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Unravelling the Herbal Formulation of Floating Microspheres for Gut Microbiome Modulation: Curren1Abhinay Challenges and Future Prospects

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Abstract

Human health is greatly influenced by the gut microbiota, and altering it has emerged as a viable treatment option for a number of illnesses. A cutting-edge medication delivery method that targets the gastrointestinal tract in a unique way and ensures localized and sustained drug release is floating microspheres. The incorporation of herbal formulations into floating microspheres for gut microbiota modification is examined in this paper, emphasizing how they may improve therapeutic efficacy while reducing systemic adverse effects. By using sophisticated methods like solvent evaporation and spray drying, together with biodegradable polymers and stabilizers, herbal bioactives—which are well-known for being compatible with gut health—can be integrated into microsphere systems. Longer stomach residence duration is made possible by the regulated buoyancy of microspheres, which guarantees the localized and continuous release of herbal components that work in concert with the gut bacteria. Notwithstanding these benefits, there are still issues, such as the stability of herbal active ingredients during processing, the need to optimize release kinetics, and regulatory obstacles related to formulations including herbal ingredients. Prospects for the future centre on advancements in biodegradable materials, the application of nanotechnology for better targeting, and customized methods for microbiota modification. These developments might help solve today's problems and turn research into useful therapeutic applications. Floating microspheres have the potential to transform gut microbiota modification techniques by bridging the gap between contemporary medication delivery technology and traditional herbal therapy..

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1. Introduction

The gut microbiota has become a key factor in preserving human health and affecting how different illnesses develop. Trillions of microorganisms make up this complex ecosystem, which interacts with the host to control immunological responses, metabolic activities, and even cerebral functions. As a result, altering the gut microbiota has gained popularity as a therapeutic target for both preventative and curative medical approaches. The creation of sophisticated drug delivery systems has attracted a lot of interest among the many strategies being investigated; floating microspheres are one such invention that presents encouraging opportunities for precisely targeted therapies [1]. As a kind of gastroretentive drug delivery method, floating microspheres are made to float in the stomach for extended periods of time, guaranteeing longer drug release and improved bioavailability. Their ability to localize therapeutic agents in the gastrointestinal tract has made them particularly valuable for modulating the gut microbiome. These microspheres can be engineered to

encapsulate herbal formulations, probiotics, or other active agents that interact with the microbiota to restore balance or exert specific beneficial effects. By facilitating controlled release and site-specific drug delivery, floating microspheres offer a sophisticated method to influence the gut ecosystem without significantly disturbing its natural composition [2].
The importance of gut microbiome modulation lies in its capacity to address a myriad of health concerns. Inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, diabetes, and even mental health issues like anxiety and depression are linked to dysbiosis, or the imbalance of gut microbial ecosystems. Conventional therapies often have limited efficacy or come with undesirable side effects, emphasizing the need for alternative strategies. Targeted modulation through innovative delivery systems such as floating microspheres offers a more focused approach, minimizing systemic exposure while enhancing therapeutic outcomes [3]. Herbal formulations are increasingly recognized as valuable tools in gut microbiome modulation. Their bioactive compounds, such as polyphenols, flavonoids, and alkaloids, have demonstrated antimicrobial, anti-inflammatory, and prebiotic effects. These natural agents can selectively promote the development of advantageous bacteria while preventing the establishment of harmful ones, contributing to the restoration of microbial balance. However, the efficacy of herbal compounds is often compromised by their poor solubility, stability, and bioavailability. Floating microspheres address these challenges by encapsulating herbal actives in a protective matrix, enhancing their solubility and protecting them from gastric degradation. The sustained release mechanism ensures a steady interaction between the bioactives and the microbiota, optimizing therapeutic potential [4].

Despite their promising applications, the development and utilization of floating microspheres for gut microbiome modulation face several challenges. Formulation complexity is a primary concern, as the microspheres must be carefully designed to achieve optimal buoyancy, drug release profiles, and stability. The choice of polymers, excipients, and preparation techniques significantly influences the performance of the microspheres [5]. Commonly used biodegradable and biocompatible polymers include chitosan, ethyl cellulose, and hydroxypropyl methylcellulose (HPMC), however careful optimization is needed to choose the best combination. Another challenge lies in ensuring the encapsulated herbal compounds remain bioactive throughout the formulation and delivery process. Environmental factors including light, heat, and moisture can cause deterioration and diminished effectiveness in many herbal substances. Advanced encapsulation techniques, such as ionotropic gelation and spray drying, have been employed to overcome these issues, but achieving scalability and cost-effectiveness remains a hurdle [6].

Furthermore, a variety of parameters, such as the microbiome's composition, stomach motility, and the microspheres' physicochemical characteristics, affect how the floating microspheres and the gut microbiota interact. Personalized approaches that consider individual variations in microbiota composition and gut physiology could enhance the effectiveness of these formulations. However, the complexity and cost associated with personalization pose practical limitations, particularly in large-scale applications [7]. The development of floating microspheres for gut microbiota modification is further complicated by regulatory issues. The use of herbal formulations often involves multiple active compounds, making it difficult to meet the stringent requirements for characterization and standardization set by regulatory bodies. Ensuring batch-to-batch consistency and demonstrating the safety and efficacy of complex formulations require robust analytical methods and comprehensive clinical studies. Future prospects for floating microspheres in gut microbiome modulation are encouraging, driven by advances in materials science, formulation technology, and microbiome research [8]. Nanotechnology, for instance, offers exciting possibilities for developing microspheres with enhanced functionalities. Nano-sized carriers can improve the encapsulation efficiency of herbal compounds, facilitate targeted delivery to specific microbial populations, and enable more precise control over release kinetics. Combining nanotechnology with floating microsphere systems could revolutionize the way gut microbiome-targeted therapies are designed and administered. Combining machine learning (ML) with artificial intelligence (AI) in the creation of floating microspheres is another promising avenue. These technologies can be leveraged to optimize formulation parameters, predict drug release profiles, and identify potential interactions with the gut microbiota. AI-driven approaches can also aid in the design of personalized therapies by analyzing individual microbiome data and tailoring formulations to specific needs [9].

Additionally, the incorporation of prebiotics and synbiotics into floating microsphere systems represents an innovative strategy to amplify their

therapeutic effects. Prebiotics, which serve as substrates for beneficial microbes, can be co-delivered with herbal bioactives to synergistically enhance their impact on the microbiome. Synbiotic formulations, combining prebiotics and probiotics, could further enhance the restoration of microbial balance and improve clinical outcomes in dysbiosis-related conditions [10]. For floating microspheres to reach their full potential, cooperation between academics, doctors, and industry stakeholders will be crucial in gut microbiome modulation. Interdisciplinary approaches that combine expertise in pharmacology, microbiology, materials science, and bioinformatics can accelerate the translation of these innovative systems from the laboratory to clinical practice. Addressing the challenges of scalability, standardization, and regulatory compliance will require concerted efforts and strategic investments [11].

The development of floating microspheres for gut microbiome modulation represents a groundbreaking approach to targeted drug delivery. By leveraging the unique advantages of this gastroretentive system, it is possible to enhance the efficacy of herbal formulations and other therapeutic agents in restoring microbial balance and treating dysbiosis-related conditions. While significant challenges remain, advances in technology and a deeper understanding of microbiome dynamics hold immense promise for overcoming these barriers. Floating microspheres have the potential to transform the area of gut microbiota regulation as research and innovation continue, providing fresh hope for better health outcomes and disease management [12].

2. Understanding Floating Microspheres

A cutting-edge drug delivery method, floating microspheres have attracted a lot of interest lately due to their potential to enhance therapeutic results in a range of medicinal applications. These cutting-edge systems are a subset of gastroretentive drug delivery systems (GRDDS), which are made to float in the gastric environment. This allows the medication to be encapsulated for an extended period of time in the stomach and release under regulated conditions. Their unique mechanism and numerous advantages over conventional drug delivery methods make floating microspheres a promising solution for addressing the limitations of traditional dosage forms [13]. At their core, floating microspheres are spherical, hollow particles with a size range typically between 1 and 1000 micrometers. They are formulated to possess a low density, allowing them to float on the gastric fluid once ingested. This floating ability is primarily attributed to the presence of air or gas within the microspheres or the use of polymers that create a buoyant matrix. The mechanism of action involves the microspheres remaining buoyant in the stomach for extended periods, during which the drug is gradually released. This ensures prolonged drug residence in the upper gastrointestinal tract, enhancing absorption and bioavailability for drugs that are site-specific to this region [14].

The advantages of floating drug delivery systems (FDDS) like floating microspheres are manifold, offering solutions to many challenges associated with oral drug administration. One of the primary benefits is enhanced gastric retention. Unlike conventional dosage forms that may rapidly transit through the gastrointestinal tract, floating microspheres remain in the stomach due to their buoyant properties. For medications that are mostly absorbed in the stomach or the top portion of the small intestine, this is especially beneficial. Floating microspheres maximize therapeutic effectiveness by prolonging the stomach residence period, which guarantees a continuous release of the medicine at the site of absorption. The capacity of floating microspheres to deliver regulated and prolonged medication release is another important benefit. Conventional dose forms frequently cause medication concentrations in the blood to fluctuate, which can have negative consequences and lead to less than ideal therapeutic results [15]. By administering the medication at a constant pace and preserving constant plasma drug levels, floating microspheres get over this restriction. This not only enhances efficacy but also reduces the frequency of dosing, improving patient compliance. Floating microspheres are particularly beneficial for drugs with poor solubility or stability in alkaline environments. Many drugs degrade or lose efficacy in the more alkaline pH of the intestines. By prolonging their stay in the acidic gastric environment, floating microspheres protect these drugs from degradation, ensuring their stability and effectiveness. This property makes floating microspheres an ideal choice for delivering drugs with narrow absorption windows or those prone to degradation in non-acidic conditions [16].

The use of floating microspheres also enables targeted drug delivery. Drugs encapsulated in these microspheres can be directed specifically to the stomach or upper gastrointestinal tract, minimizing systemic exposure and reducing the risk of off-target effects. This is especially useful in the treatment of

localized gastric conditions such as peptic ulcers, gastritis, or Helicobacter pylori infections. The localized action ensures that the drug concentration at the site of interest is maximized while minimizing exposure to other parts of the body. In addition to these therapeutic advantages, floating microspheres offer significant formulation flexibility. A wide range of polymers, including biodegradable and biocompatible options, can be used to create the microsphere matrix [17]. Chitosan, ethyl cellulose, and HPMC are examples of polymers that are used employed to achieve the desired buoyancy and release profiles. The ability to tailor the formulation enables the customization of floating microspheres for various drugs, providing a versatile platform for diverse therapeutic applications. Despite their numerous benefits, the development of floating microspheres involves several technical considerations. The selection of appropriate polymers and excipients is crucial to achieving the desired characteristics, such as buoyancy, stability, and release kinetics. The quality and functionality of the microspheres are also greatly influenced by the preparation methods used, such as solvent evaporation, ionotropic gelation, or spray drying. To guarantee consistency in drug loading, encapsulation effectiveness, and particle size, these methods need to be tuned [18].

The mechanism of floating microspheres relies not only on their intrinsic buoyant properties but also on external factors such as gastric motility, if there is food in the stomach and how much gastric fluid there is. These factors may have an impact on the microspheres' residence period and medication release characteristics. Understanding these factors and designing formulations that can adapt to varying physiological conditions is essential for ensuring consistent performance. Floating microspheres also hold potential for addressing specific therapeutic challenges beyond traditional drug delivery [19]. For instance, floating microspheres can offer sustained release in the treatment of chronic conditions like diabetes or hypertension, when long-term medication administration is necessary. This lowers the need for frequent dosage and increases patient adherence. Similarly, for drugs with a short half-life, floating microspheres can help maintain therapeutic plasma concentrations over extended periods, enhancing their effectiveness. The use of floating microspheres in combination therapies is another promising area. By co-encapsulating multiple drugs or combining the microspheres with other delivery systems, it is possible to achieve synergistic effects or address multiple therapeutic targets simultaneously. For instance, combining floating microspheres with mucoadhesive systems can further enhance gastric retention and improve the effectiveness of drugs for localized gastric conditions [19].

Furthermore, the integration of floating microspheres with emerging technologies such as nanotechnology and biosensors offer exciting possibilities. Nanotechnology can be used to create nanoscale floating particles with enhanced surface area, improving drug release and absorption. Biosensors embedded in floating microspheres could enable real-time monitoring of gastric pH or drug release, providing valuable feedback for optimizing therapy [20].

3. Herbal Formulations for Gut Microbiome Modulation

The use of herbal formulations for gut microbiome modulation is gaining considerable interest as researchers and clinicians explore natural, effective methods to maintain or restore gut health. Herbal bioactives, derived from plants, are rich in compounds such as polyphenols, flavonoids, alkaloids, terpenoids, and essential oils. These compounds have shown immense potential to interact with the gut microbiota, influencing its composition and activity to benefit overall health. When combined with advanced delivery systems like floating microspheres, herbal formulations offer a novel approach to targeted, sustained, and efficient modulation of the gut microbiome [21]. Through a variety of pathways, herbal bioactives are essential for gut health. By specifically encouraging the development of advantageous bacteria like Bifidobacterium and Lactobacillus, which are known to improve gut integrity and lower inflammation, they can function as prebiotics. Polyphenols, found abundantly in herbs like green tea, turmeric, and cinnamon, are particularly effective in modulating microbial composition. These compounds are metabolized by gut microbes into bioactive metabolites, which further exert anti-inflammatory, antioxidant, and antimicrobial effects. Such interactions create a positive feedback loop, where the microbiota and herbal compounds mutually enhance each other's beneficial effects [22].

Many herbal bioactives possess antimicrobial properties that selectively inhibit pathogenic bacteria without disrupting the beneficial microbiota. For instance, curcumin from turmeric and allicin from garlic have demonstrated the ability to suppress harmful bacteria like Clostridium difficile and

Helicobacter pylori. Simultaneously, these compounds can fortify the gut mucosal barrier, reducing the risk of infections and inflammation. Other herbs, such as aloe vera and licorice, contain bioactives that soothe the gut lining, reduce oxidative stress, and support epithelial repair. One of the most significant contributions of herbal bioactives to gut health is their ability to reduce systemic inflammation by modulating gut-derived immune responses. Chronic diseases such as obesity, diabetes, and cardiovascular disorders often originate from gut inflammation driven by microbial dysbiosis. Herbal compounds like berberine (from Berberis species) and resveratrol (from grapes) have demonstrated efficacy in modulating gut-derived inflammatory pathways, improving metabolic and immune health [23].

Despite their promising potential, herbal formulations face certain challenges when used for gut microbiome modulation. Many herbal compounds suffer from poor solubility, stability, and bioavailability, which limits their effectiveness. Additionally, the variability in absorption and metabolism of these compounds due to differences in individual gut microbiota composition can lead to inconsistent therapeutic outcomes. These limitations underscore the need for advanced delivery systems, such as floating microspheres, to optimize the performance of herbal bioactives [24]. Floating microsphere technology offers an ideal platform for the delivery of herbal formulations aimed at gut microbiome modulation. These gastroretentive systems address the limitations of conventional herbal formulations by ensuring localized, extended release of bioactives in the upper gastrointestinal tract and stomach. The relationship between herbal components and gut flora is improved by this prolonged exposure, maximizing their therapeutic potential [25].

The compatibility of herbal compounds with floating microsphere technology is rooted in the versatile nature of these delivery systems. Biocompatible and biodegradable polymers including chitosan, alginate, and HPMC are commonly used in the formulation of floating microspheres. These polymers are well-suited for encapsulating herbal bioactives, protecting them from degradation in harsh gastric conditions while ensuring their gradual release. Encapsulation also shields the bioactives from environmental factors such as light, heat, and moisture, preserving their stability and potency. Herbal bioactives often exhibit diverse physicochemical properties, ranging from hydrophobic to hydrophilic [26]. Floating microsphere technology accommodates this variability through customization of the polymer matrix and preparation methods. For instance, hydrophobic compounds like curcumin can be effectively encapsulated using lipophilic polymers or co-solvents, while hydrophilic compounds like saponins or tannins can be stabilized in hydrophilic matrices. Such adaptability allows the formulation of floating microspheres tailored to specific herbal bioactives and therapeutic needs [27].

Controlled release is another key advantage of integrating herbal bioactives with floating microspheres. The polymers used in microsphere preparation can be engineered to control the rate at which the bioactives are released, ensuring steady interaction with the gut microbiota. For example, a slow-release formulation of polyphenols from green tea could sustain their prebiotic effects over an extended period, enhancing microbial diversity and resilience. Similarly, the gradual release of antimicrobial compounds like berberine could help suppress pathogenic bacteria without overwhelming the gut ecosystem [28]. Floating microspheres also provide the opportunity to deliver multiple herbal bioactives simultaneously, enabling synergistic effects. Combining compounds with complementary actions can enhance the overall impact on gut health. For example, a formulation incorporating curcumin (anti-inflammatory), quercetin (antioxidant), and aloe vera (gut-soothing) could address multiple aspects of gut dysbiosis, from reducing inflammation to promoting microbial balance and gut barrier integrity. While floating microspheres offer numerous advantages for delivering herbal formulations, their development involves certain challenges that must be addressed. Achieving high encapsulation efficiency for herbal bioactives requires careful optimization of formulation parameters, including the choice of polymers, solvents, and preparation techniques. Herbal compounds often contain a complex mixture of active constituents, making it essential to ensure that the encapsulation process does not compromise their bioactivity or alter their therapeutic profile [29]. Another consideration is the scalability of floating microsphere production. Techniques such as solvent evaporation, spray drying, and ionotropic gelation are commonly used for preparing microspheres, but scaling these methods for commercial production while maintaining consistency and quality can be challenging. Addressing these issues will require advances in manufacturing processes and standardization protocols. The interaction of floating microspheres with the gut environment and microbiota is another critical factor influencing their

effectiveness. Factors such as gastric motility, pH, and the presence of food can affect the retention time and release behavior of microspheres [30]. Designing formulations that are robust under varying physiological conditions is essential to ensure consistent performance. From a regulatory perspective, the development of herbal formulations in floating microspheres involves navigating complex requirements for safety, efficacy, and standardization. Herbal bioactives often contain multiple active compounds, making it challenging to meet the stringent criteria for characterization and batch-to-batch consistency. To determine the safety and effectiveness of these formulations, especially for long-term usage in gut microbiota manipulation, further preclinical and clinical research will be required [31].

Looking to the future, the integration of herbal bioactives with floating microsphere technology presents exciting possibilities for personalized gut health interventions. Advances in microbiome research and analytical techniques are paving the way for individualized therapies based on a person's unique gut microbiota profile. Floating microspheres could be customized to deliver specific herbal compounds tailored to the individual's microbial composition, dietary habits, and health conditions. The combination of herbal formulations with emerging technologies such as nanotechnology and biosensors further expands the potential of floating microspheres. Nano-sized microspheres could improve the encapsulation and release properties of herbal compounds, while biosensors embedded in microspheres could provide real-time monitoring of microbiome changes and therapeutic outcomes [32].

4. Development Techniques for Floating Microspheres

The development of floating microspheres, a sophisticated drug delivery system, involves precise formulation techniques and the careful selection of materials to achieve desired characteristics such as buoyancy, controlled drug release, and stability. Floating microspheres rely on advanced formulation strategies and a judicious combination of polymers, stabilizers, and excipients to maximize how well they function in the stomach environment. Understanding these development techniques and materials is crucial for designing effective and efficient drug delivery systems tailored to specific therapeutic needs [33].

4.1. Formulation Strategies

The creation of floating microspheres involves a number of formulation techniques, each with unique benefits and difficulties. The most often utilized methods include freeze-drying, ionotropic gelation, solvent evaporation, and spray drying. These techniques are selected in accordance with the desired qualities of the finished product as well as the physicochemical parameters of the medicine and excipients [34].

4.2. Solvent Evaporation

One of the most popular methods for creating floating microspheres is the solvent evaporation approach. In order to create a homogenous solution or emulsion, the medication and polymers are dissolved in a volatile organic solvent, such as acetone or dichloromethane. An oil-in-water emulsion is then produced by dispersing the solution in an aqueous phase that contains a stabilizer, like polyvinyl alcohol (PVA). Solid microspheres are left behind as the organic solvent gradually evaporates while being stirred [35]. High encapsulation efficiency and the flexibility to regulate particle size by modifying process variables like stirring speed and emulsifier content are two benefits of this approach. Drugs that are hydrophobic or unstable in aquatic conditions are especially well suited for solvent evaporation. To guarantee that the finished product is free of leftover solvents, however, strict solvent removal procedures can be necessary [36].

4.3. Spray Drying

Spray drying is another popular technique for producing floating microspheres. In this method, a solution or suspension of the drug and polymer is atomized into a hot drying chamber, where rapid evaporation of the solvent occurs, forming solid microspheres. The buoyancy of the microspheres can be enhanced by incorporating gas-forming agents like sodium bicarbonate into the formulation. Spray drying is advantageous for its scalability and ability to produce microspheres with narrow particle size distribution. It is particularly effective for drugs that require rapid processing to maintain stability. However, the high temperatures involved in the process may not be suitable for heat-sensitive drugs or polymers [37].

4.4 Ionotropic Gelation

Ionic crosslinking of polymers results in the creation of microspheres during ionotropic gelation. A drug-carrying aqueous solution including polymers, such sodium alginate, is introduced dropwise to a calcium

chloride or other crosslinking agent solution. Gelled microspheres are the product of the ionic interaction between the crosslinking agent and the polymer. Because it doesn't use organic solvents or high temperatures, this method is easy to use, affordable, and appropriate for medications that are sensitive to heat. But the resultant microspheres might not be very strong mechanically and need to be stabilized further [38].

4.5. Freeze-Drying

Lyophilization, another name for freeze-drying, is a process that creates floating microspheres with increased stability and durability. This method involves freezing an aqueous solution or suspension of the medication and polymer, then sublimating the water under vacuum to remove it. The porous structure formed during freeze-drying contributes to the buoyancy of the microspheres. Freeze-drying is particularly beneficial for sensitive drugs and formulations intended for long-term storage. However, it is a time-consuming and expensive process that requires specialized equipment [39].

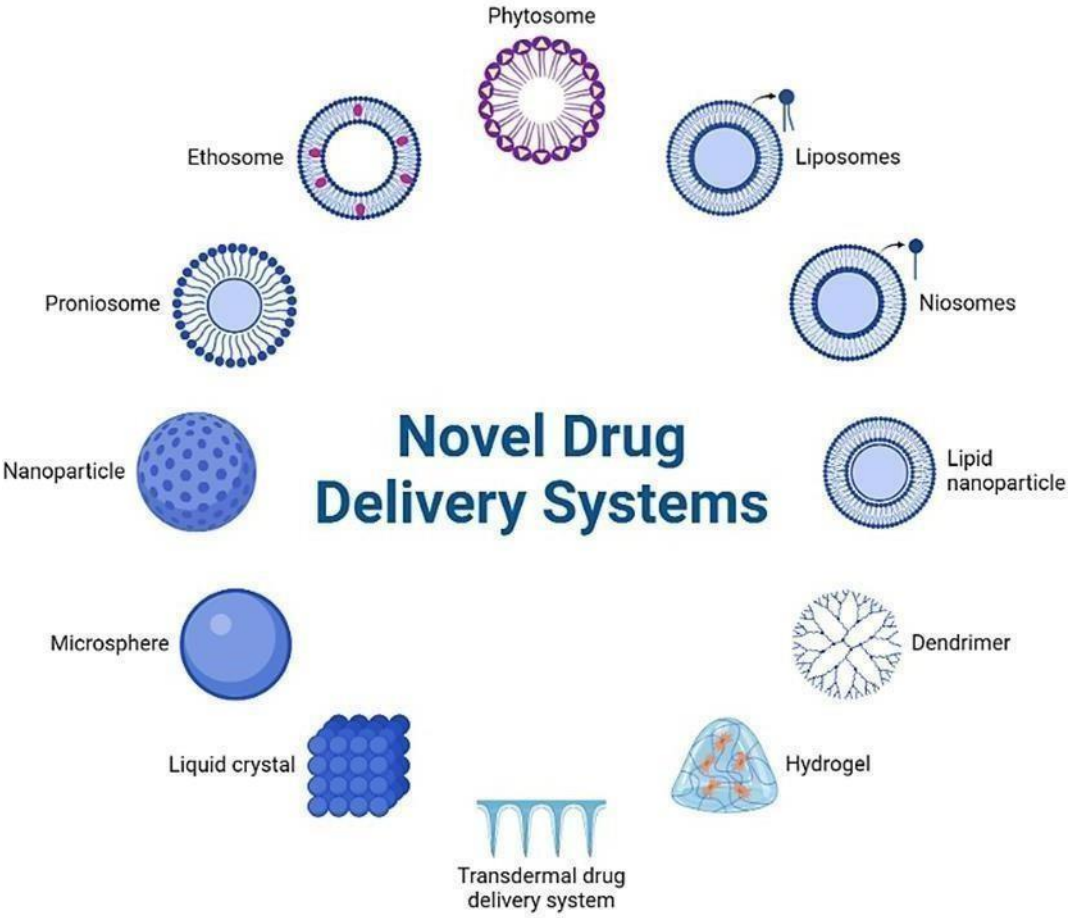

Figure 1: Novel Drug Delivery Systems

4.6. Materials Used in Floating Microspheres

The choice of materials is a critical aspect of floating microsphere development, as it directly impacts their physical properties, drug release behavior, and biocompatibility. The key materials include polymers, stabilizers, and excipients [40].

4.6.1. Polymers

Polymers form the backbone of floating microspheres, providing the structural matrix that encapsulates the drug and ensures buoyancy. Both natural and synthetic polymers are used, depending on the desired properties of the microspheres [41].

Natural polymers such as alginate, chitosan, and While gelatin is biocompatible and biodegradable, it is utilized extensively. Because it can produce gels in the presence of divalent cations, alginate is especially well-liked for ionotropic gelation. Chitosan, a cationic polymer, is used for its mucoadhesive properties, which enhance gastric retention [42].

Synthetic polymers like polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), and HPMC are preferred for their versatility and tunable properties. HPMC is commonly used for its hydrophilic nature, which helps in forming a buoyant matrix, while PLGA offers controlled drug release and high mechanical strength [43].

4.6.2. Stabilizers

Stabilizers are essential in the formulation of floating microspheres to prevent particle aggregation during the preparation process. They help maintain the uniformity of the emulsion or suspension, ensuring consistent particle size and distribution [44]. Commonly used stabilizers include:

Polyvinyl Alcohol (PVA); A widely used stabilizer in the solvent evaporation method, PVA enhances the stability of oil-in-water emulsions and prevents coalescence of droplets [45].

Polysorbates (Tween); Non-ionic surfactants like Tween 80 are used to stabilize emulsions and improve the dispersion of microspheres [46].

Bovine Serum Albumin (BSA); In some cases, BSA is used as a stabilizer and protein carrier for specific applications [47].

4.6.3. Excipients

Excipients play a supportive role in the formulation of floating microspheres, enhancing their functionality and performance [48]. Key excipients include:

Gas-Forming Agents; Sodium bicarbonate and citric acid are commonly added to formulations to generate carbon dioxide when exposed to gastric acid, enhancing buoyancy [49].

Plasticizers; Compounds like polyethylene glycol (PEG) are used to modify the flexibility and mechanical properties of the polymer matrix [50].

Cryoprotectants; In freeze-drying, mannitol and trehalose are examples of cryoprotectants that are used to the microspheres from damage during freezing and sublimation [51].

Table 1: Herbal formulation of different microspheres.

S. No.	Type of Microsphere	Polymer Used	Name of Drug	Method of Formulation	Application	References
1	Floating Microspheres	PLGA (Poly(lactic-co-glycolic acid)	Metronidazole	Solvent Evaporation	Treatment of Helicobacter pylori infection	[52]
2	Floating Microspheres	HPMC	Diclofenac Sodium	Spray Drying	Anti-inflammatory drug delivery	[53]
3	Floating Microspheres	Chitosan	Curcumin	Ionotropic Gelation	Anti-inflammatory, antioxidant delivery	[54]
4	Biodegradable Microspheres	Polycaprolactone (PCL)	Ibuprofen	Solvent Evaporation	Pain and inflammation management	[55]
5	Floating Microspheres	Alginate	Probiotic strains (Lactobacillus)	Spray Drying	Probiotic delivery for gut health	[56]
6	Floating Microspheres	Eudragit S100	Theophylline	Solvent Evaporation	Bronchodilator for asthma	[57]
7	Biodegradable Microspheres	Gelatin	Insulin	Freeze-Drying	Diabetes management	[58]

8	Floating Microspheres	Sodium Alginate	Metronidazole	Ionotropic Gelation	Gastrointestinal infections	[59]
9	Floating Microspheres	Chitosan	Diclofenac	Solvent Evaporation	Pain relief and anti-inflammatory	[60], [61]
10	Biodegradable Microspheres	PLGA	Dexamethasone	Solvent Evaporation	Inflammatory conditions treatment	[62], [63]
11	Floating Microspheres	HPMC and Eudragit S100	Paracetamol	Spray Drying	Pain and fever management	[64]
12	Floating Microspheres	Polyvinyl Alcohol (PVA)	Caffeine	Solvent Evaporation	Stimulant delivery	[65]
13	Floating Microspheres	Poly(lactic acid) (PLA)	Ondansetron	Spray Drying	Antiemetic drug for chemotherapy-induced nausea	[66]
14	Floating Microspheres	Chitosan and PCL	Ketoprofen	Solvent Evaporation	Anti-inflammatory treatment	[67]
15	Biodegradable Microspheres	PLGA	Sildenafil	Solvent Evaporation	Erectile dysfunction treatment	[68], [69]
16	Floating Microspheres	HPMC and sodium bicarbonate	Diclofenac	Spray Drying	Musculoskeletal pain relief	[60]
17	Floating Microspheres	Polyvinyl alcohol (PVA)	Methotrexate	Solvent Evaporation	Chemotherapeutic agent delivery	[70]
18	Floating Microspheres	Alginate and Eudragit S100	Metformin	Ionotropic Gelation	Diabetes treatment	[71]
19	Biodegradable Microspheres	Poly(ethylene glycol) (PEG)	5-Fluorouracil	Spray Drying	Cancer treatment	[72]
20	Floating Microspheres	Gelatin and PLGA	Testosterone	Solvent Evaporation	Hormonal replacement therapy	[73]
21	Floating Microspheres	Sodium alginate and PVA	Simvastatin	Spray Drying	Hyperlipidemia treatment	[74]
22	Floating Microspheres	PCL and Eudragit S100	Rifampicin	Solvent Evaporation	Tuberculosis treatment	[75]
23	Biodegradable Microspheres	PLGA	Amitriptyline	Solvent Evaporation	Antidepressant delivery	[76]

24	Floating Microspheres	Chitosan and PLGA	Ranitidine	Spray Drying	Acid reflux and heartburn treatment	[77]
25	Floating Microspheres	Polyvinyl Alcohol (PVA)	Ibuprofen	Solvent Evaporation	Pain management	[78]
26	Floating Microspheres	HPMC and sodium bicarbonate	Prednisolone	Spray Drying	Inflammation and autoimmune disease treatment	[79]
27	Floating Microspheres	Chitosan and PVA	Loperamide	Ionotropic Gelation	Diarrhea treatment	[20]
28	Biodegradable Microspheres	PLGA	Fluconazole	Solvent Evaporation	Antifungal treatment	[80]
29	Floating Microspheres	Chitosan and Alginate	Chlorpheniramine	Spray Drying	Antihistamine delivery	[81]
30	Floating Microspheres	HPMC and PVA	Metformin	Solvent Evaporation	Type 2 diabetes management	[82]

5. Mechanisms of Action

Microspheres represent an innovative approach to drug delivery, particularly in targeting the gastrointestinal tract (GIT) and interacting with the gut microbiota. These small, spherical particles are designed to enhance the therapeutic potential of drugs through controlled release, targeted delivery, and prolonged retention in the stomach or specific regions of the GIT. The mechanisms of action of microspheres encompass their interaction with the gut microbiota, as well as their ability to provide sustained release and localized action, which collectively improve the effectiveness of treatments and reduce systemic side effects. One of the primary ways microspheres influence gut health is through their interaction with the varied group of microorganisms living in the GIT, known as the gut microbiota [83]. These microbes are essential for immunological and digestive processes, and overall health, and their composition and activity can be modulated by therapeutic agents. Microspheres facilitate such modulation by acting as carriers for drugs, probiotics, or bioactive compounds that target specific microbial populations. Upon reaching the gut, the encapsulated agents are released in a controlled manner, allowing them to directly interact with the microbiota. For example, antibiotics encapsulated in microspheres can selectively eradicate pathogenic bacteria, while sparing beneficial microbes, thereby preserving or restoring a healthy microbial balance [84].

Additionally, microspheres can be formulated to deliver prebiotics substances that specifically promote the development of good bacteria. These prebiotics, often derived from dietary fibers or plant-based compounds, can be encapsulated within microspheres to protect them from degradation in the upper GIT. As the microspheres reach the colon, where most gut microbes reside, the prebiotics are gradually released, providing a sustained source of nutrients for beneficial bacteria like Bifidobacterium and Lactobacillus [85]. This targeted delivery minimizes the loss of prebiotics and maximizes their impact on the microbiota, promoting a healthy gut environment. Probiotic delivery is another area where microspheres demonstrate their efficacy in interacting with gut microbiota. Probiotics are living microorganisms that,

when taken in sufficient quantities, provide positive health effects [86]. However, their survival through the acidic and enzymatic conditions of the stomach is a significant challenge. Encapsulation of probiotics within microspheres protects them from these harsh conditions, ensuring their viability until they reach the intestines. Furthermore, the gradual release of probiotics from microspheres ensures their sustained presence in the gut, enhancing their colonization and interaction with native microbiota. This controlled release mechanism provides a steady supply of probiotics, which can improve gut health by enhancing the diversity and resilience of the microbial community [87].

Beyond modulating the gut microbiota, microspheres are engineered to provide sustained release and localized action in the GIT. Sustained release is achieved through the careful selection of polymers and formulation techniques, which control the rate at which the encapsulated drug or compound is released. For instance, polymers like HPMC or poly(lactic-co-glycolic acid) (PLGA) can be engineered to break down gradually in the stomach's enzymatic or acidic environment, guaranteeing a prolonged release of the medicinal substance. By avoiding the sharp increases in drug concentration that are typical with traditional dose forms, this gradual release lowers the possibility of adverse effects and increases patient compliance [88]. Microspheres' prolonged release capabilities are especially advantageous for medications whose therapeutic benefits depend on continuous exposure. For instance, in the management of long-term inflammatory diseases such ulcerative colitis or Crohn's illness, microspheres can provide a continuous supply of anti-inflammatory agents or immunomodulators to the affected regions of the GIT. This approach reduces the frequency of dosing and ensures that the therapeutic agents remain active at the site of inflammation for an extended period, promoting better disease management [89].

Localized action is another critical mechanism by which microspheres enhance the therapeutic efficacy of drugs in the GIT. By remaining buoyant and adhering to the gastric mucosa, floating microspheres can achieve prolonged retention in the stomach or other targeted regions of the GIT. By ensuring that the medication is delivered precisely where it is intended to function, this localized action minimizes systemic absorption and lowers the possibility of off-target effects. To treat Helicobacter pylori infections, for example, antibiotic-loaded microspheres can provide a high concentration of the medication in the stomach, where the bacteria live, without appreciably raising systemic drug levels [90]. This targeted delivery not only improves the eradication of the pathogen but also reduces the risk of systemic side effects and the development of antibiotic resistance. The localized action of microspheres also benefits the delivery of bioactive compounds such as enzymes, peptides, or vaccines. These compounds are often sensitive to degradation by gastric acid and digestive enzymes, which limits their effectiveness when administered orally. Encapsulation within microspheres protects these bioactives and allows their release at the intended site, where they can exert their therapeutic effects. For example, enzymes used in the treatment of pancreatic insufficiency can be encapsulated in microspheres to ensure their release in the duodenum, where they aid in digestion. Similarly, oral vaccines encapsulated in microspheres can be delivered to the Peyer’s patches in the small intestine, stimulating a localized immune response [91].

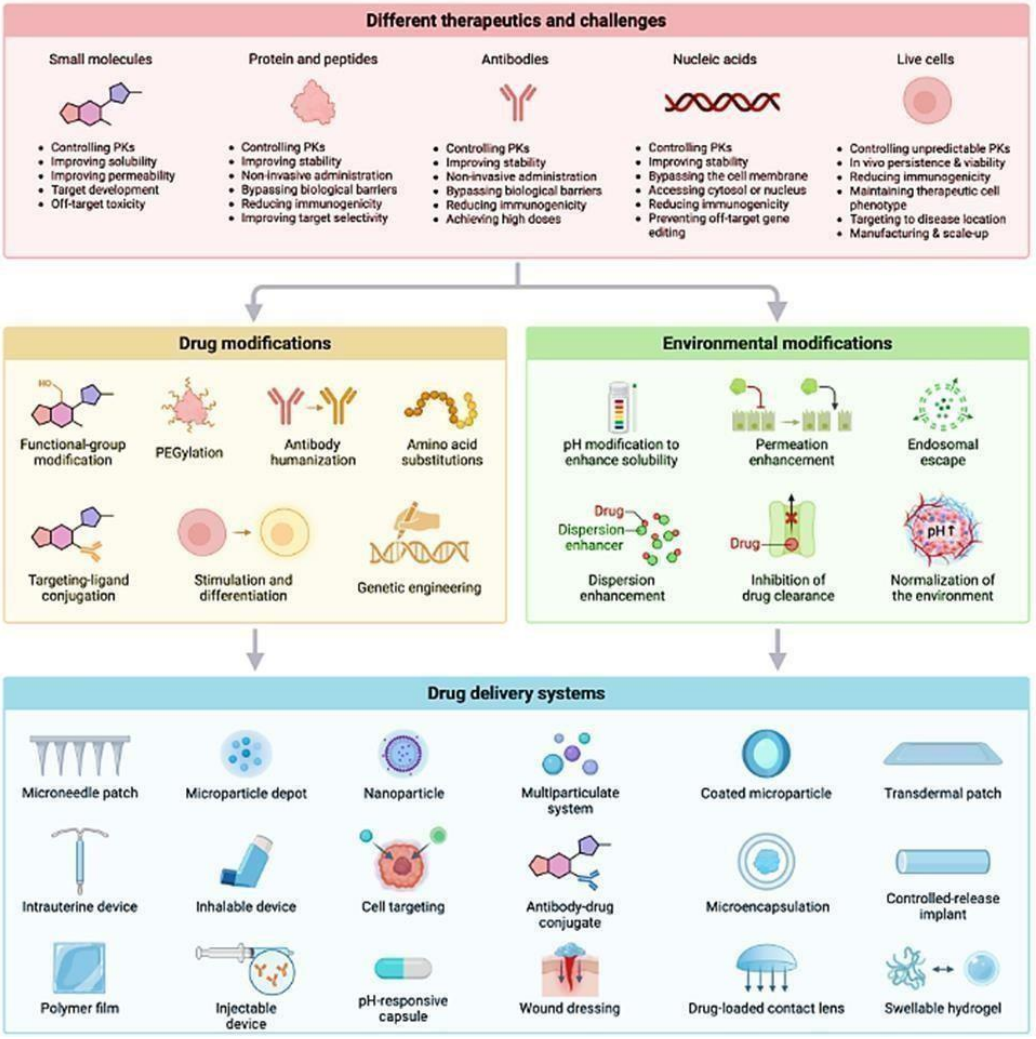

Figure 1: Commercial Drug Delivery Technologies

Microspheres' localized activity is further enhanced by their ability to react to certain stimuli in the GIT. When pH, temperature, or enzymatic activity changes, stimuli-responsive microspheres are designed to discharge their contents. Because the colon has a greater pH than the stomach or small intestine, pH-sensitive microspheres, for instance, can release their payload there. This characteristic is especially helpful when administering medications or bioactives meant to treat colonic conditions like IBD or colorectal cancer [92]. Enzyme-sensitive microspheres, on the other hand, release their contents in response to specific enzymes produced by gut bacteria, ensuring precise targeting and interaction with the microbiota. The combination of sustained release and localized action offered by microspheres not only improves the therapeutic outcomes of drugs but also opens new avenues for personalized medicine. Advances in formulation technologies and an improved understanding of the gut microbiota are enabling the development of microspheres tailored to individual patients. For example, microspheres can be designed to deliver specific drugs or bioactives based on a person's unique microbial composition, dietary habits, or disease profile. This personalized approach ensures that the therapy is optimized for maximum efficacy and minimal side effects [93].

6. Current Challenges

The development of FDDS incorporating herbal actives presents several challenges that must be addressed to fully realize their therapeutic potential. These challenges primarily center on the stability of herbal compounds during formulation, the optimization of release kinetics, and navigating regulatory hurdles specific to herbal-based systems. One of the foremost challenges is maintaining the stability of herbal actives during the microsphere formulation process. Herbal bioactives are often sensitive to environmental factors such as heat, light, oxygen, and moisture, making them susceptible to degradation during preparation. Techniques such as solvent evaporation, spray drying, and freeze-drying

often involve conditions that can destabilize these compounds, leading to a loss of potency or alterations in their chemical structure [94]. Additionally, interactions between the herbal active and the excipients, such as polymers or stabilizers, can lead to chemical incompatibilities that compromise the integrity of the final product. Developing gentle processing methods and using protective agents such as antioxidants or stabilizers is critical to preserving the bioactivity of herbal compounds throughout the formulation process. Another significant challenge lies in optimizing the release kinetics of herbal actives from the microspheres. Controlled release is a cornerstone of FDDS, and achieving the desired release profile is essential for therapeutic efficacy [95]. However, herbal actives often exhibit diverse physicochemical properties, such as varying solubility, molecular weight, and stability, which complicate their encapsulation and release. Designing microspheres that balance immediate and sustained release of active ingredients is particularly difficult when dealing with complex herbal extracts containing multiple bioactive constituents. Fine-tuning the choice of polymers, crosslinking agents, and formulation parameters is necessary to achieve predictable and reproducible release profiles. Moreover, the release must align with the pharmacokinetics of the herbal actives, ensuring that therapeutic concentrations are maintained at the site of action without premature degradation or elimination [96].

The regulatory landscape for herbal-based FDDS poses additional challenges. Herbal products are often subjected to a distinct set of regulatory requirements compared to conventional pharmaceuticals, which can vary significantly between regions. In many jurisdictions, herbal-based formulations must comply with regulations for both food supplements and medicinal products, creating a dual burden of compliance. Demonstrating the safety, efficacy, and quality of these formulations can be particularly demanding due to the complexity of herbal extracts and the lack of standardized testing methods. Regulatory agencies require robust preclinical and clinical data to support claims, which can be difficult to generate for multicomponent herbal systems. Furthermore, ensuring consistency in the quality of raw materials and mitigating batch-to-batch variability are critical for meeting regulatory standards [97].

Addressing these challenges requires a multidisciplinary approach that combines advances in formulation science, material engineering, and regulatory expertise. By leveraging novel technologies, such as nanotechnology and biocompatible excipients, and establishing standardized protocols for testing and evaluation, researchers can enhance the stability, performance, and regulatory compliance of herbal-based FDDS, paving the way for their wider acceptance and use in modern therapeutics [98].

7. Future Prospects

The future of FDDS, particularly those incorporating herbal actives for gut microbiome modulation, is poised for transformative advancements. Innovations in biodegradable polymers, integration of nanotechnology, and personalized approaches are shaping the next generation of these delivery systems, offering enhanced efficacy, precision, and adaptability to individual therapeutic needs. Biodegradable polymers are at the forefront of these advancements, addressing critical challenges in drug delivery, such as biocompatibility and controlled release [99]. Emerging biodegradable polymers like polyanhydrides, polyorthoesters, and modified versions of established materials such as poly(lactic-co-glycolic acid) (PLGA) are being tailored for specific drug release profiles and environmental responsiveness. These polymers degrade into non-toxic byproducts that are easily metabolized or excreted, making them ideal for sustained-release applications in the gastrointestinal tract. Additionally, researchers are developing polymers with enhanced mechanical properties, pH sensitivity, and enzymatic degradation profiles to allow for precise control over drug release in targeted regions of the gut. The incorporation of natural polymers, such as chitosan and alginate, alongside synthetic counterparts, is also paving the way for hybrid systems that combine the advantages of both materials [100].

The integration of nanotechnology represents another promising avenue for FDDS innovation. By combining floating microspheres with nanocarriers, such as nanoparticles, liposomes, or nanoemulsions, researchers are achieving enhanced targeting and delivery efficiency. Nanotechnology enables the encapsulation of multiple bioactive compounds, allowing for synergistic effects and the delivery of both hydrophilic and hydrophobic molecules within a single system. This approach is particularly valuable for herbal actives, which often consist of complex mixtures with diverse physicochemical properties. Moreover, nanotechnology enhances the stability of sensitive bioactives and provides improved permeability through biological barriers, such as

mucus layers or epithelial cells. Targeting strategies utilizing ligand-functionalized nanocarriers can further direct the drug to specific microbial populations or intestinal sites, thereby optimizing microbiome modulation and therapeutic outcomes [101].

Personalized approaches for gut microbiome modulation are gaining traction as a future direction for FDDS. Advances in microbiome research have revealed significant interindividual variability in microbial composition and function, influenced by factors such as genetics, diet, lifestyle, and health conditions. This variability underscores the need for tailored drug delivery systems that consider individual microbiome profiles [102]. Personalized FDDS could incorporate microbiome diagnostics and sequencing data to design formulations that target specific microbial imbalances or enhance the growth of beneficial species. For example, microspheres could be customized to release prebiotics, probiotics, or herbal actives in specific concentrations and at precise locations in the gut, aligned with an individual's unique microbiome characteristics. Additionally, machine learning and AI are being explored to predict optimal formulations and delivery parameters, accelerating the development of personalized therapeutic solutions [103].

Conclusion

Floating microspheres represent a promising and versatile drug delivery system, particularly for applications in gastrointestinal treatments, including gut microbiome modulation. These systems offer unique advantages, such as prolonged retention in the stomach, sustained release of encapsulated drugs, and the ability to target specific regions of the gastrointestinal tract. Their ability to enhance bioavailability and improve therapeutic outcomes makes them a valuable tool in modern pharmaceutics, especially for drugs that require localized delivery or need to bypass the harsh conditions of the upper gastrointestinal tract. The table presented outlines 30 different floating microsphere formulations, each designed to address various therapeutic needs by encapsulating different types of drugs in biodegradable polymers such as PLGA, HPMC, chitosan, and polycaprolactone (PCL). These polymers not only ensure controlled drug release but also provide biocompatibility and biodegradability, crucial for minimizing side effects and ensuring safe drug administration over extended periods. The use of biodegradable polymers in combination with novel formulation techniques, like spray drying and solvent evaporation, has paved the way for the development of sophisticated drug delivery systems that can be tailored to the needs of specific drugs and patient profiles. The range of drugs that can be delivered via floating microspheres spans across multiple therapeutic areas, from anti-inflammatory drugs like diclofenac to probiotics, anti-cancer agents, and even hormones like testosterone. This versatility highlights the adaptability of microsphere technology to meet the demands of diverse treatments. In particular, the integration of herbal bioactives in microsphere formulations holds great potential for treating gut-related disorders and microbiome imbalances. Herbal compounds such as curcumin, for example, can be effectively encapsulated within these microspheres to improve their stability and bioavailability, ensuring a more targeted and efficient therapeutic action. However, while the potential of floating microspheres is immense, several challenges remain. The stability of herbal bioactives during the formulation process must be carefully managed to preserve their therapeutic properties. The release kinetics of the microspheres also need to be finely tuned to ensure the drug is released at the right time and in the right amount. Furthermore, the regulatory landscape for herbal-based FDDS can be complex, as these systems must meet rigorous safety and efficacy standards before they can be brought to market. Addressing these challenges requires continued research and innovation in formulation techniques, polymer chemistry, and regulatory frameworks. Looking forward, the future of floating microsphere technology is bright. Innovations in biodegradable polymers, such as those with enhanced mechanical properties or those responsive to specific stimuli like pH and temperature, will further refine the performance of these delivery systems. The integration of nanotechnology could provide more precise targeting and enhanced stability, especially for complex herbal mixtures or delicate bioactive compounds. Moreover, the development of personalized medicine approaches, tailored to individual microbiome profiles, will open up new possibilities for gut microbiome modulation and disease prevention.

In summary, floating microspheres represent a cutting-edge solution for controlled and targeted drug delivery, offering significant therapeutic advantages for a wide range of diseases. As research progresses and new technologies emerge, these systems will undoubtedly play a key role in the future of drug delivery, improving patient outcomes and paving the way for more personalized and effective treatments.

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Author Contributions

A.T. conceptualized the study, drafted the manuscript, and provided overall supervision. **A.** contributed to the literature review and data collection. **C.K.** performed critical revisions and formatting of the manuscript. **M.Z.** assisted with analysis and interpretation of the data.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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