Gastroretentive Floating Drug Delivery Systems: Recent Advances and Applications in Antihypertensive Therapy

Shubam Sharma[1], Prof. Vinayak Munde[2]
[1]*Student, M. Pharm 2nd Yr., Department of Pharmaceutics, Dr. Vedprakash Patil Pharmacy College, Chh. Sambhajinagar*
[2]*Professor, Department of Pharmaceutics, Dr. Vedprakash Patil Pharmacy College, Chh. Sambhajinagar*

***Abstract*—Hypertension remains one of the leading causes of cardiovascular morbidity and mortality worldwide, necessitating effective and sustained pharmacological management. Conventional oral dosage forms of antihypertensive drugs often exhibit limitations such as short gastric residence time, variable absorption, frequent dosing, and fluctuating plasma drug concentrations, which may compromise therapeutic efficacy and patient compliance. Gastroprotective Floating Drug Delivery Systems (GFDDS) have emerged as a promising approach to overcome these challenges by prolonging gastric residence time and providing controlled drug release. These systems remain buoyant in the gastric environment for extended periods, allowing sustained drug delivery in the upper gastrointestinal tract where absorption is often optimal. Recent advances in polymer science, formulation technologies, nanotechnology, and multifunctional gastroprotective systems have significantly enhanced the performance of floating drug delivery systems. Several antihypertensive drugs, including propranolol, atenolol, carvedilol, metoprolol, verapamil, and diltiazem, have been successfully incorporated into floating formulations to improve bioavailability, reduce dosing frequency, and maintain therapeutic plasma concentrations. This review discusses the principles, classification, mechanisms, formulation approaches, evaluation parameters, recent technological advancements, and applications of gastroretentive floating drug delivery systems in antihypertensive therapy. Furthermore, future prospects and challenges associated with the development of advanced gastroretentive systems are highlighted.**

***Index Terms*—Gastroretentive drug delivery system, Floating drug delivery system, Antihypertensive drugs, Controlled release, Gastric retention, Bioavailability enhancement.**

I. INTRODUCTION

Hypertension is a chronic cardiovascular disorder characterized by persistently elevated arterial blood pressure and is recognized as a major risk factor for stroke, myocardial infarction, heart failure, and renal diseases. According to global health reports, hypertension affects more than one billion individuals worldwide and continues to be a significant public health challenge. Long-term management of hypertension often requires continuous administration of antihypertensive medications to maintain optimal blood pressure control.[1] Despite the availability of numerous antihypertensive agents, conventional oral drug delivery systems frequently encounter challenges such as short gastrointestinal residence time, incomplete absorption, extensive first-pass metabolism, and poor bioavailability. Many antihypertensive drugs exhibit an absorption window in the upper gastrointestinal tract, making prolonged gastric retention highly desirable for maximizing therapeutic efficacy.[2]

Gastroretentive Floating Drug Delivery Systems (GFDDS) have gained considerable attention as an innovative approach for improving oral drug delivery. These systems are designed to remain buoyant in gastric fluids for prolonged periods, thereby increasing gastric residence time and facilitating sustained drug release. As a result, GFDDS can improve bioavailability, reduce dosing frequency, and enhance patient compliance.[3]

II. CONCEPT OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive Drug Delivery Systems (GRDDS) are advanced oral drug delivery systems specifically designed to prolong the residence time of a dosage form within the stomach, thereby enhancing drug absorption and therapeutic efficacy. Conventional oral dosage forms generally pass through the stomach within a relatively short period due to normal gastric emptying processes. This rapid transit may limit the absorption of drugs that are preferentially absorbed in the stomach or upper part of the small intestine. GRDDS have been developed to overcome this limitation by retaining the dosage form in the gastric region for an extended duration and releasing the drug in a controlled manner. Prolonged gastric retention enables the maintenance of therapeutic drug concentrations, improves bioavailability, reduces dosing frequency, and enhances patient compliance.[4]

The fundamental objective of gastroretentive drug delivery systems is to increase the gastric residence time of the dosage form. By remaining in the stomach for several hours, the formulation can continuously release the drug at a predetermined rate, ensuring sustained absorption and improved therapeutic outcomes. Various approaches have been employed to achieve gastric retention, including floating systems, bioadhesive systems, expandable systems, high-density systems, and raft-forming systems. Among these, floating drug delivery systems are the most extensively studied and widely utilized because of their simplicity, effectiveness, and patient acceptability. GRDDS are particularly beneficial for drugs that possess a narrow absorption window in the gastrointestinal tract. Such drugs are absorbed efficiently only from specific regions, usually the stomach or upper small intestine. If these drugs pass rapidly through their absorption site, incomplete absorption may occur, leading to reduced bioavailability. By prolonging gastric residence time, GRDDS allow these drugs to remain in the optimal absorption region for an extended period, thereby maximizing drug uptake and therapeutic effectiveness.[5]

Another important category of drugs suitable for gastroretentive delivery includes those that are primarily absorbed in the stomach or upper intestine. Many drugs exhibit site-specific absorption characteristics and are absorbed preferentially in the proximal region of the gastrointestinal tract. Prolonging the residence time of these drugs in the stomach increases their contact with the absorptive surfaces and improves the extent of absorption. GRDDS are also advantageous for drugs that exhibit low solubility at intestinal pH. Certain drugs are highly soluble in the acidic environment of the stomach but become poorly soluble in the alkaline conditions of the intestine. When such drugs rapidly leave the stomach, their dissolution rate decreases, resulting in incomplete absorption. Retaining these drugs in the acidic gastric environment helps maintain their solubility and facilitates sustained drug release and absorption.[6]

In addition, gastroretentive systems are useful for drugs that require local action in the stomach. Examples include drugs used in the treatment of gastric ulcers, Helicobacter pylori infections, and gastroesophageal reflux disease. Prolonged retention of the dosage form within the stomach enhances local drug concentration at the target site and improves therapeutic effectiveness. Drugs with short biological half-lives also benefit significantly from gastroretentive delivery systems. Such drugs often require frequent administration to maintain therapeutic plasma concentrations. GRDDS can provide controlled and sustained drug release over an extended period, thereby reducing dosing frequency, minimizing fluctuations in plasma drug levels, and improving patient compliance. Among the various gastroretentive approaches, floating drug delivery systems (FDDS) are the most widely investigated. These systems are designed with a density lower than that of gastric fluids, enabling them to float on the stomach contents without affecting gastric emptying. While floating, the dosage form gradually releases the drug and remains in the stomach for prolonged periods. This extended gastric retention enhances bioavailability, improves therapeutic efficacy, and provides sustained drug release. Owing to these advantages, floating systems have become one of the most promising and successful strategies in the development of gastroretentive drug delivery systems.[7]

III. PRINCIPLE OF FLOATING DRUG DELIVERY SYSTEMS

Floating Drug Delivery Systems (FDDS) are a specialized category of gastroretentive drug delivery systems designed to prolong the residence time of dosage forms within the stomach. The fundamental principle of FDDS is based on buoyancy, whereby the dosage form is formulated to possess a bulk density lower than that of gastric fluids, which is approximately 1.004 g/cm³. Due to this lower density, the dosage form is capable of floating on the surface of the gastric contents rather than sinking and passing rapidly into the intestine. This floating behavior enables the formulation to remain in the stomach for an extended period, thereby enhancing gastric retention and improving drug absorption.[8]

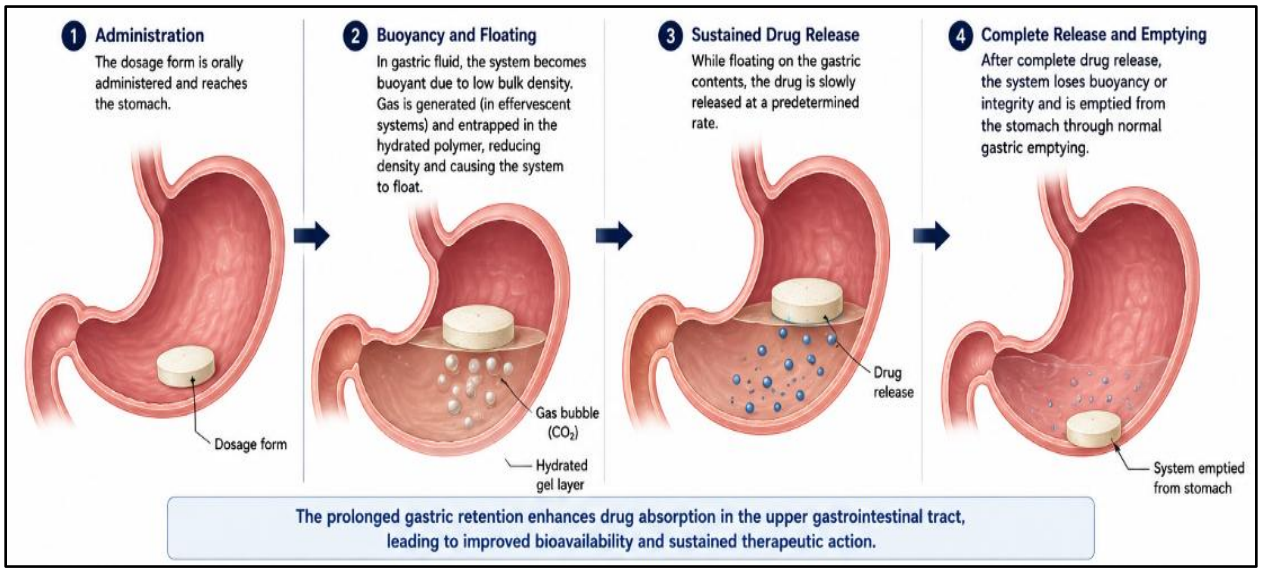

Fig. Principle of Floating Drug Delivery Systems

Upon oral administration, the floating dosage form reaches the stomach and comes into contact with gastric fluids. In most formulations, hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), sodium alginate, carbopol, or xanthan gum absorb water and swell, forming a hydrated gel layer around the dosage form.[9] In effervescent floating systems, gas-generating agents such as sodium bicarbonate and citric acid react with gastric acid to produce carbon dioxide gas. The generated gas becomes entrapped within the swollen polymer matrix, reducing the overall density of the system below that of gastric fluid. As a result, the dosage form becomes buoyant and floats on the stomach contents. While floating in the gastric environment, the dosage form remains in the stomach without significantly affecting the normal gastric emptying process. The prolonged residence of the system allows the drug to be released gradually at a predetermined and controlled rate.[10] Drug release may occur through diffusion, polymer erosion, dissolution, or a combination of these mechanisms. Because the formulation remains in the stomach for an extended duration, a continuous supply of drug is available for absorption, particularly for drugs that are absorbed primarily in the stomach or upper part of the small intestine.[11]

The prolonged gastric retention provided by floating systems offers several therapeutic advantages. It increases the contact time between the drug and the absorptive surfaces of the gastrointestinal tract, thereby enhancing drug absorption and improving oral bioavailability. This is particularly beneficial for drugs with narrow absorption windows, poor intestinal solubility, or site-specific absorption characteristics. Furthermore, sustained drug release from floating systems helps maintain relatively constant plasma drug concentrations, reducing fluctuations associated with conventional dosage forms.[12] This can minimize

adverse effects caused by peak drug concentrations and prevent sub therapeutic levels that may occur between doses. After the complete release of the drug, the integrity of the dosage form gradually diminishes through erosion, dissolution, or loss of buoyancy. Once the density of the system increases above that of gastric fluids, it is emptied from the stomach through the normal gastric emptying process and passes into the intestine for eventual elimination. Thus, floating drug delivery systems provide an effective strategy for extending gastric residence time, improving bioavailability, enhancing therapeutic efficacy, and reducing dosing frequency. Owing to these advantages, FDDS have become one of the most extensively investigated and successful approaches in gastroretentive drug delivery technology.[13]

IV. MECHANISM OF FLOATING DRUG DELIVERY SYSTEMS

After oral administration, the floating dosage form reaches the stomach and comes into contact with gastric fluid. Hydrophilic polymers present in the formulation hydrate and form a gel barrier around the dosage form. Simultaneously, gas-generating agents such as sodium bicarbonate react with gastric acid to produce carbon dioxide. The generated gas becomes entrapped within the hydrated polymer matrix, decreasing the density of the system below that of gastric fluid.[14]

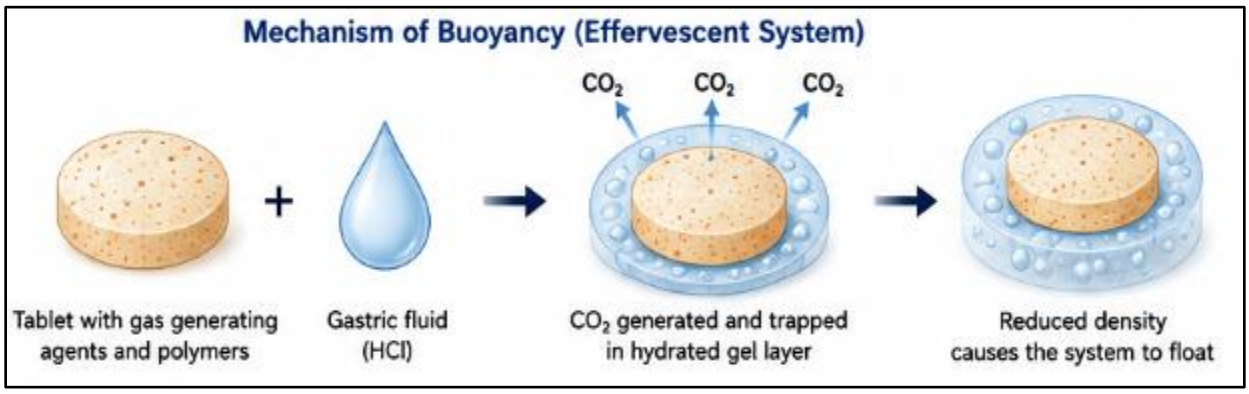

Fig: Mechanism of Buoyancy

As a result, the dosage form floats on the gastric contents and remains in the stomach for several hours. During this period, the drug is released in a controlled manner through diffusion, erosion, or a combination of both mechanisms. The extended gastric residence time enhances drug absorption and improves bioavailability.[15]

V. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

5.1. Effervescent Floating Systems

Effervescent floating systems achieve buoyancy through the generation of carbon dioxide gas. These formulations contain gas-generating agents such as sodium bicarbonate, calcium carbonate, citric acid, and tartaric acid. Upon contact with gastric acid (HCl), these agents react and produce carbon dioxide gas. The generated gas becomes trapped within the hydrated polymer matrix, reducing the density of the dosage form below that of gastric fluid and enabling it to float.[16]

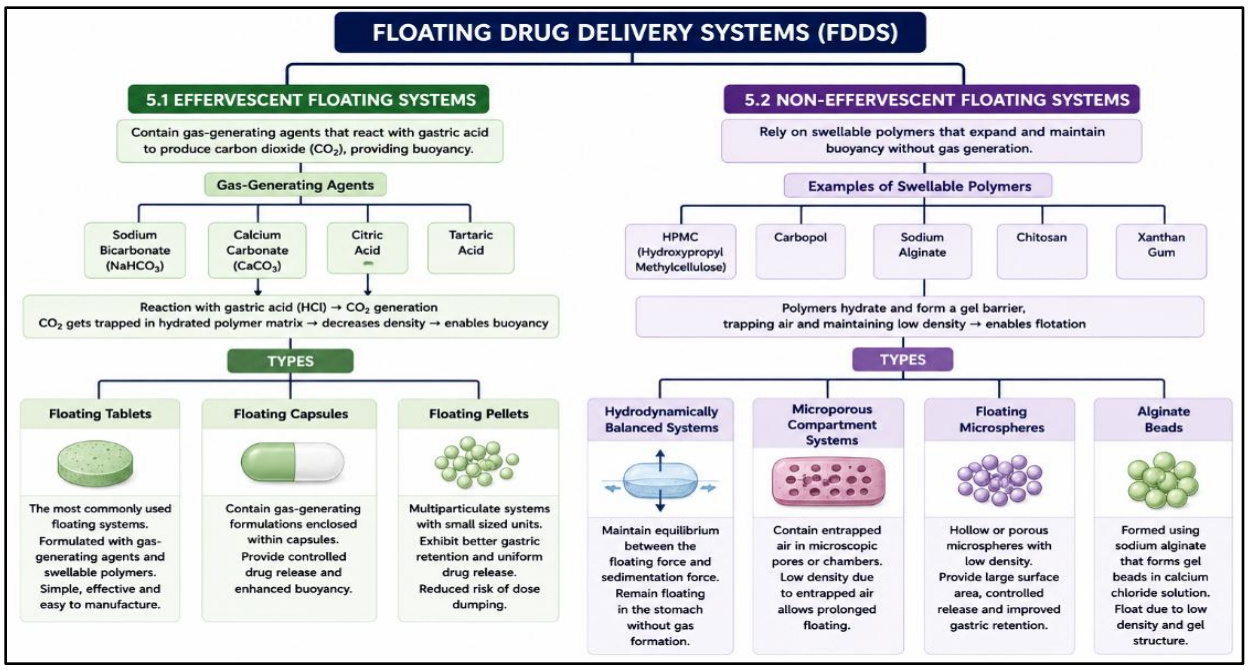

Fig: Classification of Floating Drug Delivery Systems

a) Floating Tablets

Floating tablets are the most commonly used gastroretentive dosage forms. They contain gas-generating agents along with swellable polymers. Upon hydration, the polymer matrix swells and traps carbon dioxide, resulting in buoyancy and sustained drug release.[17]

b) Floating Capsules

These systems contain gas-generating formulations enclosed within capsules. The capsule shell dissolves after administration, allowing the formulation to react with gastric fluid and produce buoyancy while releasing the drug gradually.[18]

c) Floating Pellets

Floating pellets are multiparticulate systems composed of numerous small units. These pellets exhibit prolonged gastric retention, uniform drug release, and reduced risk of dose dumping compared to single-unit systems.[19]

5.2. Non-Effervescent Floating Systems[20]

Non-effervescent floating systems do not rely on gas generation for buoyancy. Instead, they utilize swellable polymers that hydrate upon contact with gastric fluid and form a gel barrier around the dosage form. The hydrated polymer matrix traps air and maintains a density lower than gastric fluid, allowing the system to float.

Commonly used polymers include:

- Hydroxypropyl Methylcellulose (HPMC)
- Carbopol
- Sodium Alginate
- Chitosan
- Xanthan Gum

These polymers provide swelling, gel formation, controlled drug release, and prolonged gastric retention.

The non-effervescent systems are further classified into:

a) Hydrodynamically Balanced Systems (HBS)

These systems contain gel-forming polymers that maintain equilibrium between floating force and sedimentation force. They remain buoyant without producing gas and provide sustained drug release.

b) Microporous Compartment Systems

These systems contain microscopic pores or chambers filled with air. The entrapped air decreases the density of the dosage form, enabling prolonged flotation in gastric fluid.

c) Floating Microspheres

Floating microspheres are hollow spherical particles with low density. Their hollow structure allows them to float for extended periods while providing controlled drug release and enhanced bioavailability.

d) Alginate Beads

Alginate beads are prepared using sodium alginate and calcium chloride. The beads possess a porous gel structure and low density, which contribute to their buoyancy and sustained drug release properties.

VI. ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS[21-22]

Floating drug delivery systems offer several advantages:

- Prolonged gastric residence time.
- Enhanced oral bioavailability.
- Improved drug absorption.
- Sustained and controlled drug release.
- Reduced dosing frequency.
- Improved patient compliance.
- Reduced plasma concentration fluctuations.
- Better therapeutic efficacy.
- Reduced side effects associated with peak plasma levels.

VII. LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Despite their advantages, GFDDS possess certain limitations:

- Dependence on gastric fluid volume.
- Unsuitability for drugs unstable in acidic conditions.
- Variable gastric emptying rates among patients.
- Unsuitability for drugs causing gastric irritation.
- Requirement for adequate fluid intake.

VIII. RECENT ADVANCES IN FLOATING DRUG DELIVERY SYSTEMS

Recent advances in Floating Drug Delivery Systems (FDDS) have significantly improved their effectiveness, stability, drug-loading capacity, and therapeutic performance. Conventional floating systems primarily focused on prolonging gastric residence time through buoyancy; however, modern research has integrated innovative technologies such as nanotechnology, smart polymers, in situ gelation, and three-dimensional (3D) printing to overcome existing limitations and enhance drug delivery. These advanced systems provide improved gastric retention, controlled drug release, enhanced bioavailability, and better patient compliance, making them highly attractive for the treatment of chronic diseases including hypertension, diabetes, and gastrointestinal disorders.

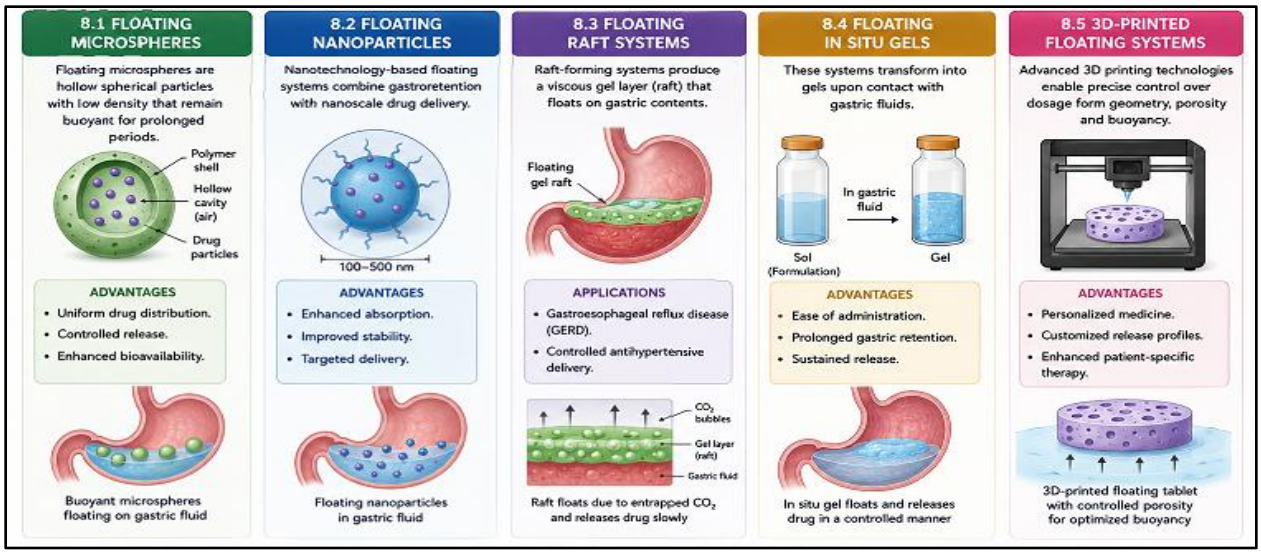

Fig: Recent Advances in Floating Drug Delivery Systems

8.1. Floating Microspheres

Floating microspheres, also known as hollow microspheres or microballoons, are one of the most extensively studied advanced floating systems. These are hollow spherical particles with a low density that enables them to remain buoyant in gastric fluids for prolonged periods. Floating microspheres are generally prepared using polymers such as ethyl cellulose, Eudragit, or hydroxypropyl methylcellulose through solvent evaporation or emulsion techniques. The hollow internal cavity decreases the density of the microspheres and allows them to float continuously in the stomach. These systems offer several advantages, including uniform drug distribution, controlled and sustained drug release, enhanced bioavailability, and reduced fluctuations in plasma drug concentration. Due to their multiparticulate nature, floating microspheres also minimize the risk of dose dumping and provide more reproducible drug absorption.[23]

8.2. Floating Nanoparticles

The integration of nanotechnology into gastroretentive systems has led to the development of floating nanoparticles. These systems combine the benefits of gastric retention with nanoscale drug delivery. Floating nanoparticles possess extremely small particle sizes, typically ranging from 10 to 1000 nm, which facilitate improved drug dissolution and absorption. Their large surface area enhances interaction with biological membranes, resulting in increased bioavailability. Additionally, nanoparticles can protect drugs from degradation and provide targeted drug delivery to specific sites within the gastrointestinal tract. Floating nanoparticles have shown significant promise for poorly soluble drugs and drugs with narrow absorption windows. Their ability to enhance stability, improve absorption, and provide controlled release makes them an important advancement in gastroretentive drug delivery technology.[24]

8.3. Floating Raft Systems

Floating raft systems represent another innovative approach in floating drug delivery. These systems are formulated using gel-forming polymers such as sodium alginate, which rapidly form a viscous and cohesive gel layer, known as a raft, upon contact with gastric fluids. The raft floats on the surface of stomach contents due to the presence of entrapped carbon dioxide generated by gas-forming agents. This floating gel barrier remains in the stomach for an extended duration and gradually releases the incorporated drug. Raft-forming systems are particularly useful in the treatment of gastroesophageal reflux disease (GERD), where they prevent reflux of gastric contents into the esophagus. Recently, these systems have also been investigated for the controlled delivery of antihypertensive drugs, enabling prolonged gastric residence and sustained drug release.[25]

8.4. Floating In Situ Gels

Floating in situ gels have emerged as a promising gastroretentive dosage form due to their simplicity and effectiveness. These formulations are administered as liquids and undergo gelation upon contact with gastric fluids due to changes in pH, temperature, or ionic concentration. The resulting gel matrix remains buoyant in the stomach and releases the drug in a controlled manner over an extended period. Floating in situ gels offer several advantages, including ease of administration, improved patient acceptability, prolonged gastric retention, and sustained drug release. They are particularly suitable for pediatric and geriatric patients who may experience difficulty swallowing conventional tablets or capsules.[26]

8.5. 3D-Printed Floating Systems

One of the most exciting recent developments in floating drug delivery is the application of three-dimensional (3D) printing technology. This advanced manufacturing technique allows precise control over the geometry, internal structure, porosity, density, and buoyancy of dosage forms. By adjusting printing parameters, researchers can design floating tablets with customized release profiles and optimized gastric retention characteristics. 3D-printed floating systems offer significant advantages, including personalized medicine, patient-specific dose customization, and tailored drug release kinetics. This technology enables the development of dosage forms that meet individual therapeutic requirements and has the potential to revolutionize future gastroretentive drug delivery systems. Recent advances in floating drug delivery systems, including floating microspheres, nanoparticles, raft systems, in situ gels, and 3D-printed formulations, have greatly expanded the capabilities of gastroretentive drug delivery. These innovative approaches provide improved gastric

retention, enhanced bioavailability, controlled drug release, and greater flexibility in formulation design, paving the way for more effective and patient-centered therapies.[27]

XI. APPLICATIONS IN ANTIHYPERTENSIVE THERAPY

Floating drug delivery systems (FDDS) have emerged as an effective approach for improving the oral delivery of several antihypertensive drugs, particularly those with poor bioavailability, short biological half-lives, extensive first-pass metabolism, or absorption windows confined to the upper gastrointestinal (GI) tract. By remaining buoyant in the stomach for an extended period, FDDS prolong gastric residence time, thereby enhancing drug dissolution, absorption, and therapeutic efficacy while reducing fluctuations in plasma drug concentration.

Propranolol hydrochloride is one of the most widely studied antihypertensive drugs for floating drug delivery due to its extensive first-pass metabolism, short elimination half-life, and narrow absorption window in the upper GI tract. Conventional dosage forms often result in incomplete absorption and reduced bioavailability. Floating formulations prolong gastric retention, allowing the drug to remain within its optimal absorption region for a longer duration, thereby enhancing bioavailability, maintaining sustained plasma drug concentrations, and prolonging therapeutic action.

Atenolol exhibits limited absorption in the lower gastrointestinal tract, making it an ideal candidate for gastroretentive drug delivery. Floating formulations increase the gastric residence time of atenolol, ensuring prolonged exposure to its primary absorption site in the stomach and upper intestine. This results in improved drug absorption, increased bioavailability, enhanced therapeutic effectiveness, and reduced variability in drug plasma levels.

Metoprolol succinate, a β_1-selective adrenergic blocker commonly used for hypertension and cardiovascular disorders, benefits from controlled-release floating matrix systems. These formulations provide sustained drug release over an extended period, minimizing frequent dosing requirements. Consequently, floating delivery systems help maintain consistent therapeutic plasma concentrations, reduce dosing frequency, and improve patient compliance, especially during long-term antihypertensive therapy.[28]

Carvedilol is characterized by poor aqueous solubility and significant first-pass hepatic metabolism, both of which contribute to its low oral bioavailability. Floating drug delivery systems prolong gastric residence time and improve drug dissolution in the acidic gastric environment. As a result, enhanced bioavailability, improved plasma concentration profiles, and better therapeutic outcomes have been reported compared with conventional dosage forms.[29]

Verapamil hydrochloride, a calcium channel blocker, possesses a well-defined absorption window in the upper gastrointestinal tract. Floating tablets retain the dosage form in the stomach for an extended period, allowing continuous drug release within its optimal absorption region. This prolonged gastric retention improves drug absorption, maintains therapeutic plasma concentrations, and provides sustained antihypertensive effects while reducing dosing frequency.[30]

Similarly, diltiazem hydrochloride, another calcium channel blocker with a relatively short half-life, has shown significant benefits when formulated as a floating dosage form. Floating formulations provide sustained drug release, improve oral bioavailability, and maintain therapeutic plasma concentrations for extended periods. These advantages reduce the need for frequent administration, enhance patient adherence to therapy, and improve overall blood pressure control.[31]

Floating drug delivery systems represent a promising strategy for antihypertensive therapy by overcoming limitations associated with conventional oral dosage forms. They enhance gastric residence time, improve drug absorption and bioavailability, provide sustained therapeutic plasma levels, reduce dosing frequency, and ultimately improve patient compliance and clinical outcomes.

X. CONCLUSION

Gastroretentive Floating Drug Delivery Systems represent a highly effective strategy for improving the oral delivery of antihypertensive drugs. By prolonging gastric residence time and enabling controlled drug release, these systems enhance bioavailability, reduce dosing frequency, and improve patient compliance. Recent advances involving floating microspheres,

nanoparticles, in situ gels, raft systems, and 3D-printed dosage forms have expanded the potential applications of gastroretentive technology. Given the increasing prevalence of hypertension and the need for long-term therapy, floating drug delivery systems offer a promising platform for optimizing antihypertensive treatment and improving therapeutic outcomes. Their continued development is expected to play a significant role in the future of controlled oral drug delivery.

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