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The Significance Of Excipients And Polymeric Innovations In The Formulation Of Floating Drug Delivery Systems

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Abstract: The contemporary trend in the advancement of oral medicinal products (MP) involves the amalgamation of targeted transport and enhancement of the release profile of the active pharmaceutical ingredient (API). A prominent strategy to actualize this concept entails the development of floating gastroretentive delivery systems, facilitating prolonged residence of the dosage form (DF) within the gastric contents. This discourse delves into the nomenclature of polymeric excipients (Es) employed in the fabrication of floating drug delivery systems (FDDS). Drawing upon findings presented in scholarly publications, predominant categories of polymers, their inherent properties, and their specific roles in diverse technological methodologies for achieving buoyancy are elucidated. Furthermore, the text delineates approaches for modifying the release of APIs within these systems and explicates the corresponding polymeric excipients utilized for such modifications. The prevailing tendencies in polymer utilization within the realm of floating dosage forms (FDF) are discussed, culminating in overarching conclusions regarding the future prospects of this trajectory.

Index Terms - floating drug delivery systems, gastroretentive drug delivery systems, polymers.

1. INTRODUCTION

Dosage forms with the capacity to stay in the stomach are known as gastroretentive systems, and they improve the regulated absorption of released medication from acidic media.[1] Four different types of modifications - mucoadhesive systems, high density systems, changed form system, and floating systems, are used to produce gastroretention. The gastroretentive drug delivery system referred to as a floating drug delivery system exhibits buoyancy within the gastric environment, facilitating prolonged retention in the stomach without impeding gastric emptying kinetics. It does this by having a bulk density lower than gastric fluids. First, in order to address the issue of dosage form swelling, Davis et al. looked at floating systems. As a result, they provided the pharmaceutical industry with an improved gastroretentive system, which is currently among the most effective controlled release dosage forms available. Even with less restrictions like pH, food presence, and gastrointestinal motility, the floating delivery system has benefits like increased drug bioavailability, extended release, and local action that greatly aid in the treatment of any illness. [2]

1.1 FLOATING DRUG DELIVERY SYSTEM

This system of FDDS was first explained by Davis in 1968. Extending the stomach residence time using FDDS is a helpful method for improving the drug's bioavailability. FDDS, whose bulk density either initially decreases to 1.004 g/cm3, less than that of gastric juice, or reaches the proper value following a specified duration of consumption. This property allows the medication to remain on the stomach's surface rather than be drained into the stomach's lower regions, protecting the mucous membranes and slowing down the rate of emptying. Flotation enables the system to precisely administer medications to the appropriate locations at the appropriate times to meet the appropriate therapeutic needs. When it comes to drugs with low intestinal fluid solubility and stability, these devices are helpful. The concept underlying Floating Drug Delivery Systems (FDDS) involves rendering the dosage form less dense than gastric juices, thereby facilitating buoyancy atop them. Functioning as hydrodynamically regulated low-density devices, FDDS demonstrate sufficient buoyancy to traverse the stomach contents while maintaining sustained buoyancy without appreciably impeding gastric emptying kinetics. Subsequent to drug release, the residual system within the stomach undergoes evacuation, leading to the elongation of the stomach residence period and the adept management of fluctuations in plasma drug concentration. The buoyant preparation concept provides a straightforward and pragmatic approach to augmenting stomach capacity. Selectively extending the stomach retention of a drug delivery system is warranted in specific cases to enhance the therapeutic efficacy of the pharmacological component. Instances include scenarios where drugs exhibit poor solubility or susceptibility to alkaline pH degradation, thereby effectively prolonging stomach retention. Moreover, this approach promotes enhanced drug absorption within the proximal segments of the gastrointestinal tract. Notably, in the treatment of certain ulcerative disorders, protracted gastric retention of the therapeutic agent enables sustained drug delivery to the stomach and proximal small intestine. Numerous advantages result from this, such as increased bioavailability and therapeutic efficacy with fewer dose requirements [3-4]

1.1.1 FLOATING DDS ADVANTAGES

Floating dosage systems exhibit gastric retentive properties and offer numerous benefits in the realm of drug delivery, including:

1. **Simplicity in Formulation:** These systems can be formulated using straightforward and conventional techniques.
2. **Precision in Drug Delivery:** They enable targeted delivery of drugs to specific sites within the body.
3. **Controlled Drug Release:** These systems facilitate controlled and gradual release of drugs over time.
4. **Localized Residual Action:** Drugs can be delivered to and maintained at specific locations within the stomach, allowing for sustained effects.
5. **Enhanced Drug Absorption:** Prolonged gastric retention time (GRT) ensures extended contact between the dosage form and its target site, leading to improved drug absorption.
6. **Mitigation of Irritation:** Drugs with slow-release rates can minimize irritation of the gastrointestinal mucosa. For instance, acidic substances like aspirin can irritate the stomach lining upon contact. Formulating such drugs as hydrodynamically balanced systems (HBS) can reduce this irritation, making them suitable for administration.
7. **Effective Prolonged Release:** Tablets or capsules of prolonged-release floating dosage forms dissolve in gastric fluid, ensuring complete dissolution before reaching the small intestine. This promotes full drug absorption even within the alkaline environment of the intestine.
8. **Diarrhoea Prevention:** In situations where rapid intestinal movement and short transit times could lead to diarrhoea and poor absorption, maintaining the drug in a floating state in the stomach proves beneficial for improved efficacy.
9. **Gastroesophageal Reflux Disorder (GERD) Treatment:** These systems can be employed in the treatment of GERD, a condition involving stomach acid flowing back into the oesophagus.
10. **Enhanced Patient Compliance:** Due to their ease of administration and patient-friendly characteristics, these systems lead to higher patient compliance with prescribed regimens. [5]

1.1.2 Floating DDS Advantages

1. The principal drawback of a floating drug delivery system stems from its requirement for an adequate volume of gastric fluids to facilitate buoyancy and prevent sinking. Nevertheless, this constraint can be addressed through the application of bio adhesive polymers that readily adhere to the gastric mucosa, ensuring sustained retention.
2. These systems are particularly advantageous for drugs that undergo considerable absorption along the entire length of the gastrointestinal tract and undergo substantial first-pass metabolism.
3. It's worth noting that certain drugs present within a floating system might trigger irritation within the gastric mucosa. [5]

Gastric emptying of floating drug delivery systems can occur in an unpredictable manner, heavily contingent upon the dimensions of the dosage form. Consequently, it is advisable for patients not to administer such dosage forms prior to bedtime.

2. The Role of Polymers in the Technological Paradigm of Floating Drug Delivery Systems

Targeted distribution and the adjusted API release are the primary benefits of floating gastroretentive devices, as previously indicated. The majority of the time, each of these characteristics is achieved by using certain Es, most of which are polymeric in nature (Figure 1).

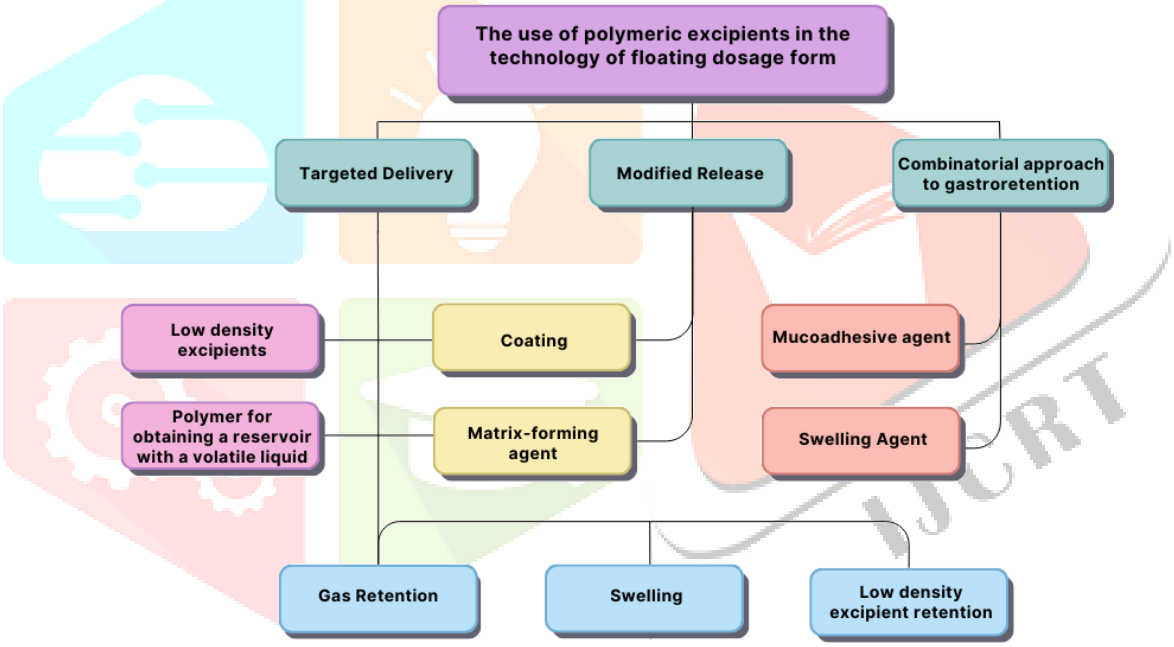

Figure 1. The application scope of polymer excipients in the technology of buoyant dosage forms

Targeted drug delivery manifests as a buoyant attribute in this instance, achievable through diverse technological approaches that typically characterize the Floating Drug Delivery (FDF) classification. Presently, two primary methodologies are discerned: the creation of systems with initially low density by incorporating air or low bulk density explosives, and the generation of systems with density that decreases post-ingestion owing to either swelling or gas production. [6]

3. Natural Polymers Applied to Floating Delivery System Technology

Generally speaking, the technology of floating systems that makes use of individual Es of a polymeric type is not restricted to any particular method of attaining buoyancy. As such, it makes sense to separate them into three categories based on where they came from: naturally occurring, semi-synthetic, and synthetic. The most common type of polymers used in FDF technology that come from natural sources are polysaccharides, which include gums, chitosan, sodium alginate (NA), pectin, and others. These materials are used in a progressive "green" manner in pharmacy, popularising natural e-steroids; yet, most of the time, research is done to identify novel excipients or ways to replace old ones. The polymers mentioned earlier typically exhibit favourable characteristics in relation to swelling index and hydration rate. However, during storage, alterations may occur

with respect to viscosity, residual moisture loss, susceptibility to microbial contamination, capacity for controlled release, and various other properties. [7]

3.1 Alginates

Alginic acid salts with varying concentrations of calcium and sodium find extensive application in floating delivery system technology. Sodium alginate, a heteropolymer formed through the combination of polyuronic acid residues of M-fragments (β-d-mannuronic acid residue) and G-fragments (α-l-guluronic acid residue), constitutes a principal component. This polysaccharide in solutions with a pH below 3, is nearly insoluble, gradually dissolves in water to yield a viscous colloidal solution (exhibiting a viscosity range of 20–400 cP at 20 ˚C for a 1% solution), and demonstrates bioadhesive properties. Sodium alginate serves as a matrix-forming material in Floating Drug Delivery (FDF) technology. Additionally, it forms water-insoluble gels with a network structure when combined with Ca^{2+} and other metal salts, facilitating the gradual adsorption and release of the Active Pharmaceutical Ingredient (API). Ionotropic gelation is frequently employed to produce microcapsules, as exemplified by Praveen et al., who incorporated myristyl alcohol into sodium alginate to create low-density granules through ionotropic gelation, resulting in porosity induced by freeze drying. This approach achieved prolonged release, immediate flotation, and a flotation duration exceeding 20 hours. Falcone et al. leveraged sodium alginate's reactivity with calcium salts to formulate two distinct 3D printing inks featuring a matrix former and a crosslinking agent. The resulting hollow filament-based drug delivery system (DF) exhibited rapid ascent and flotation for a duration of 14 hours, with 80% of the drug released gradually during this period. Adebisi et al. employed ionotropic gelation to produce floating granules of clarithromycin based on sodium alginate, coated with a mucoadhesive layer of chitosan, and incorporating olive oil to reduce the density of the delivery system. This formulation achieved a 24-hour float duration with controlled API release over 8 hours. [8]

3.2 Chitosan

Chitosan is a copolymer of glucosamine and N-acetylglucosamine, a linear amino polysaccharide. This polymer has a specific density of 1.35–1.40 g/cm^3 and is only marginally soluble in water. Exhibiting near insolubility in organic solvents and alkaline solutions (at a pH of approximately 6.5), and solubility in acids upon protonation of amino groups, this substance serves as both a matrix-forming agent and a film-forming substance within floating delivery system technology. The material imparts mucoadhesive properties to the drug delivery system (DF) due to its ionic nature. Furthermore, it is frequently employed in the formation of microcapsules through ionotropic gelation and emulsion cross-linking methodologies. Using the ionotropic gelation process, Svirskis et al. created and produced hollow floating and mucoadhesive granules containing acyclovir based on chitosan. While most of the granules' buoyancy persisted for almost three hours, causing a delayed release, the resultant DF had a zero-ascent delay time. Through ionotropic cross-linking, Praveen et al. produced floating granules containing carvedilol as the active pharmaceutical ingredient. DF showed that it could float for over 10 hours and postpone the release of medication for 8 hours. Budianto et al. demonstrated an unconventional way to create floating dosage forms: they synthesised a chitosan-like material using a grafted polyvinylpyrrolidone (PVP) molecule. Following the inclusion of pore formers, a hydrogel based on this material and containing the API amoxicillin showed a short ascending delay time, a flotation period of more than 180 min, and a delayed release of MP. [9]

3.3 Carrageenan

Carrageenans, linear sulfate polysaccharides comprised of sulfated galactose and 3,6-anhydrogalactose linked by alternating α-1,3 and β-1,4 glycosidic linkages, constitute their molecular structure. These polymers exhibit a solution viscosity of 5 cP (at 75 ˚C) and solubility in water when subjected to heating at either 20 ˚C or 80 ˚C, contingent upon the specific family. Demonstrating versatility, these polysaccharides can be crosslinked to form microcapsules and find utility in Floating Drug Delivery (FDF) technology as both gelling and retardant agents.

In the work by Zhang et al., carrageenan, employed in conjunction with sodium alginate (NA), facilitated ionotropic gelation, leading to the creation of floating granules containing B. javanica oil. The delayed release of the Active Pharmaceutical Ingredient (API) from the resulting drug delivery system (DF) was observed over a six-hour period. The buoyancy of the system was attributed to the characteristics of the matrix polymer (MP) and the high porosity of the granules. Abbas and Alhamdany, adopting the ionotropic gelation process, developed floating microcapsules containing enalapril maleate. This formulation incorporated iota-carrageenan and sodium alginate, with the resulting DF matrix's porosity and the inclusion of a blowing agent enabling buoyancy. The controlled release of API and the flotation period persisted for 24 hours. [10]

3.4 Pectins

Pectins, characterized by their high molecular weight, primarily consist of D-galacturonic acid residues linked together via α-1,4 glycosidic linkages, with potential esterification of acid and hydroxyl groups. These polymers find application in the ionotropic gelation method for the creation of microcapsules. Upon interaction with calcium ions, the resultant cross-linked gel acquires mucoadhesive properties. Additionally, pectins serve as matrix formers in the realm of floating delivery systems technology.

Alhakamy et al. employed the ionotropic gelation method to generate granules incorporating ellagic acid through the interaction of pectin with calcium ions. The resulting drug delivery system (DF) exhibited a 24-hour flotation duration, accompanied by continuous release over the same period. Abouelatta et al. utilized the ionotropic gelation process to produce floating granules of cinnarizine based on pectin. This formulation achieved an 8-hour flotation time, immediate ascent, and zero-order release kinetics within a 12-hour timeframe. [11]

3.5 Xanthan Gum

Xanthan gum, a polysaccharide, comprises two D-mannose units and a D-glucuronic acid residue as side chains, forming a main chain of D-glucose residues connected by β-1,4-glycosidic linkages. Characterized by a viscosity ranging from 1200 to 1600 cP at 25 ˚C, it is soluble in water and insoluble in organic solvents. A 1% aqueous solution of xanthan gum exhibits a pH within the range of 6.0 to 8.0. In Floating Drug Delivery (FDF) technology, xanthan gum serves as a matrix-forming agent, facilitating an extended release of the Active Pharmaceutical Ingredient (API). The material demonstrates the capability to generate foamy structures and exhibits bioadhesive properties.

Lavanya et al. employed xanthan gum as a matrix former to produce gas-forming propranolol floating tablets. The resulting gastroretentive device maintained buoyancy, allowing controlled release of the API for 12 hours, with an ascent delay time of approximately 150 seconds. Budaya and Surini utilized a co-processed excipient comprising xanthan gum and acacia gum to create floating famotidine gas-generating tablets. The resultant mixture formed a matrix that solidified into a gel with a high swelling index. The resulting tablets achieved regulated release of the API and sustained buoyancy for an entire day. [12]

3.6 Guar Gum

Guar gum, a polysaccharide, comprises a linear chain of D-mannopyranosyl units linked by β-1,4 glycosidic linkages to D-galactopyranosyl units connected through α-1,6 links. This galactomannan exhibits solubility in water and rapidly undergoes swelling, yielding a highly viscous, thixotropic sol under both cold and hot conditions. A 1% solution of guar gum possesses a moderate pH range of 5.0–7.0 and a dynamic viscosity of 4860 cP. In its dry state, the material exhibits a density of 1.492 g/cm^3.

Within the realm of Floating Drug Delivery (FDF) technology, guar gum assumes roles as a mucoadhesion agent, matrix-forming agent, and retardant. Leveraging the polymer's pronounced water-swelling capacity, the density of the drug delivery system (DF) can be reduced, and its size increased, thereby impeding premature removal from the stomach. Dey et al. employed guar gum and xanthan gum to fabricate matrix gas-forming tablets containing atenolol. The resulting DF exhibited delayed release of the Active Pharmaceutical Ingredient (API) and maintained buoyancy for 12 hours in vitro, as well as over 6 hours within the stomachs of test animals (rabbits). [13]

3.7 Other Natural Polymers

Science is interested in finding new E that is naturally occurring or in finding new ways to get materials that are currently recognised. Such papers are mostly focused on the synthesis of polymers for further application in the field of gastroretentive drug delivery technology.

Hendrika et al., as an example, extracted pectin from the peel of Musa balbisiana ABB (banana) and applied it in an ionotropic gelation process with calcium chloride to formulate amoxicillin granules. To ensure buoyancy, a gas-forming agent (sodium bicarbonate) was incorporated into the composition. The drug delivery system (DF) exhibited an ascent delay time of 20 seconds, a flotation period exceeding 12 hours, and the release of the Active Pharmaceutical Ingredient (API) followed the Higuchi kinetics model with a duration of 5 hours.

Hyaluronic acid was employed by Liu et al. as a gelling agent in the extrusion and subsequent freeze-drying process to create tablets containing dihydromyricetin. The addition of sodium bicarbonate, a blowing agent, and cetyl alcohol, a low-density agent, produced buoyancy. The ideal DF produced flotation and postponed the release of the API for 24 hours. Khoder et al. were given floating ciprofloxacin granules, which were further treated with calcium chloride, and used as a gel-conjugate of bovine serum albumin with NA. Because of the foamy structure of this delivery system, the flotation duration was up to 48 hours, and DF offered a 3-hour delayed release of API.

For the fabrication of gas-forming famotidine microcapsules through ionotropic gelation utilizing sodium alginate (NA), Mahor et al. isolated a polysaccharide derived from D-xylose and D-glucuronic acid obtained from the seeds of Mimosa pudica. The resultant substance served multifunctionally as a mucoadhesive and retardant. Chitosan was introduced to decelerate the release of famotidine and enhance adherence to mucous membranes. The resulting drug delivery system (DF) exhibited a 12-hour buoyancy and achieved controlled release of the Active Pharmaceutical Ingredient (API). [14]

In a similar vein, Taranally et al. engineered floating metoprolol tartrate granules via ionotropic gelation, employing a composite of pectin, xanthan gum, and locust bean gum. The formulation, facilitated by the high porosity of the calcium pectinate matrix and the inclusion of a gas-forming agent, achieved prolonged flotation exceeding 12 hours. The resulting DF exhibited pulsatile release characteristics.

Xu et al. presented a non-standard approach by creating a hybrid gel of starch and microcrystalline cellulose, which after freeze-drying exhibited great porosity and low density because of the three-dimensional structure. Based on the derived excipient, ranitidine-loaded tablets maintained their buoyancy for a full day.

By creating pores during the sublimation of camphor, Kukati et al. were able to produce buoyancy in their floating tablets, which were based on a matrix of locust bean gum. For 12 hours, DF maintained buoyancy and zero-order release kinetics without experiencing an ascension delay. Razavi et al. employed xanthan gum and a hydrocolloid that was separated from Orchis morio as a matrix forming for metformin-containing floating flatulent tablets. The resultant dose form in vivo showed a 12-hour delay in the stomach's API release. [15]

To create metformin gas-forming tablets, xanthan gum and a powder made from Tamarindus indica seed kernels, Razavi et al., were utilised as matrix-forming ingredients. DF gave a continuous delivery of API for 12 hours while floating for over 24 hours. Employing chitosan as a coating to confer mucoadhesive properties, galactomannan derived from Caesalpinia pulcherrima (Thombre and Gide) was integrated with sodium alginate (NA) as a matrix former to fabricate amoxicillin granules via ionotropic gelation. The resulting drug delivery system (DF) demonstrated the capacity for controlled release of the Active Pharmaceutical Ingredient (API) and sustained buoyancy for a duration of eight hours, attributed to its elevated porosity and the incorporation of calcium carbonate as a gas-forming agent. [16]

4. Semi-Synthetic Polymers Employed in the Field of FDDS

A class of semi-synthetic polymers that are primarily represented by several cellulose derivatives, including sodium carboxymethyl cellulose (NaCMC), hydroxypropyl cellulose (HPC), ethyl cellulose ether (EC) and hydroxypropyl methylcellulose (HPMC). These Es are extensively utilised to create floating delivery systems since they are readily available, thoroughly researched, and come in a variety of grades that are specifically created to meet different purposes. [17]

4.1 EC

Ethyl cellulose (EC) is a polymer characterized by a lengthy chain composed of β-anhydroglucose units linked through acetal linkages. Possessing a bulk density of 0.4 g/cm^3, it exhibits near insolubility in water, glycerol, and propylene glycol. Additionally, it has an affinity for trace amounts of water and demonstrates solubility in various organic solvents. In the context of Floating Drug Delivery (FDF) technology, EC finds application in the creation of water-insoluble coatings, enabling a modified release of the pharmaceutical compound and the retention of gas within the system. Beyond this application, EC is employed as a density-reducing agent and for the removal of solvents in the production of microspheres.

By removing the solvent, Kohli et al. created hollow repaglinide microspheres via EC. First-order API release kinetics, 0% ascent delay time, and 12-hour buoyancy retention were all supplied by the resultant DF. Liu et al. produced gossypol gas-forming tablets by combining EC (10 cP) with HPMC K4M to create a more robust matrix. DFs had a delayed release of API, a 12-hour floating period, and an ascent delay duration of less than one minute. Kim and colleagues applied the low density, hydrophobic qualities that influence the release and penetration of water into DF and EC, as well as the capacity of HPMC to create stable gels, after obtaining sodium ecabeta tablets through moulding and freeze-drying. [18]

The resultant porous DF offered delayed release of API, had 0% ascent delay time, and maintained gastroretentive qualities for 12 hours in vivo. In order to create floating microspheres of clarithromycin, Nashar et al. devised a composition and technology. HPMC E5 had a smaller particle size, a higher loading and release rate of the API, and EC provided the development of a skeleton upon removal of the solvent. The resultant DF gave a gradual release of clarithromycin and floated up right away. It could also remain on the surface of the dissolution medium for eight hours. [19]

4.2 HPMC

Hydroxypropyl methylcellulose (HPMC), denoted as O-(2-hydroxypropylated) and partially O-methylated cellulose, is a known polymer in pharmaceutical formulations. This polymer exhibits solubility in water, forming a colloidal solution with a viscosity ranging from 3 to 100,000 cP for a 2% aqueous solution, dependent on the specific brand. Despite HPMC's bulk density and post-compaction density being lower than that of gastric juice at 0.341 and 0.557 g/cm^3, respectively, the actual density is higher at 1.326 g/cm^3. In the realm of Floating Drug Delivery (FDF) technology, HPMC serves the dual functions of a matrix-forming agent and a mucoadhesion-promoting agent. The fabrication of non-gas-forming FDFs and the expansion of gastroretentive delivery systems involve utilizing high-viscosity hypromellose grades as matrices. These matrices exhibit the ability to both retain carbon dioxide released during the reaction of a gas-forming mixture and swell significantly upon contact with a liquid. [20].

Shinde et al. synthesized delayed-release matrix floating tablets containing Losartan. The formulation comprised three distinct layers: a buoyant pressed layer, consisting of a blend of HPMC K4M and sodium bicarbonate, wherein the polymer retained the liberated gas; an immediate-release core; and an intermediary pressed coating utilizing HPMC E50. The tablets exhibited a floating duration of nearly 12 hours, ascended within 5 minutes, and achieved an API release period of 6 hours. In a similar context, Sungthongjeen et al. developed theophylline tablets employing matrices of HPMC grades K100LV, K4M, and K100M. The delayed release of the API and the retention of gas resulting from the reaction between sodium bicarbonate and citric acid were assured through the formation of the hypromellose gel. Depending on their composition, the resultant tablets containing each type of HPMC gave rise times that were less than 15 minutes, flotation

times that were greater than 480 minutes, and theophylline releases that were delayed. Cefuroxime axetil was the active ingredient in the floating tablets created by Rao et al. The HPMC brand K4M served as the tablet's gas-retaining matrix. The optimized composition of the drug delivery system (DF) conformed to the Korsmeier-Peppas release kinetics model over a 12-hour period, demonstrated buoyancy for 6 hours in vivo and 12 hours in vitro, and exhibited a 2-minute ascent delay time. Jadi et al. administered floating tablets of propranolol, employing HPMC K4M as a matrix former and Compritol 888 ATO (glyceryl behenate) as a low-density excipient. The resulting drug delivery system (DF) achieved a delayed release of the Active Pharmaceutical Ingredient (API) for 10 hours, with zero ascent delay time and a flotation duration of 12 hours. Based on HPMC K4M, Malladi and Jukanti created clarithromycin matrix pills that float because of pores created when camphor was sublimated and added to the mixture. The optimised DF exhibited a delayed release of API, a flotation time exceeding 12 hours, and a zero-rise time delay of 10s. [21]

4.3 NaCMC

The sodium salt derivative of polycarboxymethyl cellulose ether is identified as NaCMC. The bulk density and post-compaction viscosity of 1% aqueous solutions range from 5 to 20,000 cP, contingent upon the specific brand. Carmellose sodium, a water-soluble polymer, exhibits notable water-absorption capabilities and serves as a gelling agent with a high swelling index. This compound is strategically employed in formulating matrices for gastroretentive systems, ensuring the rapid formation of a gel layer on the system's surface and a significant augmentation in the dimensions of the drug delivery system (DF). [22]

To formulate floating tablets, Venkateswarlu and Chandrasekhar utilized NaCMC and HPMC as matrix formers and retardants. The addition of cetyl alcohol to the formulation served to decelerate the release of CO_2, concurrently reducing the density of the system. This ensured the guaranteed flotation of the drug delivery system upon contact with the dissolving medium. The optimized tablet composition exhibited an 8-second ascent delay time, a 12-hour flotation duration, and an 8-hour sustained release. Similarly, Rapolu et al. employed a combination of NaCMC and HPMC K15M as matrix-forming agents to develop floating gas-forming tablets. The resulting drug delivery system demonstrated a sustained ascent delay time of 3.25 minutes, a flotation duration of nearly 12 hours, and sustained release of the Active Pharmaceutical Ingredient (API), metronidazole. [23]

4.4 HPC

Hydroxypropyl cellulose (HPC), a partially substituted polyhydroxypropyl cellulose ether, is widely employed in the domain of floating drug delivery systems. Its versatile applications include serving as a thickening agent in microencapsulation, functioning as a matrix former, and constituting the principal component of filaments in additively manufactured drug delivery systems. Hyprolose exhibits insolubility in hot water, with solubility varying based on its specific grade. Possessing an approximate bulk density of 0.5 g/cm^3, it demonstrates varying degrees of solubility in methanol, ethanol, dichloromethane, propylene glycol, and water below 38 °C, forming a colloidal solution. Notably, this polymer attains the lowest actual density, resulting in superior buoyancy when compared to other cellulose ethers such as NaCMC and HPMC.

Giri et al. prepared filaments with stearic acid using high-performance computing (HPC), which were subsequently utilised to 3D print theophylline tablets with hollow interiors using fused deposition modelling (FDM). The DF demonstrated zero-order drug release kinetics, no ascent delay, and stayed buoyant for 10 hours. By creating a core tablet that contained theophylline and placing it in a 3D-printed housing, Dumpa et al. successfully fabricated a floating drug delivery system (DF) employing the Tablet-in-Device (TiD) methodology. Fused Deposition Modeling (FDM) filaments were generated from hydroxypropyl cellulose (HPC) and ethyl cellulose (EC) through the application of hot extrusion. The resulting tablets exhibited a zero-rise delay time, a flotation duration of up to six hours, and a pulsatile release delay of six hours attributed to the presence of voids in the framework. In a similar vein, Vo et al. employed hot extrusion to produce cinnarizine-loaded filaments based on hydroxypropyl cellulose (HPC), subsequently utilized in the fabrication

of hollow tablets using FDM 3D printing. Depending on the composition, the resultant DF showed zero-order release kinetics from 6 to 12 hours, immediate floating, and a flotation duration of more than 12 hours. [24]

4.5 Other Semi-Synthetic Polymers

The variety of polymeric materials utilised in the process of creating floating dosage forms is mostly restricted to the previously mentioned instances. Nonetheless, there are instances of the application of different semi-synthetic polymer variations in the publications.

Bhardwaj et al. employed cellulose acetate (CA), a water-insoluble excipient commonly utilized for the creation of semi-permeable coatings or matrices in sustained-release tablets. In their study, CA was utilized to fabricate floating films combined with a gas-forming agent and 5-fluorouracil. The resulting films were incorporated into capsules containing the drug formulation, and upon disintegration, exhibited ascent delay times ranging from 85 to 142 seconds and flotation durations spanning 17 to 23 hours, consequently leading to a delayed release of the Active Pharmaceutical Ingredient (API).

Asa and Mirzaeei, in a separate investigation, formulated ciprofloxacin microcapsules utilizing cellulose acetate and the solvent removal technique. The resultant drug delivery system (DF) exhibited prompt flotation, rapid surfacing, and continuous release of the API over a twenty-four-hour period. Hydroxyethyl cellulose (HEC), a prevalent non-ionic water-soluble polymer employed as a binder and coating agent in tablet manufacturing processes, was investigated by Kim et al. Due to HEC's faster and more vigorous swelling properties compared to hydroxypropyl methylcellulose (HPMC), the researchers attempted to employ HEC as a matrix-forming agent in combination with HPMC. However, the resulting gel structure proved unable to withstand the stresses associated with carbon dioxide release during the production of gas-forming floating tablets. [25]

5. Polymeric Materials Employed in the Technology of Buoyant Drug Delivery Systems

5.1 Aliphatic Polyesters

Aliphatic polyesters encompass synthetic homopolymers or copolymers derived from glycolic acid, lactic acid, glycolide, and hydroxycaproic acid, exemplified by polymers such as polycaprolactone and polylactic acid. Specifically, polylactic acid, also denoted as polylactide (PLA), represents a thermoplastic polyester derived from 2-hydroxypropanoic acid. This polymer melts between 165 and 180 ◦C and is soluble in a variety of organic solvents but insoluble in water. This substance has a rather high specific gravity of 1.21–1.28 g/cm^3, and its tensile strength varies from 35–85 MPa depending on its molecular weight. PLA can function as a mucoadhesive and is utilised in the FDF technique to create fibres for 3D printing or insoluble coatings. [26]

Malik et al. employed this polymer to electrospin nanofibers that were loaded with diacerein. The resultant DF enhanced the solubility of the API, floated for more than three days, had no rise delay time, and offered a controlled release of the medication for thirty hours. Its low density was caused by air cavities and mucoadhesion qualities. Fu et al. used the same method to produce a floating DF of riboflavin. Using polylactide-based filaments, a 3D printer was used to build the case, which has a cavity and is shaped like a cylinder; tablet cores with a K15M HPMC matrix were obtained through direct compression. The test animals, rabbits, were given the collected DF, which was kept in their stomachs and gave a continuous release of API for almost three days. [27]

Derived through the synthesis of ε-caprolactone, polycaprolactone (PCL) constitutes a polyester characterized by a molecular weight within the range of 80,000 to 150,000. The polymer exhibits solubility in specific organic solvents while remaining insoluble in water. Notably, PCL manifests a melting temperature in the range of 58–63 ˚C and demonstrates a tensile strength ranging from 20 to 35 MPa PCL can be utilised to create films, microcapsules, and microspheres - floating systems. For instance, Lee et al. used PCL and PLA to create

hollow microspheres that contained metformin and fenofibrate. These microspheres were then coated with PCL-based shells that contained either piroxicam or fenofibrate. Because it contained olive oil, which acts as a density-reducing agent, had a cavity, maintained buoyancy for over twenty-four hours, and offered delayed release of API, DF showed immediate flotation. [28]

5.2 Polyethylene Glycol (PEG)

PEG is a water-soluble polymer of ethylene glycol that can be either liquid or solid depending on its molecular weight, which typically ranges from 200 to 35,000. The density of the material varies from 1.11 to 1.21 g/cm^3, depending on the brand. It functions as an adhesion-promoting agent and matrix-forming agent in FDF technology. Melt foaming method and composition were developed by Vasvari et al. to create a floating metronidazole delivery system. Because PEG 4000 is polymeric, it allowed for a high air capture rate during component mixing and the creation of a stearic acid matrix, which delayed the release of the active pharmaceutical ingredient. According to the Korsmeier-Peppas kinetic model, the resultant DF released metronidazole with no ascent delay and maintained buoyancy for 10 hours. Acyclovir is delivered in a gastroretentive manner by Haimhofer et al. via ultrasound-induced foaming (Ultrasonic Batch Technology). A porous bulk comprising a solidified combination of stearic acid and PEG 4000 comprised the matrix of this DF. This method produced a foam with mucoadhesive qualities that guaranteed flotation during release in line with the zero-order kinetics model within 10 hours and no rising delay. [29]

5.3 Polyethylene Oxide (PEO)

PEO, or non-ionic ethylene oxide homopolymers, melt around 65–70 ˚C and are soluble in water and some organic solvents. These polymers have a real density of about 1.3 g/cm^3. PEO grades with high molecular weights are used as matrix formers in the technique to create floating delivery systems; additionally, the excipients reported have remarkable mucoadhesive qualities and may also swell to greatly increase in size.
PEO (Polyox WSR205 and Polyox WSR N12K) was utilised by Jagdale et al. to produce pulsing bisoprolol tablets. The moulded covering that was placed on top of the previously acquired core included a combination of these polymers and blowing agents. Within three minutes, the tablets rose to the top of the dissolving medium, stayed afloat for nine hours, and postponed the pulsatile release for up to four hours. Cvijic et al. employed PEO samples ranging in molecular weight from 1,000,000 to 7,000,000 to create floating gas-forming ranitidine tablets. A delayed release of API, a flotation time of 90 to 640 minutes, and an ascent delay time of 90 to 150 seconds were observed in manufactured tablets with different compositions. [30]

5.4 Polymethacrylates

Methacrylic acid, dimethylaminoethyl methacrylates, and methacrylic acid esters in different ratios are synthesised into cationic and anionic polymers known as polymethacrylates. Polymethacrylates are employed as mucoadhesive agents, film coatings, matrix elements that offer modified release, and solvent removal to produce microspheres.
Bansal et al. employed a 1:1 copolymer of methacrylic acid and methyl methacrylate (Eudragit S-100) to create hollow microspheres containing itopride hydrochloride using the solvent removal technique. In vivo gastroretention of over 8 hours, zero ascent delay, 24-hour flotation period, and delayed API release were all seen in DF. Gupta et al. devised the formulation and technology for creating famotidine hollow microspheres based on Eudragit S-100. DF made using the solvent removal process had a flotation time, an instantaneous rise to the surface, and a continuous release of the API for up to 20 hours. Gupta et al. developed pantoprazole hollow microspheres using a mixture of a type B ammonio methacrylate copolymer (Eudragit RS100) and a methacrylic acid-methyl methacrylate copolymer (1:1), Magnesium stearate was also a component of the medicinal composition used to reduce density. The resultant DF floated immediately, maintained its buoyancy, and released itself continuously for 12 hours. Using acrycoat S 100 as a polymer, Ekta et al. used solvent removal to create hollow microspheres of carvedilol. DF provided a delayed release of API, was kept on the surface of the dissolving liquid for 12 hours, and exhibited no rising delay. [31]

5.5 Carbomers

Carbomers, classified as synthetic acrylic acid polymers, possess a high molecular weight and are crosslinked through the utilization of allyl sucrose or allyl esters of pentaerythritol. Characterized by their three-dimensional cross-linking structure, these polymers demonstrate substantial swelling in glycerin and water, yet they do not undergo dissolution. Notably, carbomers exhibit low bulk and post-compaction densities, measuring within the range of 0.2–0.4 g/cm³ and 0.3–0.4 g/cm³, respectively. They serve as matrix formers and low-density Es in the technology used to create floating delivery systems. They also give DF mucoadhesive qualities and a notable size increase. [32]

Employing the solvent removal methodology, Ma et al. generated gabapentin microspheres utilizing carbomer (Carbopol 934). The resultant drug delivery system (DF) exhibited rapid flotation, adhering to the surface of the dissolution medium for a duration of 9 hours. This system further manifested a delayed release of the Active Pharmaceutical Ingredient (API) spanning 12 hours, attributed to the porous structure and low density of the utilized polymer. In a parallel investigation, Wani et al. utilized carbomer (Carbopol 971P) and hydroxypropyl methylcellulose (HPMC K4M) to formulate a matrix-forming blend containing losartan for encapsulation. The synergistic swelling properties of both polymers, coupled with their low bulk densities, contributed to the establishment of a stable buoyant gel, enhanced by carbopol's capacity to form an insoluble network structure. [33]

In vivo, the encapsulated formulation and the ensuing gel achieved a prolonged residence time in the gastric environment, exceeding 8 hours. The drug delivery system (DF) maintained buoyancy in the dissolving medium for a duration exceeding 12 hours, resulting in a delayed release of the Active Pharmaceutical Ingredient (API) during this temporal span. Kumar et al. employed a combination of carbomer (Carbopol 934) and hydroxypropyl methylcellulose (HPMC) to formulate gas-forming floating tablets containing the calcium disodium salt of ethylenediaminetetraacetic acid. The resulting drug delivery system exhibited the capability to retain the tablets in the stomach for six hours in vivo, concurrently sustaining buoyancy and controlled release of the API for a period of up to twenty-four hours. Fernandes and Rathnanand utilized carbomer (Carbopol 934P), along with HPMC E50 and K4M, to fabricate carvedilol and nicotinamide cocrystal gassing tablets, creating a matrix for CO_2 retention. The resultant drug delivery system provided a delayed release of the API over a 12-hour interval, featuring an ascent delay time of 11 seconds and a flotation duration of 14 hours [33].

5.6 Polyvinyl Alcohol (PVA)

PVA is a synthetic thermoplastic polymer that dissolves in water and has a molecular weight of 20,000-200,000. PVA has a polymer density that varies from 1.19 to 1.31 g/cm^3 and melts at 228 ºC (completely hydrolyzed grades) or 180-190 ºC (partially hydrolyzed grades). It is utilised in the process of producing FDF, a material for 3D printing filaments, and in conjunction with other Es, it is utilised in the creation of microspheres. Based on the TiD principle, Huanbutta and Sangnim created floating tablets of metronidazole. The PVA case, which was created using a 3D printer, was shaped like a cylinder with an air chamber and a cell for the core. A unique pore was created at the bottom of the cylinder to slow down the API's transfer into the dissolution media. The final dose form floated for over 4 hours, released metronidazole under control for 8 hours, and did not exhibit an ascension delay [34].

5.7 Additional Synthetic Polymers

Apart from the aforementioned Es, which are extensively employed to acquire diverse DFs, scientists frequently conduct experiments utilising diverse materials that are sought after in different scientific domains. As an illustrative example, Kulinowski et al. engineered a metronidazole delivery system employing a composite fiber derived from a thermoplastic polymer, specifically Nylon 12, combined with carbon fiber. Nylon 12, known for its common utilization in selective laser sintering (SLS) for 3D printing applications, facilitated the formation of a porous and insoluble matrix. This matrix exhibited a network structure with

seamlessly integrated Active Pharmaceutical Ingredient (API). The resultant DF released metronidazole gradually over a period of 0.5 to 5 hours, had zero rise time delay, and floated for 30 to 600 minutes. By using Kumaraswamy et al.'s removal technique, porous floating microspheres with a matrix made of polypropylene glycol and water-insoluble polycarbonates were produced. This increased the release of repaglinide into the aquatic environment. According to the Korsmeier-Peppas kinetics model, the resultant DF had no ascent delay, maintained buoyancy for 12 hours, and allowed the release of API for 8 hours. Treesinchai et al. created floating tablets utilising expanded polypropylene powder (Accurel® MP1004) and using a non-standard method for choosing low-density Es to produce flotation. [35]

A zero-rise delay time and a flotation time of more than eight hours were offered by the polymer that the HPMC matrix managed to retain. The formulation of clarithromycin, known as the "fanicular cylindrical system," was created by Rajput et al. and included polyacrylamide, HPMC E15 LV, PEG 6000, and carbomer (Carbopol 934P). The resultant system floated for three hours due to swelling and offered delayed release of API for eight hours. To attain the best DF performance, any of the aforementioned polymers can be utilised singly or in a variety of combinations. Furthermore, these Es's characteristics enable them to be utilised in delivery systems to accomplish flotation by combining many strategies for flotation at the same time. [36]

Conclusions

Endowed with targeted delivery to the stomach and engineered for modified release, floating drug delivery systems contribute to enhanced bioavailability and diminished losses of the medicinally potent substance employed, consequently mitigating its associated side effects. This advancement concurrently broadens the prospects of oral dosage forms and diversifies the spectrum of Active Pharmaceutical Ingredients (APIs) amenable to such applications. Polymeric excipients, traditionally classified according to their origin, play a pivotal role in the realm of floating dosage forms. Their intrinsic functional properties are instrumental in ensuring the realization of distinctive attributes inherent to these systems, specifically modified release and gastroretention facilitated by flotation. These qualities include low density, the capacity to swell significantly, and the creation of stable gels.

The investigation conducted by the cited sources identified the most viable and efficient methodologies for achieving buoyancy in the development of Floating Drug Delivery Systems (FDF). Of particular significance, one-component gas-forming systems emerged as paramount due to their capacity to establish matrices characterized by prolonged structural integrity, erosion resistance, controlled release of Active Pharmaceutical Ingredients (APIs), and resilience against collapse amidst the expeditious carbon dioxide formation reaction. These systems typically leverage semi-synthetic and synthetic polymers, including Hydroxypropyl Methylcellulose (HPMC), Sodium Carboxymethylcellulose (NaCMC), carbomers, and Polyethylene Oxide (PEO). Concurrently, multi-component drug delivery systems attain buoyancy through the incorporation of structural features such as pores, cavities, or low-density entities within the matrix. In instances where the ionotropic gelation method is employed, commonly utilized polymers encompass Sodium Alginate (NA), chitosan, and pectin. Alternatively, when employing the solvent removal technique, polymers such as Ethyl Cellulose (EC) and polymethacrylates take precedence, as they can form robust, water-insoluble scaffolds.

Using 3D printing techniques to obtain FDF has emerged as a cutting-edge path for technological advancement. Extrusion (FDM) printing is the predominant technique, as indicated by the volume of publications, for producing floating delivery systems based on API-containing filaments or TiD devices. This approach can be used to a wide range of thermoplastic polymers, including HPC, PLA, PEG, PVA, and PVP, and is also appropriate for usage in pharmacy settings. Furthermore, there's a propensity to modify existing additive technologies and materials for the intended usage. For instance, work is being done on using SLS printing to create floating tablets made of nylon. The introduction of materials that were not previously commonly utilised as excipients in pharmacy is a potential area. These materials are typically hydrophilic polymers like egg albumin, bovine albumin, and hyaluronic acid or insoluble polymers like polypropylene, polycarbonates, etc. At the same time, a great deal of effort is focused on creating graft copolymers using

natural and synthetic components in order to obtain fundamentally new Es, such as polysaccharides extracted from plant materials or polymers.

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