serves as a matrix-forming agent, aiding in the attainment of prolonged release of Active Pharmaceutical Ingredients (APIs). Furthermore, xanthan gum possesses bioadhesive properties and the capability to create foamy structures, contributing to its versatility in various applications.[17,18]

3.1.4 Gellan gum: Gellan gum is a high molecular weight polysaccharide derived from pseudomonas species through fermentation, particularly from the microbe Sphingomonas elodea and other non-toxic gram-negative bacteria. It's an anionic deacetylated linear polysaccharide consisting of glucuronic acid, rhamnose, and glucose. Structurally, it comprises four linked monosaccharides, including one molecule of glucuronic acid and two molecules of glucose. It's commercially available in two forms: high or low acyl content.
This gum exhibits remarkable gel strength and exceptional stability, flexibility, clarity, film-forming ability, and thermally reversible gel characteristics. It appears as an off-white, water-soluble powder. Gellan gum forms a gel upon the addition of cations, allowing for control over the thickness and texture of various products by adjusting the cationic salt concentration.
Gellan gum readily disperses and hydrates in both hot and cold water, resulting in a viscous solution. Its properties make it a promising candidate for various floating dosage forms, as highlighted by several researchers.[21]

Advantages of gellan gum:-
- Employed to modulate the rate of drug release within formulations, either accelerating or decelerating it.
- Exhibits solubility in water.
- Demonstrates high viscosity even at low concentrations.
- Offers the potential advantage of facilitating drug release via zero-order kinetics.
- Certain tablets containing xanthan gum and citric acid display buoyancy for durations exceeding 24 hours.[20]

3.1.5 Sodium alginate: Sodium alginate primarily comprises the sodium salt of alginic acid, which constitutes a blend of polyuronic acids containing residues of D-mannuronic acid and L-guluronic acid. The block structure and molecular weight of various sodium alginate samples have been subject to research and examination.

- Typical Properties: The pH of a 1% w/v aqueous solution registers at 7.2, indicating a neutral acidity/alkalinity balance.

- Solubility: Sodium alginate demonstrates limited solubility in ethanol (95%), ether, chloroform, and ethanol/water mixtures with over 30% ethanol content. It is similarly insoluble in other organic solvents and acidic aqueous solutions with a pH below 3. However, it gradually dissolves in water, resulting in a viscous colloidal solution.

- Viscosity (dynamic): Various grades of sodium alginate are commercially accessible, yielding aqueous solutions with diverse viscosities. Typically, a 1% w/v aqueous solution at 20°C exhibits a viscosity ranging from 20–400 mPa s (20–400 cP). Viscosity levels may fluctuate based on factors such as concentration, pH, temperature, or the presence of metal ions. Notably, viscosity diminishes beyond a pH of 10.[22]

3.2 Semi-Synthetic polymers: A category of semi-synthetic polymers commonly utilized in the development of floating dosage forms includes various cellulose derivatives. These derivatives encompass Ethyl cellulose ether (EC), Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), and Sodium carboxymethyl cellulose (NaCMC). These polymers are extensively researched, commercially available, and offer a diverse range of grades tailored to specific requirements. Consequently, they are widely employed in the fabrication of floating delivery systems.

3.2.1Ethyl cellulose ether (EC):- EC is characterized as a long-chain polymer composed of β-anhydroglucose units linked via acetal bonds[11,12] The polymer exhibits limited solubility in water, glycerol, and propylene glycol, but it can absorb minimal quantities of water. It readily dissolves in various organic solvents and typically possesses a bulk density of approximately 0.4 g/cm³.[18]
EC was employed in the fabrication of hollow repaglinide microspheres via solvent removal technique. The resultant dosage form exhibited first-order release kinetics of the active pharmaceutical ingredient (API), with no discernible lag time in onset and maintained buoyancy for a duration of 12 hours.[23]

3.2.2 Hydroxypropyl methylcellulose (HPMC):- HPMC is a cellulose derivative that undergoes partial O-methylation and O-(2-hydroxypropylation). When introduced to water, this polymer readily dissolves, resulting in the formation of a colloidal solution. The viscosity of a 2% aqueous solution varies depending on the brand, typically spanning from 3 to 100,000 centipoise (cP).[17,18]
A matrix composed of high-viscosity hypromellose grades demonstrates the capacity to capture CO_2 liberated during the gas-forming mixture reaction. Moreover, it undergoes substantial expansion when in contact with a liquid. This characteristic finds application in developing non-gas-forming FDFs and gastroretentive delivery systems that undergo size augmentation.[24,27]

3.2.3 Soduim carboxymethyl cellulose (NaCMC): NaCMC, or sodium carboxymethyl cellulose, represents the sodium salt derivative of polycarboxymethyl cellulose ether. Carmellose sodium, as it is also known, is a water-soluble polymer renowned for its ability to absorb considerable quantities of water. It functions as a gelling agent, exhibiting a notably high swelling index. The viscosity of 1% aqueous solutions varies across different brands, typically ranging from 5 to 20,000 cP. Factors such as bulk density and compaction influence its properties, with bulk densities typically falling between 0.52 and 0.78 g/cm³.[18,27] Venkateswarlu and Chandrasekhar incorporated NaCMC and HPMC as matrix formers and retardants in the fabrication of floating tablets. The buoyancy of the tablets was ensured by the generation of CO_2 upon exposure to the dissolution medium. Additionally, cetyl alcohol was included in the formulation to prolong the release kinetics while simultaneously reducing the overall density of the system. Tablets formulated with the optimal composition exhibited a rise time delay of 8 seconds, a flotation duration exceeding 12 hours, and sustained release characteristics lasting 8 hours.[28]

3.2.4 Hydroxypropyl cellulose: HPC, a partially substituted poly hydroxypropyl cellulose ether, finds extensive application as an excipient in floating drug delivery systems. It serves multiple roles, including as a matrix former, a thickener in microencapsulation, and a primary constituent of filaments utilized in the manufacture of drug formulations via additive technologies.[18,29]
In their study, they employed HPC in conjunction with stearic acid to fabricate filaments, which were subsequently utilized for 3D printing via fused deposition modeling (FDM). The resulting hollow tablets containing theophylline exhibited buoyancy for a duration of 10 hours, showed no delay in ascent, and demonstrated zero-order drug release kinetics[30]. They achieved a floating drug formulation (DF) using the Tablet-in-Device (TiD) approach, where a core tablet containing theophylline was enclosed within a 3D-printed housing. The filaments for 3D printing were produced through hot extrusion of hydroxypropyl cellulose (HPC) and ethyl cellulose (EC). The resulting tablets, with cavities within the framework, exhibited no delay in rise time, floated for up to 6 hours, and demonstrated a pulsatile release delay of 6 hours.[31]

3.3 Synthetics polymers: Synthetic polymers are gaining increasing significance in the field of pharmaceuticals, serving various roles such as binders, film coating agents, and more. These polymers are macromolecules characterized by their large size and containing a diverse array of functional groups. They can be classified as either purely synthetic or as modified forms of natural polymers, known as semi-synthetic. Examples of synthetic polymers commonly used include

- Hydroxypropyl methyl cellulose
- Ethyl cellulose

Despite their utility, synthetic polymers come with certain disadvantages, including:
- High cost and potential environmental pollution
- Acute and chronic adverse effects
- Poor biocompatibility
- Potential for inflammatory responses and local reactions.[32]

3.3.1 Hydroxypropyl methyl cellulose: Hydroxypropyl methylcellulose ethers are part of a diverse family of polymers that are white to off-white, odourless, and soluble in water. They possess properties such as binding, water retention, thickening, film formation, and lubrication.

These semi-synthetic polymers are inert and viscoelastic, commonly utilized as excipients and components for controlled delivery in oral medications. They are present in a wide range of commercial products.
Some common synonyms for hydroxypropyl methylcellulose ethers include Hypromellose, Methocel, Metolose, Pharmacoat, Benecel MHPC, and E464.

Functional Categories:
- 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.[33]

General Properties of Hypromellose:
- Apparent density ranges from 0.25 to 0.70 g/cm³
- Refractive index: 1.336
- Surface tension: 42 to 56 mN/m

Solubility: Hydroxypropyl methylcellulose (HPMC) demonstrates solubility in cold water, leading to the formation of a viscous colloidal solution. However, it is generally insoluble in hot water, chloroform, ethanol (95%), and ether. Nonetheless, it exhibits solubility in various solvent mixtures such as ethanol and dichloromethane, methanol and dichloromethane, as well as water and alcohol blends. Specific grades of HPMC may also dissolve in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Additionally, certain grades may swell when exposed to ethanol.[34]

Advantages:
- Being water-soluble and one of the most abundant polymers in nature.
- Utilized effectively as a thickener, film former, and water retention agent.
- The hydrophilic matrix represents a straightforward sustained release technology for oral dosage forms[35].

3.3.2 Ethyl cellulose: Ethocel, comprising ethyl cellulose polymers, has been a staple in the pharmaceutical sector for more than half a century. It's a preferred choice in pharmaceutical formulations due to its versatility. It serves multiple functions including taste-masking of bitter actives, safeguarding against moisture, stabilization, coating for extended-release multiparticulates, microencapsulation of actives, serving as an extended-release binder in inert matrix systems, and aiding in solvent and extrusion granulation processes.

Solubility: Ethyl cellulose, a cellulose ether derived from cellulose, is characterized by its water-insoluble nature. Formed through partial O-ethylation of cellulose, it typically contains an ethoxy content ranging between 44-51%. Under physiological pH conditions, ethyl cellulose remains insoluble; however, exposure to gastric juice induces swelling, rendering it permeable to water. This property facilitates extended modified drug release, enhancing patient compliance with pharmaceutical regimens.

Applications: Ethyl cellulose (EC) presents limitations in wet extrusion processes due to its significant elastic properties; however, it can be effectively utilized as a matrix former when combined with certain plasticizing agents. Coarse Ethyl cellulose (CPEC) and fine particle Ethyl cellulose (FPEC) exhibit potential as diluents alongside high molecular weight polyethylene oxide (PEO), serving as both an extrusion aid and a binder. FPEC, in particular, has demonstrated the ability to form wet granulation products with water alone. In formulations, microcrystalline cellulose (MCC) is often incorporated to enhance plasticity in the wetted mass during extrusion and in the resulting extrudate during spheronization.
Ethyl cellulose stands out as an ideal polymer for developing products capable of modified drug release. While only a few Ethyl cellulose polymers have received approval for general pharmaceutical use, they are extensively employed in extended-release solid dosage formulations. Various types of Ethyl cellulose, such as Ethocel 4, Ethocel 10, and Ethocel 45, vary in polymer chain length, dissolution rate, and solution viscosity. Ethyl cellulose is particularly suited for the preparation of modified release coatings.[36]

IV.FATORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

4.1 Formulation factors:

Size of tablets: - The retention of floating dosage forms within the stomach is contingent upon the size of the tablets. Smaller tablets tend to be emptied from the stomach during the digestive phase, whereas larger ones are typically expelled during housekeeping waves. To investigate this phenomenon, floating and non-floating capsules of three different sizes were formulated: small units with a diameter of 4.8 mm, medium units with a diameter of 7.5 mm, and large units with a diameter of 9.9 mm. Analysis revealed that floating dosage units remained buoyant regardless of their size within the gastric contents throughout their residence in the gastrointestinal tract. In contrast, non-floating dosage units sank and remained in the lower part of the stomach. Floating units positioned away from the gastro-duodenal junction were shielded from peristaltic waves during the digestive phase, while non-floating forms remained near the pylorus and were subjected to propelling and retropelling waves.[37]

Density of tablets: The gastric residence time of a dosage form is primarily influenced by its density. Buoyant dosage forms, with a density lower than that of gastric fluids, float in the stomach away from the pyloric sphincter, leading to prolonged retention. Reported densities of such dosage forms are often less than 1.0 g/ml, indicating a density lower than that of gastric contents. However, studies on the floating force kinetics of these dosage forms have indicated that the bulk density alone is not the most suitable parameter for describing their buoyancy capabilities.[38]

Viscosity grade of polymer: The drug release and floating characteristics of Floating Drug Delivery Systems (FDDS) are significantly influenced by the viscosity of polymers and their interactions. Studies have indicated that low viscosity polymers, such as HPMC K100 LV, offer more advantages compared to high viscosity polymers like HPMC K4M in enhancing floating properties. Furthermore, there is an observed decrease in the release rate as the viscosity of the polymer increases.[39]

Shape of tablets: The size of a dosage form indeed plays a crucial role in influencing gastric retention. The mean gastric residence times of non-floating dosage forms can vary significantly, with size being a key factor. Dosage forms can generally be categorized into small, medium, and large units.

In a fed state, smaller units tend to be emptied from the stomach during the digestive phase, whereas larger units are emptied during housekeeping waves. Typically, the larger the size of the dosage form, the longer it will remain in the stomach due to the impediment it poses to passing through the pyloric antrum into the intestine. This prolonged retention time for larger dosage forms can have implications for drug absorption and release kinetics, potentially altering the therapeutic effects of the medication. Therefore, understanding the relationship between dosage form size and gastric retention time is essential in optimizing drug delivery strategies.[40]

4.2 Idiosyncratic factors:

Gender: Women typically have slower gastric emptying times compared to men. For instance, the mean ambulatory gastric retention time (GRT) in meals for men is around 3.4±0.4 hours, whereas for age and race-matched women, it tends to be longer, approximately 4.6±1.2 hours. Interestingly, these differences persist regardless of factors such as weight, height, and body surface area.[41]

Age: Lower gastric emptying times are often observed in elderly individuals compared to younger subjects. Both intrasubject and intersubject variations are evident in gastric and intestinal transit times. Notably, elderly individuals, particularly those aged over 70 years, tend to have significantly longer gastric retention times.[42]

Posture: i) When individuals are in an upright position, floating dosage forms are shielded against postprandial emptying because they remain above the gastric contents, regardless of their size. Consequently, floating dosage forms exhibit prolonged and more consistent gastric retention times compared to conventional dosage forms, which sink to the lower part of the distal stomach and are subsequently expelled through the pylorus by antral peristaltic movements.

ii) Conversely, in the supine position, there is no reliable protection against early and erratic emptying. Large dosage forms, both conventional and floating, experience prolonged retention in supine subjects. Floating forms may initially remain buoyant between the lesser and greater curvature of the stomach, but as they move distally, they can be swept away by peristaltic movements that propel gastric contents toward the pylorus. This can lead to a significant reduction in gastric retention time compared to upright subjects.[42]

Food intake and Nature of food: Dietary factors such as food intake, the composition of food, caloric content, and frequency of feeding significantly impact the gastric retention of dosage forms. The presence or absence of food in the stomach can influence the gastric retention time (GRT) of a dosage form. Typically, when food is present, it tends to increase the GRT of the dosage form, thereby enhancing drug absorption by prolonging its residence at the absorption site. For instance, in a gamma scintigraphic study involving a bilayer floating capsule of misoprostol.[43]

Feeding regimen: In the presence of food, gastric residence time (GRT) tends to increase, resulting in enhanced drug dissolution of the dosage form at the optimal site for absorption. Studies have indicated that following a meal rich in fats and proteins, a GRT of 4 to 10 hours can be observed. This extended retention time allows for prolonged exposure of the drug to the absorption site in the gastrointestinal tract, potentially leading to improved drug absorption and bioavailability.[42]

Table 3: Floating Drug Delivery Products Available in the Market[44]

Brand Name	Active ingredient	Clinical Importance
Cifran OD ®	Ciprofloxacin	Urinary tract infection
Madopar ®	L-DOPA and Benserazide	Parkinsonism
Valrelease ®	Diazepam	Sedative –Hypnotic
Topalkan ®	Aluminum -magnesium antacid	Antacid
Liquid Gavison ®	Aluminium hydroxide	Heart burn
Conviron	Ferrous sulphate	*Pernicious anaemia*
Cytotec®	Misoprostol	Gastric Ulcer

V.MECHHANISMS:

Floating drug delivery systems (FDDS) are designed with a lower bulk density compared to gastric fluids, allowing them to remain buoyant in the stomach for an extended duration without interfering with gastric emptying rates. During the floating phase within the gastric contents, the drug is gradually released from the system at a controlled rate. Once drug release is complete, the residual system is expelled from the stomach, leading to an increased Gastrointestinal Residence Time (GRT) and improved control over plasma drug concentration fluctuations.

In addition to requiring a minimal gastric content to maintain buoyancy, a minimum level of floating force (F) is essential to ensure reliable buoyancy of the dosage form on the meal's surface. To measure the kinetics of floating force, a novel apparatus has been developed for determining resultant weight. This apparatus continuously measures the force equivalent to F over time, necessary to sustain the submerged object.

The effectiveness of the floating drug delivery system is enhanced when F exhibits a higher positive value. This apparatus plays a crucial role in optimizing FDDS, particularly in ensuring the stability and durability of the floating forces generated, thus mitigating the drawbacks associated with unpredictable variations in intra-gastric buoyancy capability. (fig.4)

The formula used to calculate the floating force (F) is expressed as:

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

Where:

- F = represents the total vertical force,
- Df = denotes fluid density,
- Ds = signifies object density,
- V= stands for volume, and
- g = represents the acceleration due to gravity.[13]

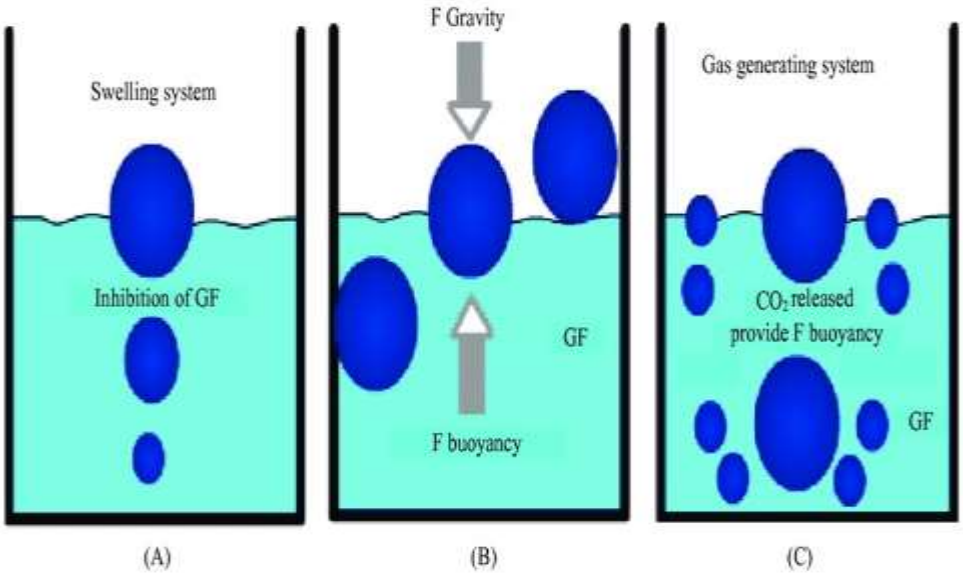


Fig.4: Mechanism of Floating Drug Delivery System

VI.FINDINGS: POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

Table 5: Findings

S.no	Name of researcher/year	Title	Findings	Ref.no
01	*Nagendra R et al./2024*	*Floating Drug Delivery System: A Review.*	Floating drug delivery systems enhance both patient compliance and drug bioavailability by a prolongation of the gastric residence period and the regulation of drug release.	45
02	Jasleen Singh et al./2023	Prospectives of Natural Polymers In Gastroretentive Floating Drug Delivery System: A Review.	Use of polymers including guar gum, xanthan gum, tamarind gum, starch, pectin, okra has been reported by researchers to sustained the release of drug over prolonged period.	46
03	Blynskaya.E.V et al./2022	Polymeric Excipients in the Technology of Floating Drug Delivery Systems.	The current trends in the use of polymers in the technology of floating dosage forms (FDF) and generalized conclusions about the prospects of this direction are outlined.	47
04	Vrettos.N et al./2021	Gastroretentive Technologies in Tandem with Controlled-Release Strategies: A Potent Answer to Oral Drug Bioavailability and Patient Compliance Implications.	The paper reviews different gastroretentive drug delivery technologies and controlled-release strategies that can be combined and summarises examples of formulations currently in clinical development and commercially available gastroretentive controlled-release products.	25
05	Giri.B.R et al./2020	Fabrication of Intragastric Floating, Controlled Release 3D Printed Theophylline Tablets Using Hot-Melt Extrusion and Fused Deposition Modeling.	3DP coupled with HME, could be an effective blueprint to produce controlled-release GRFTs, providing the advantage of simplicity and versatility compared to the conventional methods.	30
06	Tripathi J et al./2019	Current State and Future Perspectives on Gastroretentive Drug Delivery Systems.	The significance of in vitro and in vivo evaluation parameters of various GRDDS is summarized along with their applications.	24
07	Zubedi.S.S et al./2018	Floating Tablets and its Polymers.	Natural polymers like guar gum, chitosan, xanthan gum, Gellan gum and sodium alginate are mentioned in the article. Synthetic polymers mentioned are HPMC, Eudragit, and Ethylcellulose.	48
08	Odeku.O.A et al/2017	Formulation of floating metronidazole microspheres using cassava starch (Manihot esculenta) as polymer.	The results showed that pregelatinized cassava could be useful in the formulation of floating gastroretentive metronidazole microspheres.	49

09	Kohli.S et al/2016	Ethylcellulose Floating Microspheres of Antidiabetic Agent: In Vitro and in Vivo Evaluation.	The investigation revealed the promising potential of gastro retentive microspheres for delivering RG for the treatment of non-insulin dependent diabetes mellitus (NIDDM).	23
10	Kaushik.A et al/2015	Role of excipients and polymeric advancements in preparation of floating drug delivery systems.	Have discussed all natural and synthetic systems with their effect on the release and other parameters which are essential for the floating formulation development.	17

VII.CONCLUSION/ FUTURE PROSPECT:

Floating drug delivery systems (FDDS) offer an added advantage, particularly for drugs primarily absorbed in the upper segments of the gastrointestinal (GI) tract, such as the stomach, duodenum, and jejunum. Polymers play a crucial role in achieving controlled drug release from the dosage form. They serve various functions in formulations, including gelling, emulsifying, increasing viscosity, and retarding the rate of drug release. Thus, understanding the role of polymers in drug delivery is pivotal in pharmaceutical science.

Nevertheless, there remains a significant need for further research to address various physiological and pharmaceutical barriers and to develop more effective dosage forms. It is essential to focus on overcoming these challenges to enhance the performance of FDDS. Future research endeavours in FDDS should aim to discover methods for precisely controlling the rate of drug release into the GI tract. This optimization is crucial for improving the pharmacokinetic and toxicological profiles of medicinal agents.

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