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Controlled Drug Delivery of Furosemides Using Floating Tablet System

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Abstract

The development of gastroretentive drug delivery systems (GRDDS) has gained interest, particularly for drugs like furosemide with narrow absorption windows in the upper gastrointestinal (GI) tract. Furosemide, a commonly used diuretic, faces challenges due to limited bioavailability and rapid elimination, requiring frequent dosing and affecting patient compliance. This review highlights the formulation and evaluation of floating furosemide tablets as an effective strategy to enhance therapeutic efficacy. Floating tablets allow prolonged gastric retention, providing controlled release and maintaining optimal drug concentration within the absorption site. Key formulation aspects are discussed, including pre-formulation studies to assess drug-excipient compatibility, solubility, flow properties, and buoyancy, which are crucial for floating tablet stability and effectiveness. Various polymers and gas-generating agents are outlined for their roles in achieving buoyancy, improving stability, and controlling drug release. In vitro evaluation methods, such as buoyancy, swelling, and drug release studies, are examined to evaluate the tablet's performance and release kinetics. Despite challenges like formulation complexity and variability in gastric motility, ongoing research, and optimization in GRDDS for furosemide show promising potential. Prospects in this area could lead to better management of conditions treated with furosemide and improved patient outcomes.

Keywords: Gastroretentative furosemide buoyancy, bioavailability effervescent, Furosemide, Floating tablets, Controlled release

INTRODUCTION

Furosemide is a widely used loop diuretic prescribed primarily for managing edema associated with conditions like congestive heart failure, liver cirrhosis, and kidney disorders, as well as for treating hypertension. Its mechanism of action involves inhibiting the sodium-potassium-chloride (Na^+–K^+–$2Cl^-$) co-transporter in the loop of Henle within the kidneys, increasing the excretion of sodium, chloride, and water. This action reduces blood volume, relieving edema and lowering blood pressure in conditions like congestive heart failure and hypertension. Furosemide's rapid and powerful diuretic effect makes it highly effective in acute settings, yet its pharmacokinetics limit sustained therapeutic effects [1].

Conventional oral formulations of furosemide face several limitations, primarily due to its low and variable bioavailability (10–90%) and narrow absorption window in the upper gastrointestinal (GI) tract. This results in erratic absorption, leading to fluctuations in therapeutic plasma concentrations. Moreover, rapid gastric emptying limits the time available for absorption, which can cause sub-therapeutic levels and compromised efficacy,

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especially in patients with variable GI motility [2].

Floating drug delivery systems (FDDS) offer a promising approach to address the challenges associated with conventional furosemide formulations. FDDS is a gastroretentive technology that allows the dosage form to remain buoyant in the stomach for extended periods, increasing gastric residence time. This prolonged retention ensures a more consistent release and absorption of furosemide in the upper GI tract, thereby, improving bioavailability, stabilizing plasma concentrations, and enhancing therapeutic effectiveness [3]. Floating drug systems are shown in Figure 1.

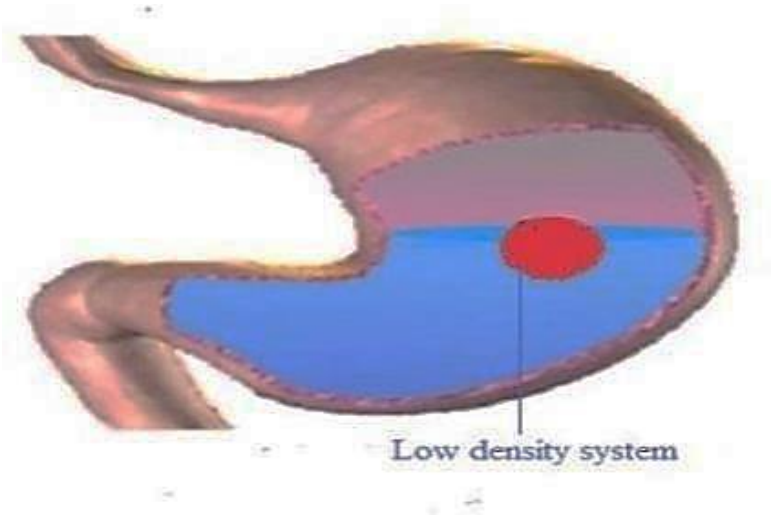

Figure 1. Floating drug system.

PREFORMULATION STUDIES

Preformulation studies play a crucial role in developing a stable and effective floating furosemide tablet. These studies provide foundational information about the drug's physicochemical properties, interactions with excipients, and factors that could influence the drug's bioavailability and stability in the final formulation.

- *Drug-Excipients Compatibility Studies:* The compatibility of furosemide with different excipients is evaluated to prevent any adverse chemical interactions that could impact the drug's stability and efficacy. Techniques, such as differential scanning calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), and Thermogravimetric Analysis (TGA) are commonly used. These tests help identify any changes in the thermal or chemical profiles of furosemide when mixed with excipients like hydroxypropyl methylcellulose (HPMC), carbopol, and sodium bicarbonate, which are essential for the tablet's floating mechanism [4].
- *Powder Flow Properties:* Good powder flow is necessary for ensuring uniform weight and content in each tablet. For this purpose, parameters, such as angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio are evaluated. An acceptable angle of repose (usually below 30°) indicates good flow, while Carr's index and Hausner ratio values provide insight into the compressibility of the powder mixture, important for direct compression methods in tablet formulation [5]. Parameters of flow properties are shown in Table 1.
- *pH Stability and Solubility Studies*: Furosemide has limited solubility in higher pH environments, which may impact its absorption in the GI tract. Solubility studies are conducted across different pH values to determine the drug's behavior in acidic environments like the stomach. The pH stability studies, on the other hand, help identify any degradation risk when exposed to acidic conditions. Observing degradation could indicate the need for protective excipients to maintain drug stability throughout the release period [5].
- *Buoyancy and Gas Generation:* For a floating tablet, maintaining buoyancy in the stomach is key for prolonged gastric retention. This buoyancy is achieved through gas-generating agents like

sodium bicarbonate, which release CO_2 in the acidic gastric environment, keeping the tablet afloat. Preformulation studies assess parameters like buoyancy lag time (the time it takes to float) and total floating duration. The goal is to ensure the tablet floats within a few minutes and remains buoyant for 8–12 hours to ensure adequate gastric residence time [5].

- *Particle Size Analysis:* Particle size can influence the drug's dissolution rate and bioavailability. A smaller particle size generally enhances the surface area, improving the dissolution rate. Preformulation studies typically include particle size analysis to achieve an optimal range, ensuring efficient dissolution and absorption [6].
- *Moisture Content Analysis:* Moisture can affect the stability of furosemide, potentially causing degradation or changes in its physicochemical properties. Moisture content is evaluated using Karl Fischer titration or a loss-on-drying method to ensure the powder blend remains within the acceptable range for stability [6].

Table 1. Parameters of flow properties.

Flow Property	Parameters		
	Angle of Repose	**Hausner's Ratio**	**Carr's Index**
Excellent	25-30	1.0-1.11	<10
Good	31-35	1.12-1.18	11-15
Fair	36-40	1.19-1.25	16-20
Passable	41-45	1.26-1.34	21-25
Poor	46-55	1.35-1.45	26-31
Very Poor	56-65	1.46-1.59	32-37
Very Very Poor	>66	>1.60	>38

Table 2. Preformulation parameters of drug.

Parameter	Method	Observation	Acceptable
Drug-Excipient Compatibility	FTIR, DSC, TGA	No significant interaction observed.	
Angle of Repose	Funnel Method	27°	Less than 30°.
Bulk Density	Bulk Density Apparatus	0.52 g/mL	–
Tapped Density	Tapped Density Apparatus	0.61 g/mL	–
Carr's Index	Calculated	14.8%	5–15%
Hausner Ratio	Calculated	1.17	1.12–1.18
Solubility (pH 1.2)	Shake Flask Method	10 mg/mL	High solubility in acidic pH.
Buoyancy Lag Time	Dissolution Medium (0.1 N HCl)	60 seconds	Less than 5 minutes.
Total Floating Duration	Dissolution Medium (0.1 N HCl)	12 hours	More than 8 hours.

Formulation Development [7, 8]

Floating furosemide tablets are formulated using buoyant agents (like sodium bicarbonate) and polymers (such as HPMC) to ensure prolonged gastric retention. The floating mechanism enhances bioavailability by keeping the tablet in the stomach, allowing controlled drug release. Binders and lubricants improve tablet integrity and stability, optimizing therapeutic effectiveness and patient compliance. Selection of excipients:

Matrix-Forming Polymers

- *Hydroxypropyl Methylcellulose (HPMC):* HPMC, specifically K4M and K15M grades, is widely used due to its swellable and gel-forming properties, which help to prolong gastric retention time. The hydrated gel layer formed by HPMC controls the release of furosemide by slowing drug

diffusion and extending the floating effect. Higher viscosity HPMC grades provide better drug retention and extended-release profiles, with K15M showing slightly prolonged effects compared to K4M.

- *Carbopol and Xanthan Gum:* Carbopol can be combined with HPMC to improve matrix stability, enhancing the extended-release effect. Xanthan gum, a natural polysaccharide, also serves as an alternative polymer that maintains floating properties and releases the drug in a controlled manner by forming a gel layer.

Gas-Generating Agents

Sodium Bicarbonate and Citric Acid

These excipients are essential for creating effervescence, which produces CO_2 when exposed to gastric acid. The CO_2 generated causes the tablet to float, maintaining it in the upper gastric environment where furosemide absorption is most effective. Studies suggest that a ratio of 1:1 for sodium bicarbonate to citric acid optimizes gas generation, ensuring quick and sustained floating with minimal lag time.

Fillers and Binders

Lactose and Micro-Crystalline Cellulose (MCC)

Lactose and MCC are often used as fillers and binders, aiding in tablet compression and hardness. MCC additionally helps in maintaining structural integrity during swelling, preventing early disintegration. Lactose also ensures uniform mixing, enhancing the consistency of drug content within each tablet.

Lubricants and Glidants

- *Magnesium Stearate and Talc:* These excipients enhance powder flow properties and prevent sticking during compression, crucial for high-speed tablet manufacturing. Magnesium stearate is particularly useful in maintaining tablet durability during the floating phase without affecting drug release.
- *pH Modifiers:* Some formulations include pH modifiers to maintain an optimal pH level around the tablet. Since furosemide is weakly acidic, maintaining a slightly acidic micro-environment around the tablet enhances its solubility and release rate in the stomach. Citric acid can serve dual functions as a pH modifier and part of the gas-generating system.

Formulation Techniques

Formulation techniques for floating furosemide tablets typically focus on prolonging gastric retention and enhancing bioavailability by using controlled-release and floating mechanisms, as furosemide has poor solubility in stomach acid. Some current techniques include:

Polymeric Floating Systems

These systems use hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC) K4M and K100M, to create a matrix that swells and remains buoyant in the gastric environment (shown in Figure 2). Sodium bicarbonate is often added to generate gas, facilitating tablet floatation for extended gastric retention.

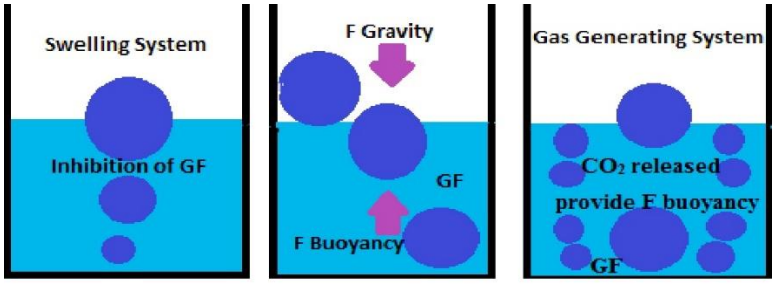

Figure 2. Different floating techniques.

Effervescent Systems

This method combines furosemide with effervescent agents like sodium bicarbonate and citric acid to produce carbon dioxide, enabling the tablet to float (shown in Figure 3).

This approach often integrates polymers that regulate the release rate to maintain the drug in the stomach for several hours.

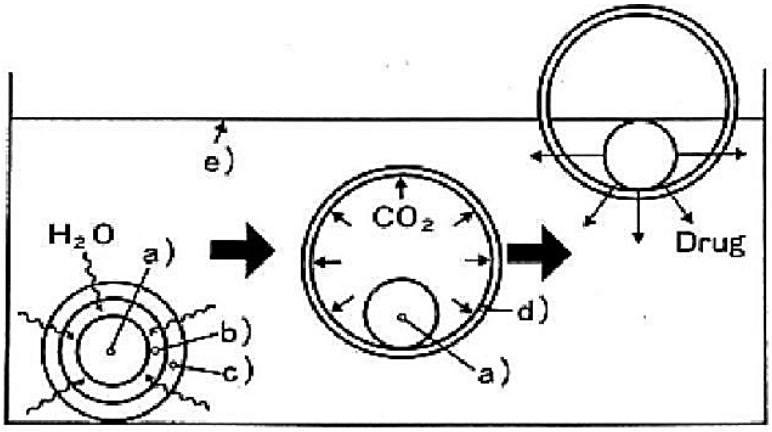

Figure 3. Effervescent technique.

GASTRO RETENTIVE FLOATING FILMS

A newer approach involves forming floating polymeric films, where furosemide is dispersed in a film matrix made of polymers like sodium carboxymethyl cellulose and sodium alginate. These films are prepared using solvent casting methods and contain solubility enhancers (e.g., sodium hydroxide), achieving prolonged drug release while maintaining floatation.

Evaluation

- *Floating Lag Time and Duration:* Floating Lag Time (FLT): This measures the time taken for a tablet to begin floating once placed in simulated gastric fluid. For effective retention, a floating tablet should have a short FLT, often less than 5 minutes.
- *Total Floating Duration (TFD):* This assesses how long the tablet remains floating, usually exceeding 8 hours for sustained-release drugs like furosemide. Maintaining buoyancy helps enhance drug absorption within the stomach.

Tablet Integrity and Mechanical Strength

- *Hardness:* Using a hardness tester, measure the pressure a tablet can withstand before breaking. Aulton's Pharmaceutics recommends a range suitable for handling without disintegration.
- *Friability:* Using a friability, this test checks resistance to chipping or crumbling, ideally below 1% to prevent degradation in packaging or handling.
- *In Vitro Dissolution Studies:* In simulated gastric fluid, typically with a pH of 1.2, dissolution studies are conducted to measure the release profile of the drug over time, often up to 12 hours. A sustained-release profile helps maintain consistent plasma drug levels. According to Remington, zero-order or non-Fickian diffusion models often describe these release kinetics for floating tablets, ensuring steady delivery and efficacy.
- *Drug Content Uniformity:* Testing is performed to ensure each tablet contains the specified drug amount, usually within 90–110% of the labeled dose. This helps maintain dosing accuracy, a critical quality criterion in pharmacopoeial standards like the USP.
- *Swelling Index:* To measure swelling, tablets are weighed at intervals after being immersed in gastric fluid. Higher swelling indicates effective hydration and polymer expansion, which aids in floatation and drug release over time.

- *Weight Variation and Size Consistency:* Weight variation ensures uniformity across tablets. Texts like Remington provide tolerance limits based on dosage form and weight. Consistent thickness and diameter also help achieve controlled release [9, 10].

In-Vitro Drug Release Study of Floating Tablets [11]

In vitro drug release studies are critical for evaluating the release profile and effectiveness of floating tablets. This process simulates the gastrointestinal (GI) conditions and helps determine the drug's release kinetics, stability, and floating capabilities. Typically, these studies are conducted using USP dissolution apparatus II (paddle method), with the medium set to 900 ml of 0.1 N hydrochloric acid (pH 1.2) to mimic gastric fluid conditions. The temperature is maintained at 37 ± 0.5°C, and the paddle speed is generally set at 50–100 rpm [10].

PROCEDURE

The floating tablet is placed in the dissolution medium.

Samples are withdrawn at specific intervals (e.g., 1, 2, 4, 6, and 8 hours) and analyzed using UV spectroscopy or high-performance liquid chromatography determine the concentration of the released drug.

A fresh dissolution medium is added after each sample to maintain the volume.

Data Analysis

Drug release data are analyzed using kinetic models, such as zero-order, first-order, and Higuchi models to determine the release mechanism. For floating tablets, a sustained release profile is desirable, ensuring prolonged gastric retention and gradual drug release, which is particularly beneficial for drugs like furosemide with a narrow absorption window in the upper GI tract [11]. Graphical representations of drug release with time are shown in Figure 4.

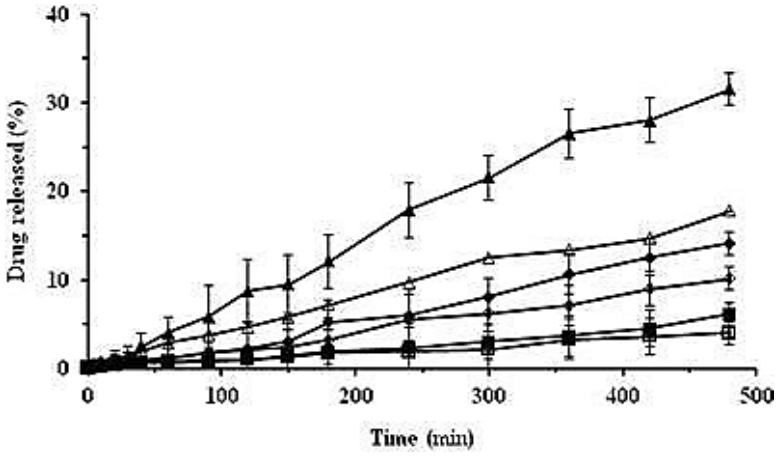

Figure 4. Graphical representation of drug release with time.

In-Vivo Evaluation and Pharmacokinetics Studies [12]

- *Objective:* To assess the floating behavior, release profile, and absorption characteristics of the furosemide floating tablet in an in vivo setting.
- *Animal Model:* Commonly, small animal models like rabbits or rats are used, though larger animals or human studies might be pursued in advanced research stages.
- *Floating Capacity:* Radiographic studies (e.g., using X-ray imaging) are often utilized to confirm the tablet's floating behavior and its residence time in the stomach.
- *Release Profile:* Blood samples are collected at regular intervals to evaluate the release of furosemide. Plasma drug concentrations are analyzed, often through techniques, such as High-

Performance Liquid Chromatography (HPLC).

- *Comparative Study:* Typically, the floating tablet is compared with a non-floating or standard tablet to demonstrate enhanced bioavailability or extended-release.

Pharmacokinetic Studies Key Parameters

The Pharmacokinetic Parameters Analyzed Include

Cmax (maximum concentration of drug in plasma), Tmax (time to reach Cmax), AUC (area under the curve), which reflects overall drug exposure, and t½ (half-life of the drug).

- *Analysis and Results:* The results aim to show improved pharmacokinetics, such as a delayed Tmax and an increased AUC, demonstrating enhanced drug release and absorption with the floating tablet.
- *Statistical Analysis:* Bio-equivalence studies or statistical analyses are conducted to validate the results, comparing the pharmacokinetic parameters between the floating and reference tablets.

CHALLENGES AND FUTURE PROSPECTS

Challenges

- *Formulation Stability:* Physical and Chemical Stability: Ensuring that the floating tablet maintains its structural integrity and therapeutic efficacy throughout its shelf life can be challenging. Factors, such as humidity and temperature can affect stability. Buoyancy: Maintaining buoyancy over the desired duration in gastric fluids can be difficult. The tablet must float for a sufficient time to release the drug effectively.
- *Controlled Release:* Achieving a controlled and sustained release profile while ensuring that the drug is available in a bioactive form is crucial. This requires precise formulation strategies to balance hydrophilic and hydrophobic components.
- *Bioavailability Issues:* Furosemide has variable bioavailability due to its extensive first-pass metabolism. Formulating a floating tablet that improves its absorption while minimizing the impact of gastric emptying rates is a challenge.
- *Manufacturing Complexity:* The production process for floating tablets can be more complex than that of conventional tablets. This includes the need for specific excipients that promote floating and controlled release, which can increase production costs and time.
- *Patient Compliance:* While floating tablets can enhance drug absorption, the need for specific dosing regimens and the possibility of variable gastric conditions can affect patient compliance.

Prospects

- *Advanced Formulation Techniques:* Innovations in materials science, such as the use of super disintegrants, polymers, and hydrogels, could enhance the buoyancy and controlled release of furosemide. This includes utilizing nanotechnology and 3D printing for precise drug delivery systems.
- *Personalized Medicine:* Future developments could focus on personalized floating tablet formulations that consider individual patient profiles, including metabolic rates and gastric conditions, leading to tailored therapeutic regimens.
- *Combination Therapies:* Formulating floating tablets that combine furosemide with other active ingredients could enhance therapeutic efficacy and address multiple conditions, such as hypertension and fluid retention.
- *Regulatory Advances:* As the pharmaceutical landscape evolves, regulatory bodies may establish clearer guidelines for the development and approval of advanced drug delivery systems like floating tablets, streamlining the path to market.
- *Clinical Studies:* More clinical trials assessing the pharmacokinetics and pharmacodynamics of floating furosemide tablets can provide essential data to support their efficacy and safety, paving the way for wider acceptance and use in clinical practice.
- *Smart Drug Delivery Systems:* The integration of smart technologies, such as sensors that can monitor gastric pH or pressure, could enhance the functionality of floating tablets, allowing for real-

time adjustments to the drug release profile based on the physiological conditions. Future prospects are shown in Figure 5.

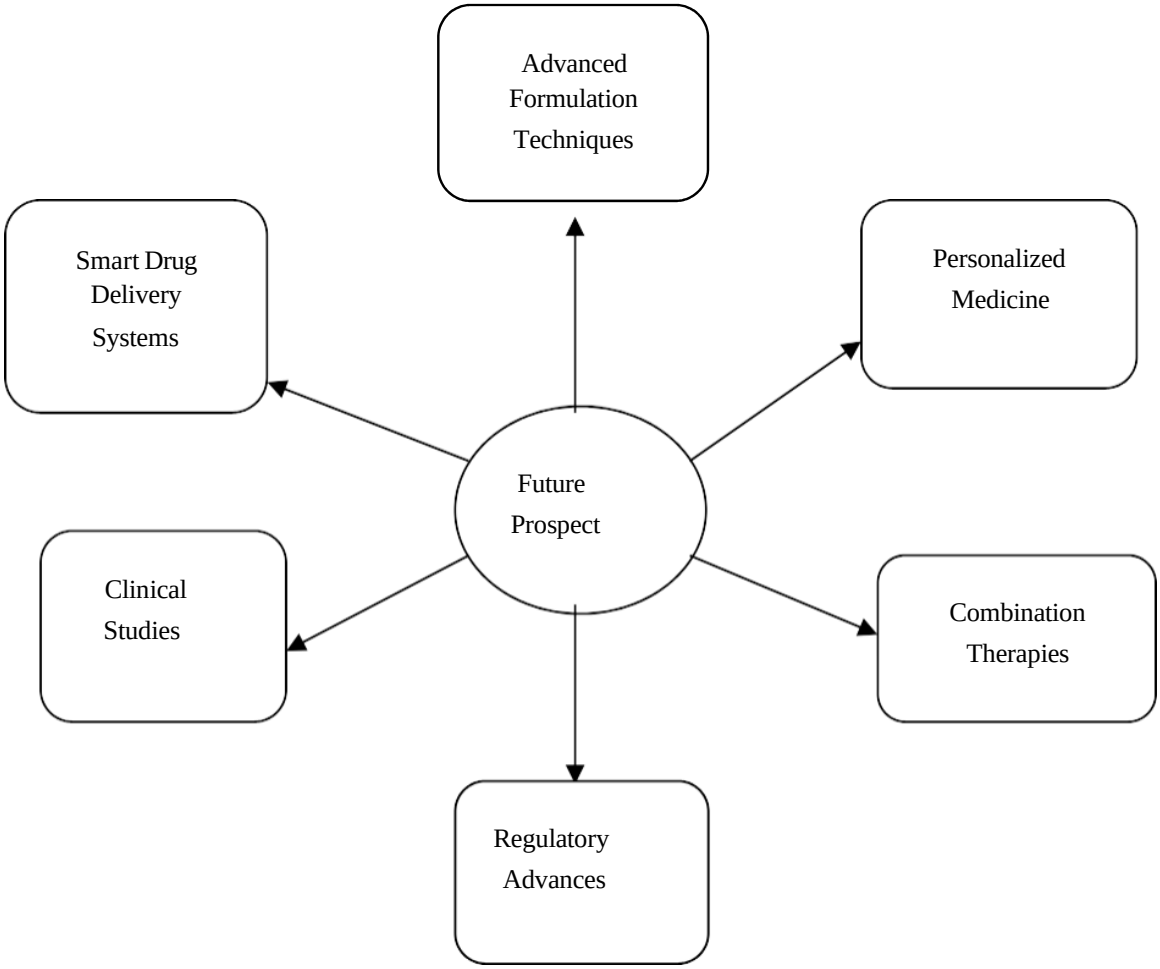

Figure 5. Future prospects.

CONCLUSIONS

The formulation development and evaluation of furosemide floating tablets demonstrated the potential for enhancing the drug's therapeutic efficacy through prolonged gastric retention and controlled release. The optimized formulation showed good buoyancy, remaining afloat for extended periods, which allows sustained drug release in the stomach. Evaluation results confirmed the tablet's stability, desirable release profile, and improved bioavailability, making it a promising approach for managing conditions requiring furosemide. The study supports floating tablet technology as an effective drug delivery system, especially for drugs like furosemide that benefit from targeted release in the upper gastrointestinal tract. While floating tablets of furosemide face several formulation and clinical challenges, ongoing research and technological advancements hold significant promise for improving their design, efficacy, and patient compliance. Prospects in this area could lead to better management of conditions treated with furosemide and improved patient outcomes.

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