RESEARCH ARTICLE

SAMRIDDHI Volume 14, Issue 4, 2022 Print ISSN: 2229-7111 Online ISSN: 2454-5767

Formulation and Evaluation of a Furosemide Nanosuspension Using High-Pressure Homogenization for Enhanced Dissolution Rate

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Abstract

This study addresses the significant biopharmaceutical challenges of furosemide, a Biopharmaceutics Classification System (BCS) Class IV drug, by developing a nanosuspension to enhance its dissolution rate. Furosemide nanosuspensions were produced using high-pressure homogenization (HPH), a robust top-down nanosizing technique, with Poloxamer 407 as a steric stabilizer. A systematic optimization was conducted using a 3^2 full factorial design, investigating the effects of stabilizer concentration (X1: 2%, 3.5%, 5% w/v) and homogenization pressure (X2: 500, 750, 1000 bar) on the formulation's critical quality attributes. The optimized formulation (FH5), prepared with 3.5% (w/v) Poloxamer 407 at 750 bar, yielded nanoparticles with a mean particle size of 347.8±4.6 nm, a narrow size distribution (polydispersity index of 0.149±0.034), and a zeta potential of −37.8±3.4 mV, indicating good physical stability. This formulation also achieved a high drug content of 93.0±5.8%. Crucially, *in vitro* dissolution studies in simulated gastric fluid (pH 1.2) demonstrated a profound enhancement in dissolution, with 94.58±0.35% of the drug released within 10 minutes, compared to the practical insolubility of the bulk drug. Drug release kinetics were best described by a Zero-order model, governed by Fickian diffusion. These findings demonstrate that HPH is a highly effective strategy for producing a stable furosemide nanosuspension, offering significant potential to improve the oral bioavailability of this therapeutically important compound.

Keywords: Furosemide; Nanosuspension; High-Pressure Homogenization; Poloxamer 407; Dissolution Enhancement; BCS Class IV.

SAMRIDDHI : A Journal of Physical Sciences, Engineering and Technology (2022); DOI: 10.18090/samriddhi.v14i04.35

Introduction

The therapeutic efficacy of many orally administered drugs is constrained by their limited aqueous solubility, a major hurdle in contemporary pharmaceutical development. A substantial portion of new chemical entities, estimated at around 40%, are poorly soluble in water, which can result in incomplete absorption and variable clinical outcomes(1) The Biopharmaceutics Classification System (BCS) offers a framework for classifying drug substances based on these properties. Specifically, compounds in BCS Class II (poor solubility, high permeability) and Class IV (poor solubility, poor permeability) present significant formulation challenges, as the rate at which they dissolve in the gastrointestinal tract often becomes the rate-limiting step for their absorption into the bloodstream.(2)(3).

Among the various strategies to enhance the bioavailability of these challenging compounds, the production of drug nanocrystals in the form of nanosuspensions has proven to be a highly effective and broadly applicable approach.

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How to cite this article: Patel, M., Patel, P. (2022). Formulation and Evaluation of a Furosemide Nanosuspension Using High-Pressure Homogenization for Enhanced Dissolution Rate. *SAMRIDDHI : A Journal of Physical Sciences, Engineering and Technology,* 14(4), 1-7.

Source of support: Nil

Conflict of interest: None

A nanosuspension consists of a colloidal dispersion of pure, sub-micron drug particles (generally <1000 nm) within an aqueous vehicle, stabilized by a minimal amount of surfactant or polymer. The primary benefit of this technology stems from the dramatic increase in the drug's surface area-to-volume ratio upon particle size reduction. This relationship is quantified by the Noyes-Whitney equation, which establishes

a direct proportionality between dissolution rate and surface area, meaning that nanocrystals can dissolve much more rapidly than their micro-sized counterparts. An additional advantage, explained by the Ostwald-Freundlich equation, is an increase in the drug's saturation solubility, driven by the higher dissolution pressure of smaller particles.(4).

Furosemide serves as a pertinent example of such a challenging compound. This powerful loop diuretic is a cornerstone in treating edema linked to congestive heart failure and hypertension.[7] However, its clinical utility is compromised by its classification as a BCS Class IV agent, signifying both poor solubility and poor permeability(3). it is considered practically insoluble.[1] This characteristic is the principal cause of its low and inconsistent oral bioavailability, reported to be between 37% and 51% (5). Since furosemide absorption occurs primarily in the stomach and proximal small intestine, enhancing its dissolution rate in this acidic milieu is essential for achieving more reliable therapeutic effects.

High-pressure homogenization (HPH) represents a leading 'top-down' technology for producing nanosuspensions, valued for its scalability and industrial applicability (6). HPH operates by propelling a coarse drug slurry through a narrow homogenization gap under immense pressure. This action generates powerful disruptive forces, including cavitation and high shear stress, which comminute the larger drug crystals into nanoparticles(1). A significant benefit of this method is its reliance on an aqueous medium, avoiding the use of potentially toxic organic solvents. To prevent the newly formed, high-energy nanoparticles from re-aggregating, a stabilizer is required. In this work, Poloxamer 407 (Pluronic® F-127) was chosen for this role due to its GRAS status and effective stabilization mechanism(7). As a non-ionic triblock copolymer, its central hydrophobic polyoxypropylene (PPO) segment adsorbs onto the drug particle, while its hydrophilic polyoxyethylene (PEO) chains project into the surrounding liquid, forming a steric shield that physically hinders particle agglomeration(8).

This research utilized a Quality by Design (QbD) framework to methodically optimize the formulation. A 3^2 full factorial experimental design was implemented to explore the relationship between two key independent variables—the concentration of Poloxamer 407 (a critical material attribute, CMA) and the applied homogenization pressure (a critical process parameter, CPP)—and the final product's quality attributes.[8] The ultimate goal was to identify a formulation for a stable furosemide nanosuspension that exhibits a markedly improved dissolution rate, offering a viable path to surmount the drug's inherent biopharmaceutical weaknesses.

Materials and Methods

Materials

Furosemide (USP grade) was generously provided as a gift sample by Aventis Pharma (Ankleshwar, Gujarat, India). Poloxamer 407 (Pluronic® F-127) was purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and reagents were of analytical grade. All aqueous solutions were prepared using double-distilled and deionized water.

UV Spectroscopy:

A UV-visible spectrophotometric method was established for the quantification of furosemide. Simulated gastric fluid (SGF, pH 1.2) was used as the analytical medium for all absorbance measurements. The wavelength of maximum absorbance (λmax) was determined by scanning from 200 to 400 nm and was confirmed to be 272 nm. For quantitative analysis, a standard curve was generated by measuring the absorbance of a series of furosemide solutions of known concentrations in SGF, which showed strong linearity within the relevant analytical range.

Drug-Excipient Compatibility Studies

Fourier-Transform Infrared (FT-IR) Spectroscopy

The potential for chemical interactions between furosemide and Poloxamer 407 was evaluated using Fourier-transform infrared (FT-IR) spectroscopy. Spectra were collected for pure furosemide, pure Poloxamer 407, and a 1:1 (w/w) physical blend of the two components. For analysis, each sample was prepared as a potassium bromide (KBr) pellet and scanned from 4000 to 400 cm^{-1} with a Bruker FTIR instrument (7).

Differential Scanning Calorimetry (DSC)

Thermal analysis was conducted to evaluate the physical state of furosemide within the formulation. Thermograms were obtained for pure furosemide, pure Poloxamer 407, and the lyophilized optimized nanosuspension (FH5) using a DSC-60 thermal analyzer (Shimadzu, Japan). Accurately weighed samples (3–5 mg) were hermetically sealed in aluminum pans. The analysis was performed by heating the samples from 30°C to 300°C at a linear rate of 10°C/min under a continuous nitrogen gas purge (50 mL/min)(9).

Preparation of Furosemide Nanosuspensions by HPH

A top-down HPH process was used to produce the furosemide nanosuspensions. Initially, a pre-suspension was formed by dispersing 120 mg of furosemide powder into an aqueous solution containing the specified concentration of Poloxamer 407 (2%, 3.5%, or 5% w/v) with the aid of magnetic stirring. A small quantity of acetone was introduced as a wetting agent to ensure uniform dispersion of the drug. This initial slurry was then passed through a high-pressure homogenizer for 10 cycles at one of the designated pressures (500, 750, or 1000 bar) to produce the final nanosuspension(10)(11).

Factorial Design

A 3^2 full factorial experimental design was implemented to systematically optimize the nanosuspension formulation. The

Table 1: The 3^2 Factorial Design Layout for Furosemide Nanosuspension Preparation.

Batch Code	*Independent Variable X1: Poloxamer 407 Conc. (%)*	*Independent Variable X2: Pressure (bar)*
FH1	2 (-1)	500 (-1)
FH2	3.5 (0)	500 (-1)
FH3	5 (+1)	500 (-1)
FH4	2 (-1)	750 (0)
FH5	3.5 (0)	750 (0)
FH6	5 (+1)	750 (0)
FH7	2 (-1)	1000 (+1)
FH8	3.5 (0)	1000 (+1)
FH9	5 (+1)	1000 (+1)

two independent variables selected were the concentration of Poloxamer 407 (X1) and the homogenization pressure (X2). Each variable was evaluated at three equidistant levels: low (-1), medium (0), and high (+1). The dependent variables, or responses, measured were mean particle size (Y1), polydispersity index (Y2), and drug content (Y3). The complete design, comprising nine experimental runs, is detailed in Table 1.

Physicochemical Characterization of Nanosuspensions

Particle Size, PDI, and Zeta Potential

The mean particle size (Z-average), polydispersity index (PDI), and zeta potential of the prepared nanosuspensions were determined by Dynamic Light Scattering (DLS) using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). Prior to measurement, samples were appropriately diluted with deionized water to achieve an optimal scattering intensity. All measurements were conducted at 25°C and performed in triplicate(9).All measurements were performed in triplicate.

Drug Content

Drug content was quantified using an indirect separation method. A sample of the nanosuspension was centrifuged at 15,000 rpm for 40 minutes at 25°C, which served to separate the solid nanoparticles from the aqueous phase. The resulting clear supernatant, containing any free (unincorporated) drug, was carefully collected. The concentration of furosemide in the supernatant was then determined spectrophotometrically at 272 nm. The drug content was expressed as the percentage of the initial drug amount that was successfully incorporated into the sedimented nanoparticles(12).

Scanning Electron Microscopy (SEM)

The surface morphology of the nanoparticles in the optimized formulation was visualized using a JEOL JSM-6380 LV scanning electron microscope. A drop of the diluted nanosuspension was placed on an aluminum stub and flash-frozen, followed by lyophilization to remove the aqueous phase. The dried sample was then mounted and sputter-coated with a thin layer of gold/palladium under an argon atmosphere to render it electrically conductive for imaging

In Vitro Dissolution Study

In vitro dissolution tests were performed using a USP Apparatus II (paddle type) to evaluate the release profiles of the nanosuspensions. Each test was run in 250 mL of SGF (pH 1.2 with 0.5% Tween 80 for sink conditions) at 37±0.5°C with a paddle rotation speed of 100 rpm to simulate gastric conditions. A volume of nanosuspension corresponding to 40 mg of furosemide was introduced into each vessel. At specified intervals (2, 4, 6, 8, and 10 minutes), 5 mL samples were collected, passed through a 0.1 µm PTFE syringe filter, and analyzed by UV spectroscopy to determine the concentration of dissolved drug. To maintain a constant volume, each withdrawal was compensated with an equal volume of fresh, pre-heated dissolution medium(13).

Kinetic Modeling of Drug Release

To elucidate the mechanism of drug release from the optimized nanosuspension, the *in vitro* dissolution data were fitted to several mathematical models: Zero-order (cumulative % drug release vs. time), First-order (log cumulative % drug remaining vs. time), Higuchi (cumulative % drug release vs. square root of time), and the Korsmeyer-Peppas equation (log cumulative % drug release vs. log time). The model that provided the best fit was determined by comparing the coefficient of determination (R2) values, with the highest R2 value indicating the most appropriate model (14).

Stability Studies

The physical and chemical stability of the optimized nanosuspension (FH5) was evaluated over a 30-day period. The formulation was aliquoted into sealed glass vials and stored under two distinct conditions: refrigerated (4±2°C) and ambient room temperature (25±2°C / 60±5% RH). Samples were withdrawn at day 0 and day 30 and analyzed for any changes in mean particle size, PDI, and drug content to assess for potential particle aggregation, crystal growth (Ostwald ripening), or chemical degradation.

Results and Discussion

Drug-Excipient Compatibility

The compatibility between furosemide and Poloxamer 407 is a prerequisite for a stable formulation. FT-IR analysis (Figure 1) confirmed the absence of chemical interactions. The spectrum of the physical mixture was a simple superposition of the spectra of the individual components, with all of furosemide's characteristic peaks—including the N-H stretch, the carboxylic acid C=O stretch, and the sulfonamide S=O stretch—retained without significant shifts.

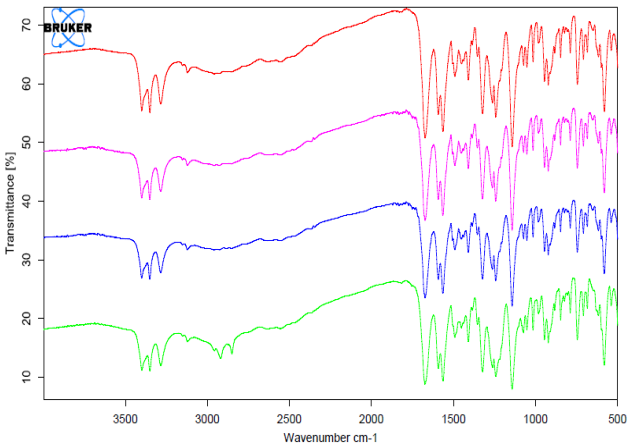

Figure 1: Overlay spectra of FTIR

DSC analysis provided insight into the physical state of the drug. The thermogram of pure furosemide showed a sharp endothermic peak corresponding to its melting point. In the thermogram of the lyophilized optimized nanosuspension (FH5, Figure 2), this drug peak was still present but was broader, slightly shifted, and exhibited reduced intensity. This change suggests a decrease in the drug's crystallinity and a partial conversion to a more amorphous state during the high-energy HPH process. This phenomenon is common in nanosizing and is known to contribute to enhanced solubility and dissolution rates(15). The persistence of a melting peak confirms that furosemide remained in its solid, non-solubilized state within the nanoparticles.

Optimization of Furosemide Nanosuspension and Selection of Optimized Batch

The 3^2 factorial design was successfully employed to systematically evaluate the influence of Poloxamer 407 concentration and homogenization pressure on the formulation's critical quality attributes. The results for all nine formulations are summarized in Table 2.

Selecting the optimized formulation requires a holistic analysis beyond a single parameter. While formulation FH8, prepared at the highest pressure (1000 bar), yielded the smallest mean particle size (220.0 nm), it was ultimately suboptimal due to other critical deficiencies. The primary goal is a stable and homogenous system. The PDI, a measure of size distribution uniformity, is crucial; a value below 0.2 is desirable for a monodisperse population. Formulation FH5 exhibited an excellent PDI of 0.149, indicating high uniformity. In stark contrast, FH8 had an extremely high PDI of 0.789, signifying a very broad and heterogeneous particle population that is prone to physical instability via Ostwald ripening.

Furthermore, drug content reflects process efficiency. FH5 showed the highest drug content at 93.0%, indicating minimal loss. Conversely, FH8 had the lowest drug content at 65.0%, suggesting inefficient drug incorporation or significant loss at the highest energy input. This observation supports the hypothesis of an optimal energy "sweet spot." While the increased energy at 1000 bar is sufficient for further particle comminution, it appears to induce a high-energy, unstable state in the nanoparticles, promoting rapid re-aggregation and leading to a polydisperse system with poor drug retention. The 750 bar pressure used for FH5 achieves significant size reduction without this detrimental instability. Although the zeta potential of FH8 (–43.1 mV) was more negative than that of FH5 (–37.8 mV), both values are well below the –30 mV threshold generally considered sufficient for electrostatic stability. Therefore, based on its optimal balance of small particle size, outstanding homogeneity (low PDI), excellent stability, and maximum drug loading, FH5 was selected as the optimized batch for all further characterization.

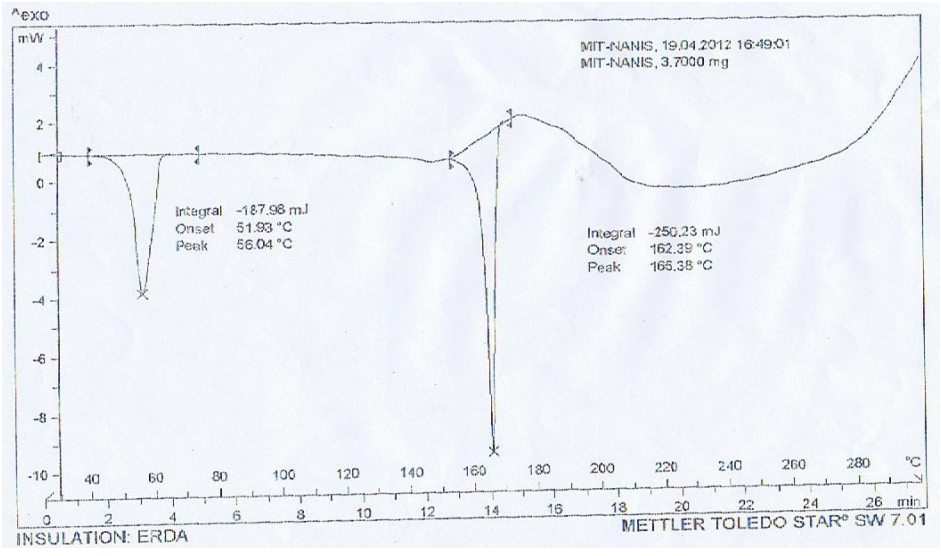

Figure 2: DSC graph of optimized formulation

Table 2: Physicochemical Characterization of Furosemide Nanosuspension Formulations (FH1-FH9). All values are expressed as mean ± SD (n=3).

Batch Code	*Particle Size (nm)*	*Polydispersity Index (PDI)*	*Zeta Potential (mV)*	*Drug Content (%)*
FH1	344.8±2.3	0.194±0.022	−32.1±2.1	78.0±9.0
FH2	332.5±4.5	0.623±0.047	−26.1±3.4	80.0±6.0
FH3	347.8±2.7	0.560±0.087	−29.0±6.7	91.0±2.3
FH4	323.1±7.7	0.441±0.045	−28.9±6.9	69.0±2.2
FH5	347.8±4.6	0.149±0.034	−37.8±3.4	93.0±5.8
FH6	331.7±8.0	0.734±0.056	−35.8±6.8	83.0±6.8
FH7	277.1±3.4	0.541±0.046	−38.6±5.7	77.0±2.3
FH8	220.0±5.8	0.789±0.058	−43.1±3.4	65.0±5.6
FH9	233.0±5.3	0.921±0.021	−38.7±1.2	72.0±4.5

Table 3: Cumulative Percentage of Drug Dissolved from Nanosuspension Formulations (FH1-FH9) in SGF (pH 1.2).

Time (min)	*FH1*	*FH2*	*FH3*	*FH4*	*FH5*	*FH6*	*FH7*	*FH8*	*FH9*
0	0	0	0	0	0	0	0	0	0
2	16.50	16.04	16.50	15.58	16.50	16.50	17.41	17.41	17.41
4	31.56	30.77	30.56	28.02	31.58	30.77	31.54	30.85	31.31
6	57.35	50.25	51.06	49.83	60.62	49.89	50.68	50.56	50.60
8	84.93	83.35	79.91	79.70	88.60	76.95	78.79	78.60	78.35
10	91.68	90.60	92.10	91.47	94.58	92.20	95.22	97.56	94.06

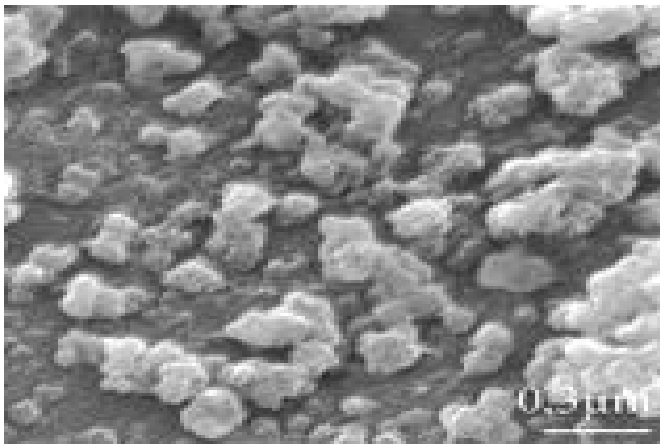

Figure 3: SEM Image of Batch FH5.

Physicochemical Characterization of the Optimized Formulation (FH5)

The optimized formulation, FH5, was characterized by a mean particle size of 347.8±4.6 nm, a PDI of 0.149±0.034, a zeta potential of −37.8±3.4 mV, and a drug content of 93.0±5.8%. SEM imaging of the freeze-dried FH5 formulation (Figure 3) revealed distinct, relatively spherical nanoparticles, corroborating the DLS particle size data. The morphology is consistent with particles produced via HPH, and the observed porous nature is favorable for rapid solvent ingress and dissolution (16). The porous nature suggests successful incorporation of the drug within the nanoparticle structure.

In Vitro Dissolution and Diffusion Performance

The *in vitro* dissolution profiles (Table 3) confirmed that all nanosuspension formulations dramatically enhanced the dissolution rate of furosemide compared to its known practical insolubility in acidic media(17). The optimized formulation, FH5, was particularly effective, releasing 60.62% of the drug within 6 minutes and achieving a near-complete release of 94.58% within 10 minutes. This rapid dissolution is a direct consequence of the massive increase in the drug's effective surface area, as predicted by the Noyes-Whitney equation, and is further aided by the improved wettability of the hydrophobic drug particles afforded by the Poloxamer 407 stabilizer(4).

Drug Release Kinetics

To understand the release mechanism, the dissolution data for FH5 were fitted to kinetic models (Table 4). The data best fit the Zero-order model, as indicated by the highest correlation coefficient (R2=0.977). This suggests that the

Table 4: Kinetic Modeling of *In Vitro* Drug Release Data for Optimized Batch FH5.

Model	*Equation*	*Correlation Coefficient (R2)*
Zero-Order	Cumulative % Release vs. Time	0.977
First-Order	Log % Remaining vs. Time	0.895
Higuchi	Cumulative % Release vs. Time	0.954
Korsmeyer-Peppas	Log % Release vs. Log Time	0.968

Table 5: Stability Study of the Optimized Furosemide Nanosuspension (FH5) over 30 Days.

Parameter	*Time 0*	*30 Days (Room Temp, 25°C)*	*30 Days (Refrigerated, 4°C)*
Particle Size (nm)	347.8	358.2	349.1
PDI	0.149	0.165	0.152
Drug Content (%)	93.0	90.5	92.6

drug is released from the nanosuspension at a constant rate, independent of the remaining drug concentration. Further analysis with the Korsmeyer-Peppas model yielded a release exponent (n) of 0.488. For spherical particles, an n value of ≤0.5 is indicative of Fickian diffusion, meaning the release is primarily driven by the concentration gradient between the nanoparticle surface and the bulk dissolution medium.

Stability of the Optimized Nanosuspension

The stability results, presented in Table 5, are not just an academic exercise but have direct translational importance for the formulation's potential real-world application. The superior stability of the nanosuspension under refrigerated conditions (4°C) is a key finding. The minimal changes observed in particle size, PDI, and drug content at this temperature indicate that the lower kinetic energy effectively suppresses Ostwald ripening, a primary mechanism of physical instability for nanosystems.[1] In contrast, at room temperature (25°C), a nominal increase in particle size and PDI was observed, consistent with slow particle growth. This finding establishes a critical control parameter for the formulation's shelf-life and dictates that refrigeration would be the required storage condition to ensure product quality, performance, and a viable shelf-life in any future clinical or commercial setting (8).

Conclusion

This study successfully demonstrates that high-pressure homogenization is an effective and scalable top-down technique for producing a stable furosemide nanosuspension. Through a systematic, QbD-based factorial design, an optimized formulation (FH5) was identified, prepared with 3.5% Poloxamer 407 at a pressure of 750 bar. This formulation exhibited highly desirable physicochemical characteristics, including a uniform particle size in the nanometer range, high drug loading efficiency, and excellent physical stability, particularly under refrigerated storage. Most significantly, the nanosuspension formulation resulted in a profound enhancement of the *in vitro* dissolution rate of furosemide in a simulated gastric environment, with over 94% of the drug dissolving within 10 minutes. This represents a critical improvement for a drug whose absorption is severely limited by its poor solubility. The findings confirm that nanosizing via HPH is a viable and potent strategy for overcoming the biopharmaceutical challenges associated with furosemide, showing significant promise for improving its oral bioavailability and therapeutic consistency. This work provides a strong foundation for subsequent *in vivo* evaluation.

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