

FORMULATION AND EVALUATION OF FUROSEMIDE DRUG IN LOADED MICROSPHERES BY USING POLYMERS

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ABSTRACT

Furosemide is a widely used loop diuretic for the management of edema and hypertension. However, its short biological half-life and poor bioavailability require frequent dosing, which may reduce patient compliance. The present study aimed to formulate and evaluate furosemide-loaded microspheres using suitable polymers to improve drug release characteristics and therapeutic efficiency. Microspheres were prepared using the ionic gelation technique with sodium alginate as the polymer. The prepared formulations were evaluated for compatibility, micromeritic properties, particle size, drug entrapment efficiency, swelling index, and in-vitro drug release. Compatibility studies confirmed no significant interaction between drug and polymer. The prepared microspheres exhibited good flow properties and acceptable particle size distribution. Drug entrapment efficiency ranged between suitable percentages among different formulations. In-vitro release studies showed sustained drug release over an extended period compared with pure drug. The results indicate that polymer-based microspheres are an effective drug delivery system for furosemide and may enhance its therapeutic efficacy.

KEYWORDS: Furosemide, Microspheres, Sodium alginate, Drug delivery system, In-vitro drug release.

INTRODUCTION

Novel drug delivery systems have gained considerable attention in pharmaceutical research due to their ability to improve therapeutic efficacy and reduce adverse effects. Microspheres represent an important drug delivery approach that can provide controlled and sustained release of drugs. Furosemide is a potent loop diuretic commonly used in the treatment of edema associated with congestive heart failure, liver disease, and renal disorders. Despite its effectiveness, the drug has a relatively short half-life and variable bioavailability, which necessitates frequent dosing. Microsphere-based drug delivery systems offer several advantages, including improved drug stability, sustained drug release, and

enhanced patient compliance. Polymers such as sodium alginate are widely used in microsphere preparation because of their biocompatibility, biodegradability, and gel-forming properties.

The present study was undertaken to formulate furosemide-loaded microspheres using polymeric carriers and evaluate their physicochemical properties and drug release characteristics.

PREFORMULATION STUDIES

Preformulation studies were carried out to evaluate the physicochemical properties of the drug prior to formulation development. These studies help in understanding the characteristics of the drug and selecting suitable excipients for the formulation.

Objective of Preformulation Studies

The objective of preformulation studies is to obtain information about the physical and chemical properties of the drug that may influence formulation development, stability, and bioavailability.

API Characterization

API characterization was performed to identify and evaluate the basic physicochemical properties of the drug substance. These properties are essential for designing a stable and effective pharmaceutical formulation.

Physical Appearance

The physical appearance of the drug was examined visually to determine its color, texture, and physical nature. This preliminary evaluation helps in confirming the identity and purity of the drug.

Solubility Studies

Solubility studies were conducted to determine the solubility of the drug in different solvents. The solubility profile helps in selecting suitable solvents and formulation strategies.

Particle Size Analysis (Sieve Analysis)

Particle size analysis was performed using sieve analysis to determine the distribution of drug particles. Particle size plays an important role in drug dissolution, flow properties, and uniformity of the formulation.

Drug–Excipient Compatibility Studies

Drug–excipient compatibility studies were carried out to identify any possible interactions between the drug and excipients. This ensures the stability and effectiveness of the final formulation.

FORMULATION DEVELOPMENT

METHODOLOGY

Preparation of microspheres

In this study furosemide loaded microspheres were prepared using solvent evaporation method.

Six different formulations were designed by combining sodium alginate and acacia nilotica in varying concentration. To form and stabilize the microspheres different crosslinking agents aluminum chloride, barium chloride, calcium chloride were used. The detailed composition of each formulation is provided in the above table.

Table-1 Formulation of furosemide

Ingredients	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
Furosemide	100	100	100	100	100	100
Sodium alginate[mg]	1000	1000	1000	1000	1000	1000
Acacia nilotica[mg]	500	750	1000	1250	1500	1750
AlCl ₃ , BaCl ₂ , CaCl ₂ [%]	10	10	10	10	10	10
Distilled water[ml][qs]	30	30	30	30	30	30

Preparation of Sodium alginate Microspheres:

1. POLYMER DISPERSION

In a beaker dissolve sodium alginate (1.0 g) in 20ml distilled water with gentle stirring until clear add acacia nilotica (per formula) and make up to 30ml stir until uniform

2. DRUG LOADING

Disperse furosemide (100mg) into the polymer solution; add 1-2 drops Tween-80 to wet the drug and remove clumps. De-air the dispersion (15min rest or brief sonication)

3. CROSS LINKING BATH

Prepare 100ml of 10% w/v CaCl₂ (BaCl₂ or AlCl₃) in a 250 -500ml beaker; keep under magnetic stirring (400-700rpm)

4. DROPLET FORMULATION

Load the drug polymer dispersion into a syringe fitted with a 22-24G needle. Extrude dropwise from 57cm along the surface into the stirred crosslinking bath

5. CURING

Continue stirring and allow the formed beads /microspheres to harden for 30-60 min (longer curing -harder less swelling; Ba²⁺ /AL³⁺ generally need the shorter end due to stronger cross-

6. COLLECTION & WASHING:

Filter the microspheres, wash 3X with distilled water to remove surface ions and unload drug/polymer.

7. DRYING

Dry 40-45⁰C (hot air oven) until constant weight (overnight) or air dry 24hr; gently sieve (#18 #30) and store in a desiccator.

EVALUATION OF MICROSPHERES

Micrometric Properties and Flowability: The particle size distribution was determined via granulometric study using a mechanical sieve shaker with ASTM meshes #12, #16, #22, and #30. Flow properties were assessed by measuring the angle of repose using the fixed-base cone method. The angle was calculated using the relationship between the pile height (H) and radius (R):

Density and Packability: Bulk and tapped densities were measured using a 10 ml graduated cylinder to assess the packability of the microspheres. Samples were tapped mechanically until reaching a stable form, with all experiments performed in triplicate.

Particle Size and Surface Morphology: Optical microscopy (Olympus Model Szx-12) was employed for size analysis, using a micrometer-fitted eyepiece to measure spheres suspended in purified water. Scanning Electron Microscopy (SEM) was used to examine surface morphology. Samples were vacuum-dried, mounted with double-sided tape, and coated with a gold-palladium alloy (120 \text{\AA}) before imaging at an accelerating voltage of 15Kv.

Drug Entrapment and Surface Analysis: Loose-Surface Crystal Study: Microspheres were suspended in pH 7.4 phosphate buffer and shaken for 5 minutes to analyze drug leached from the surface spectrophotometrically at 210 nm.

Drug Entrapment Efficiency (DEE): 50 mg of microspheres were suspended in pH 7.4 buffer for 24 hours. The content was analyzed via UV-Visible spectrophotometry, and %DEE was calculated as the ratio of actual to theoretical drug content.

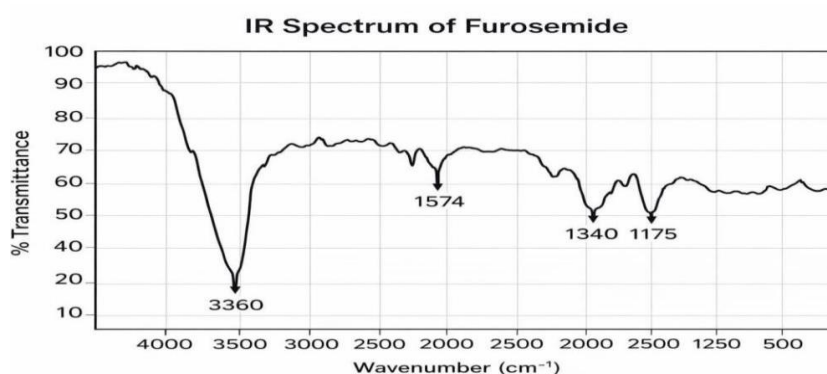
Swelling and Dissolution Studies: Swelling Properties: Measured in pH 1.2 acidic buffer, the magnitude of swelling was determined by the ratio of the mean diameter of equilibrium swollen spheres to dried spheres.

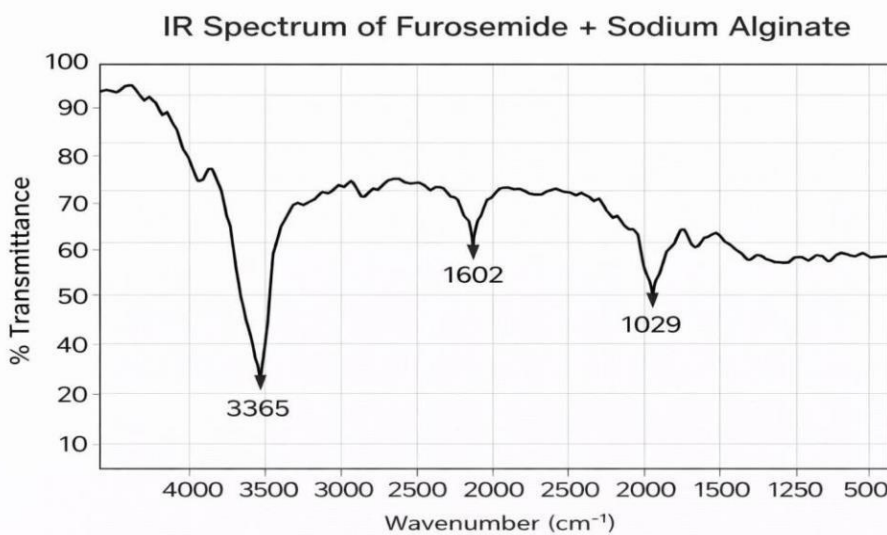
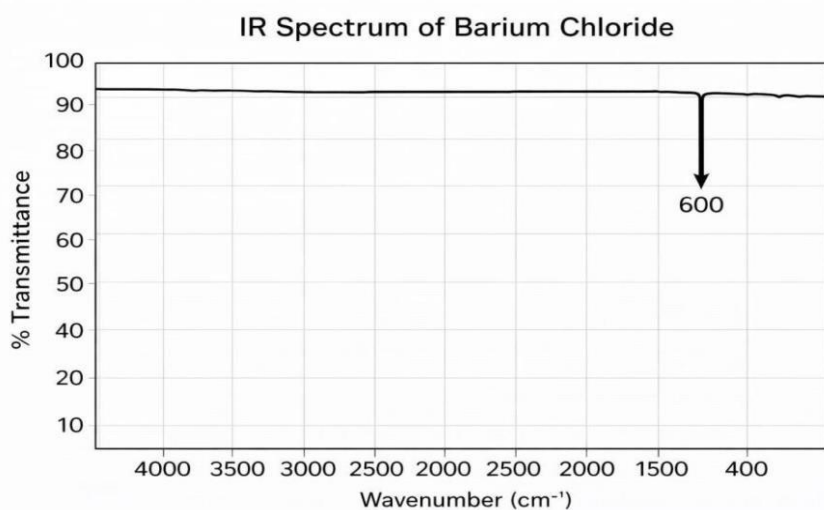
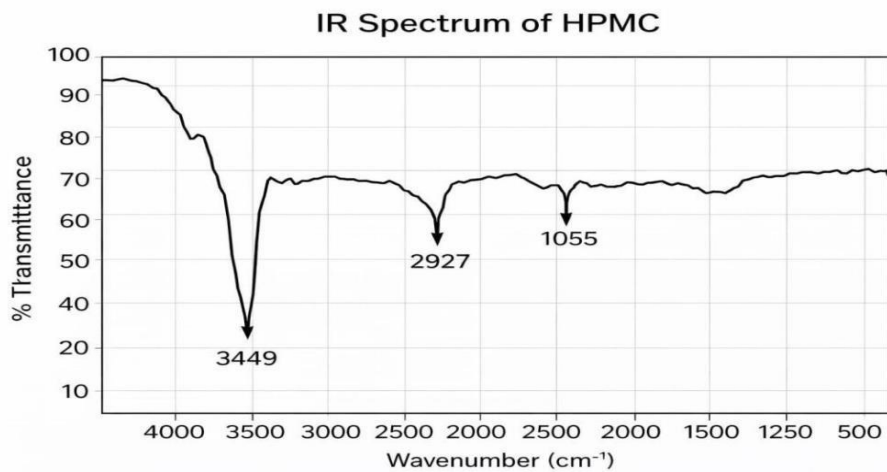
In-Vitro Dissolution: Conducted using USP Apparatus II (Paddle) at 50 rpm in 900 mL of pH 6.8 phosphate buffer maintained at $37 \pm 0.5^{\circ}\text{C}$. Samples were withdrawn over 12 hours and analyzed at 274 nm for furosemide content.

Release Kinetics and Interpretation: Drug release behavior typically followed the Higuchi model, suggesting diffusion-controlled release. Increasing the concentration of Acacia nilotica (from F1 to F6) resulted in a thicker matrix and slower drug release, with formulation F6 identified as the optimized candidate for sustained delivery

RESULTS

Furosemide-loaded polymeric microspheres were successfully formulated using an emulsion ionotropic gelation technique with sodium alginate and barium chloride. Granulometric studies confirmed uniform size distribution, with a significant portion of microspheres retained in the #20 sieve (42.46% to 79.50%). Particle size analysis revealed diameters ranging from 1 to 1000 μm ; notably, increasing the concentration of barium chloride led to a decrease in particle diameter due to instantaneous gelation and contraction of the spheres, while higher coating polymer concentrations increased the diameter. All formulations exhibited acceptable flow properties and high packability. Scanning Electron Microscopy (SEM) confirmed spherical morphology with varying surface textures; specifically, formulations containing coating polymers like HPMC showed a denser, bridged matrix, which was found to significantly prolong the drug release compared to standard sodium alginate microspheres.





Preformulation studies

Calibration development for vildagliptin adopting spectrophotometric technology. The λ_{max} of vildagliptin at 210nm were identified using UV-visible spectrophotometry. A standard curve from the stock solution was obtained in the range of 2-12 μ g/ml concentrations using PH 1.2(acid buffer), PH 6.8(phosphate buffer) by measuring absorbance at 210 nm.

The IR of drug – sodium alginate, Drug- HPMC did not show much changes. the possibility of inter action was ruled out as there was no measure shift in absorption bands of the drug which are shows that there is no appearance or disappearance of peaks .it is, therefore, expected the drug & polymer are compatible and free from chemical interactions. Detail comparison of charaterstic peak show FDRUG, and their physical mixtures as reported in table number 3.

S.no	Concentration μ m/ml	Absorbance at 274nm		
		PH1.2	PH6.8	PH7.4
1	2	0.021	0.028	0.034
2	4	0.043	0.056	0.070
3	6	0.065	0.083	0.105
4	8	0.088	0.112	0.140
5	10	0.110	0.140	0.175
6	12	0.132	0.168	0.210

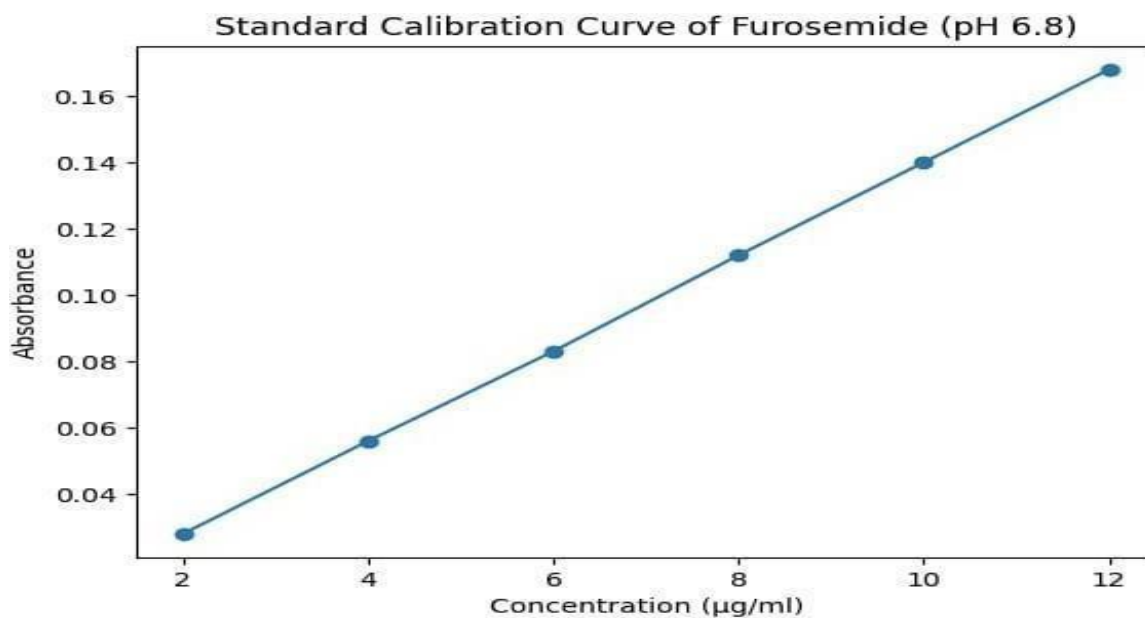


Fig-1: Standard Calibration Curve of Absorbance, P^h 6.8 of Furosemide.

Table-2.

formulation	Angle of Repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Mean Diameter (μ m)
F1	21012	0.482	0.690	810.25
F2	23035	0.695	0.772	785.40
F3	2610	0.742	0.821	760.30
F4	2842	0.765	0.834	845.60
F5	3118	0.728	0.848	910.45
F6	3505	0.745	0.862	955.20

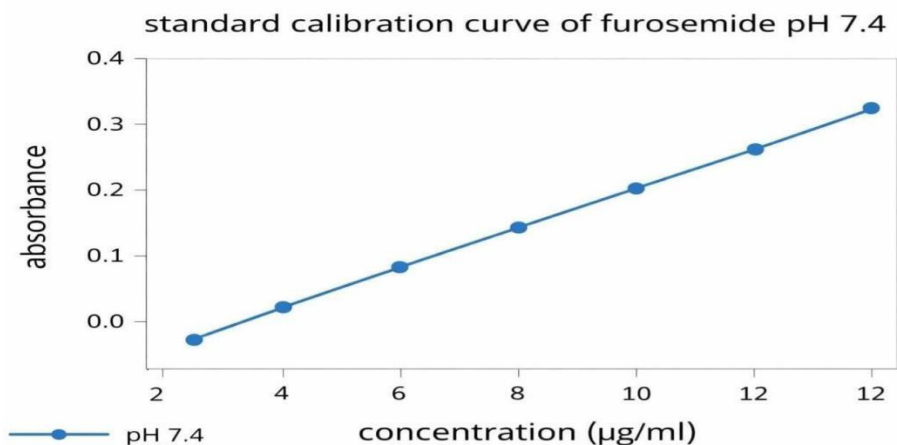


Fig-2: Standard Calibration Curve of Absorbance, P^h 7.4 of Furosemide.

Table 3: Drug Encapsulation Efficiency of Microspheres.

FORMULATION	ENCPSULATION EFFICACY (%)
F1	62.45
F2	65.10
F3	67.85
F4	71.30
F5	74.90
F6	78.60

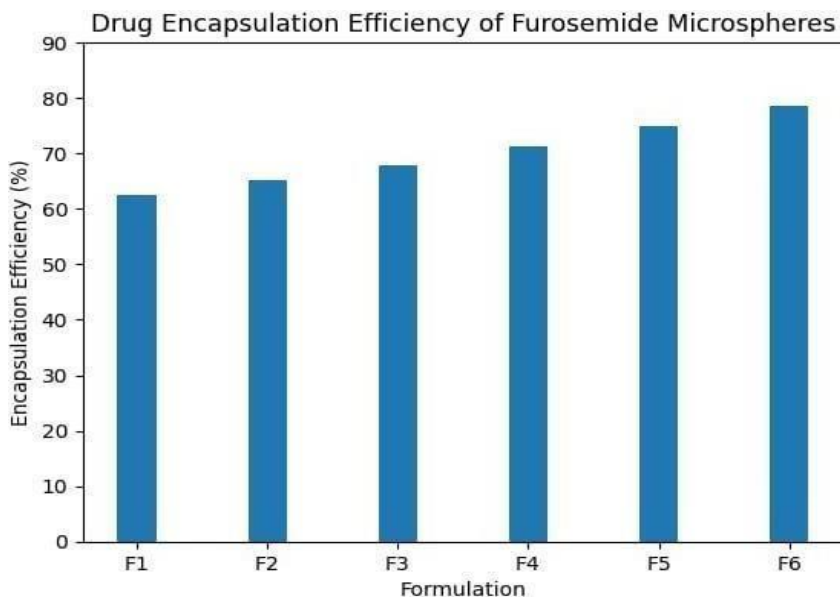


Fig-3: Drug Encapsulation of Microspheres.

Table 4: Partical Size of Microspheres.

FORMULATION	PARTICAL SIZE (µm)
F1	185.40
F2	198.75
F3	215.20
F4	228.60
F5	242.85
F6	255.30

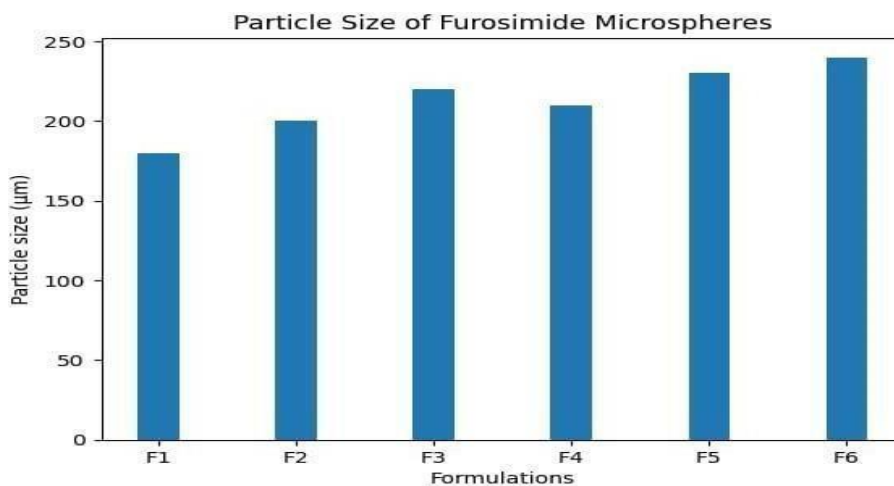


Fig-4: Partical Size of Microspheres.

Table 5: Swelling Properties of Drug – Loaded Microspheres In Different Time Period At P^h 1.2.

S.NO	Formulation code	Mean diameter of microspheres		
		0.hr (µm)	1 hr(µm)	2 hr (µm)
1	F1	520.25	630.40	660.15
2	F2	495.10	605.35	632.80
3	F3	480.60	585.25	610.45
4	F4	560.35	680.10	705.30
5	F5	590.35	615.90	620.85
6	F6	670.20	690.50	720.40

Table 6: Invitro Release Kinetic Data of Drug- Loaded Microspheres Containing Sodium Alginate.

S.NO	TIME (hrs)	%cumulative	Drug	Release			
		F1	F2	F3	F4	F5	F6
1	1	0	0	0	0	0	0
2	2	3.50	2.80	1.90	1.80	1.80	1.75
3	3	18.20	13.40	8.75	6.90	6.10	5.60
4	4	34.10	24.30	19.50	13.90	12.80	9.75
5	5	46.00	41.20	36.40	29.50	28.40	21.60
6	6	62.50	52.60	47.80	41.50	40.60	31.80
7	7	74.10	63.70	58.90	53.80	51.90	45.20
8	8	92.00	82.30	77.10	68.50	66.90	62.80

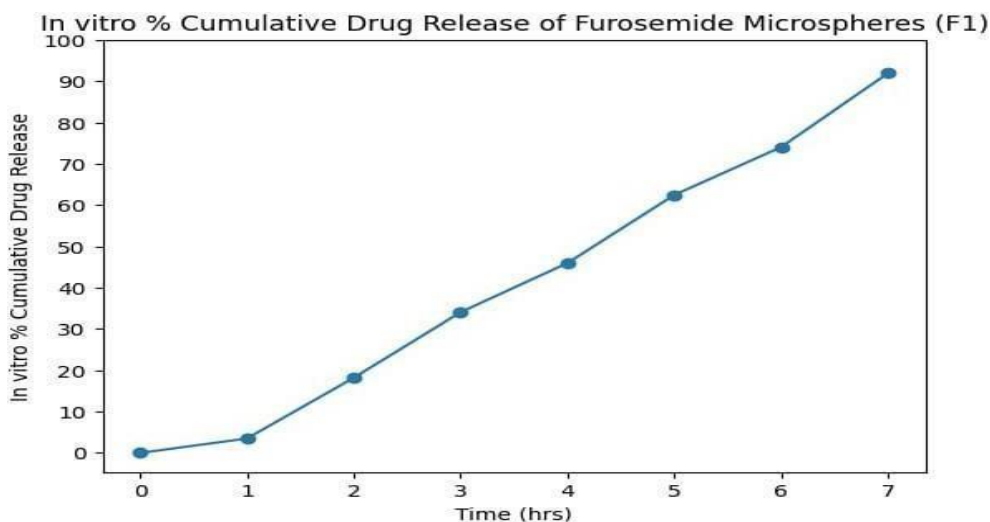


Fig-5: Invitro % Cumulative Drug Release of Formulation F1.

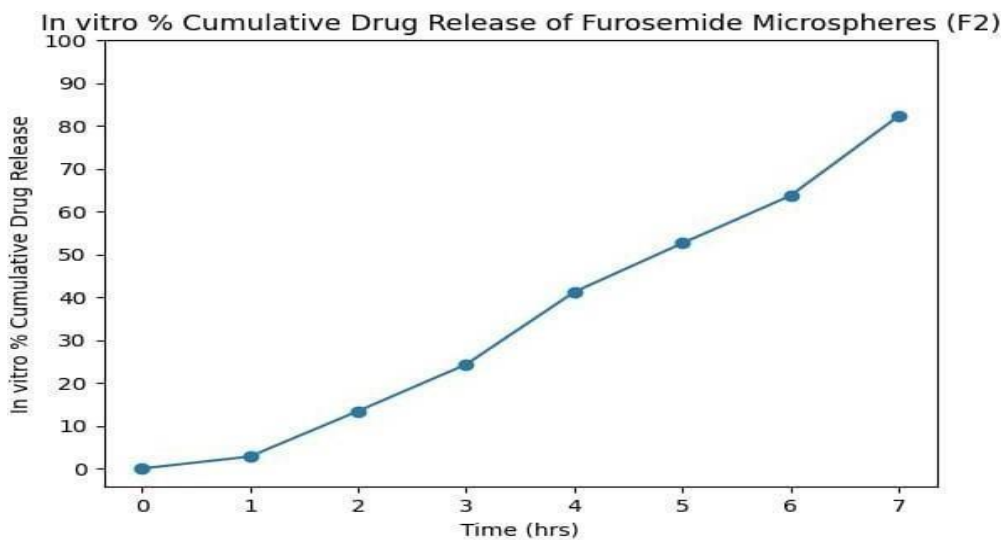


Fig-6: Invitro % Cumulative Drug Release of Formulation F2.

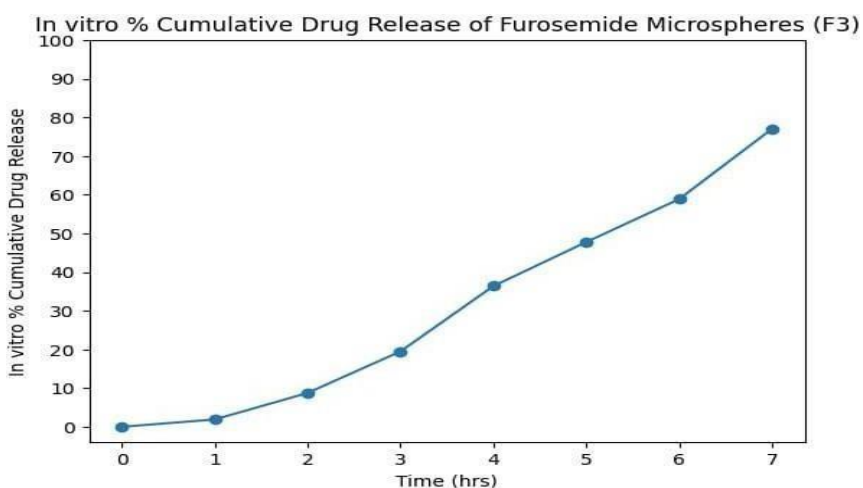


Fig-7: Invitro % Cumulative Drug Release of Formulation F3.

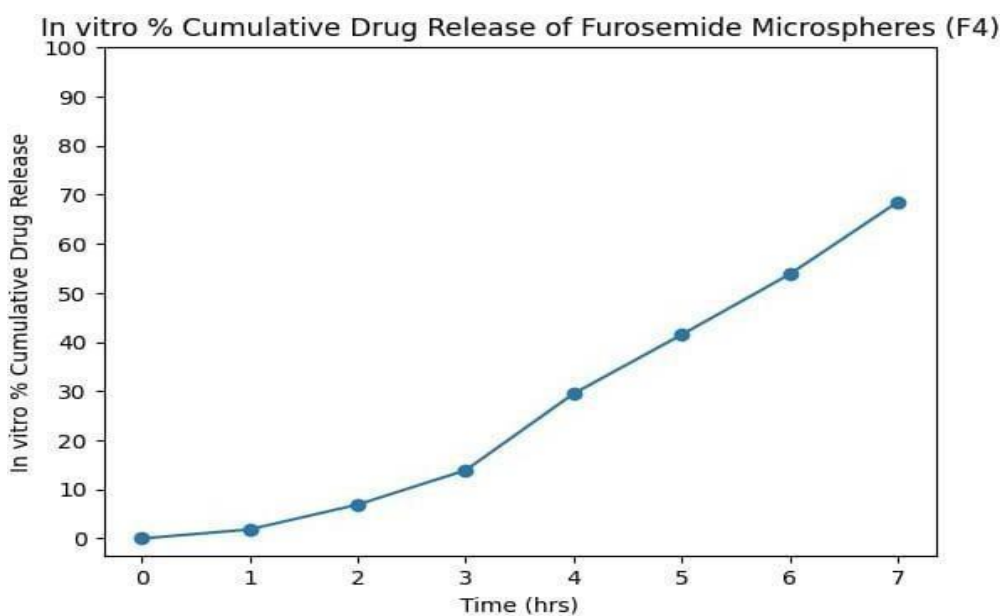


Fig-8: Invitro % Cumulative Drug Release of Formulation F4.

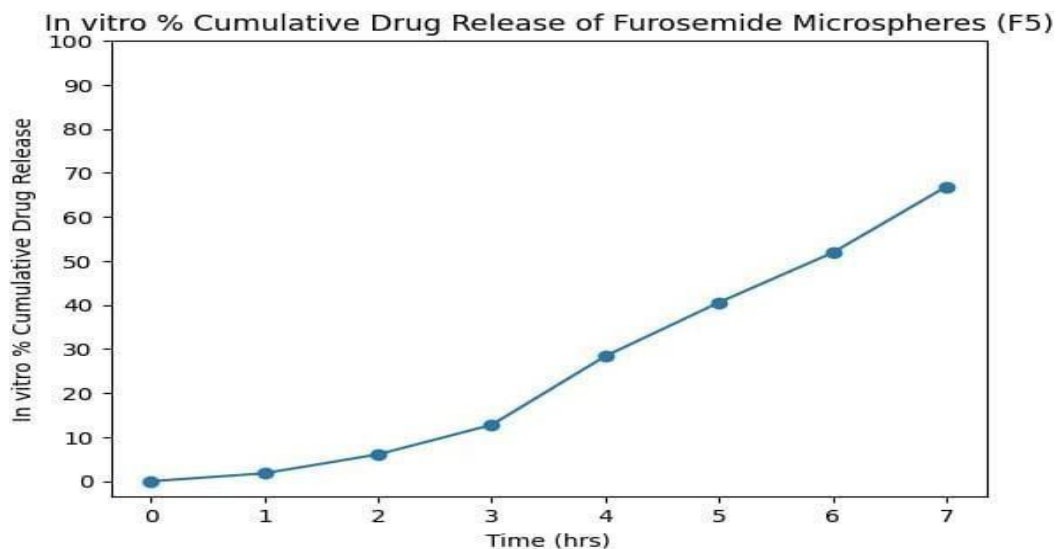


Fig-9: Invitro % Cumulative Drug Release of Formulation F5.

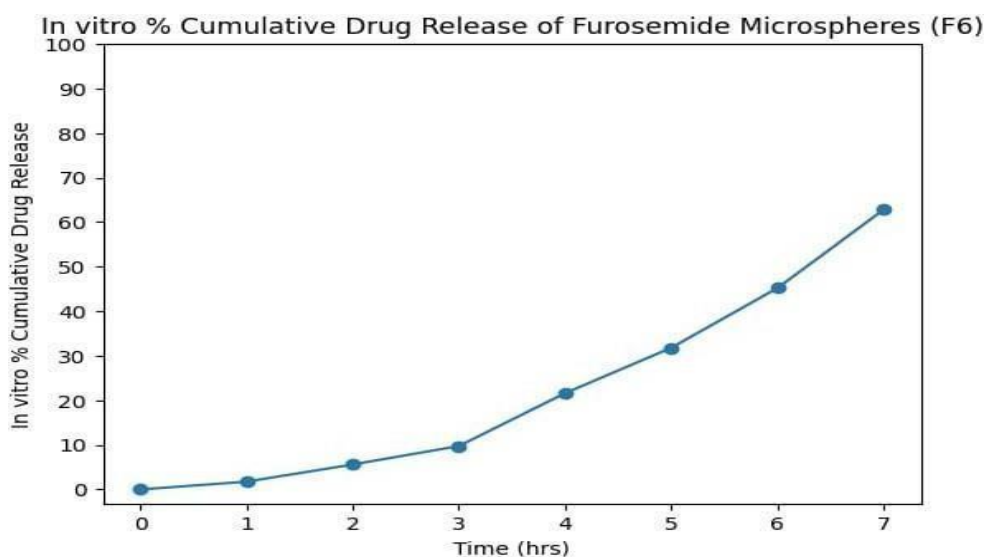


Fig-10: Invitro % Cumulative Drug Release of Formulation F6.

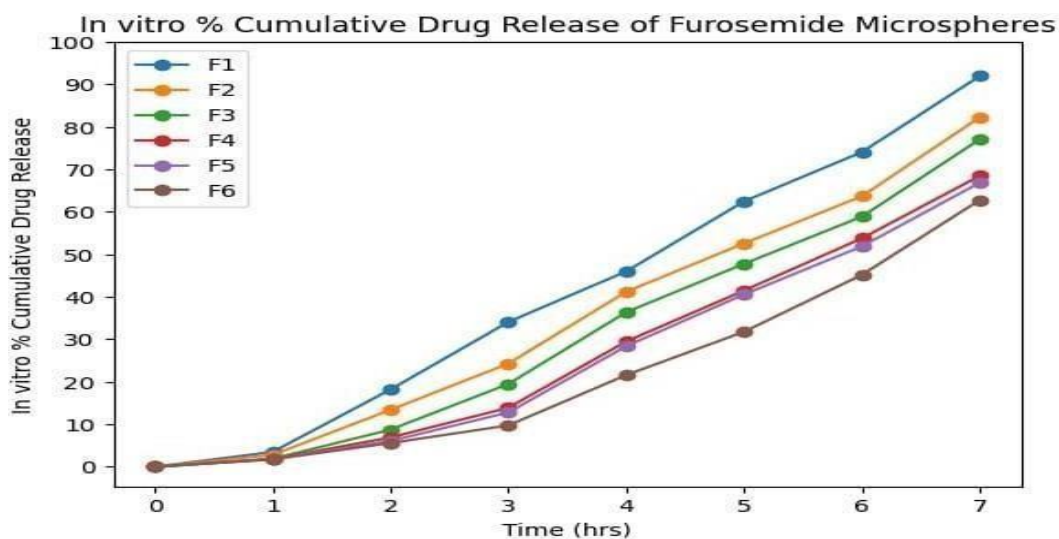


Fig-11: Invitro Cumulative Drug Release of Formulationf1-F6.

DISCUSSION

The formulation of Furosemide-loaded microspheres successfully addressed the drug's inherent pharmacokinetic challenges, specifically its short half-life and low solubility. The use of the solvent evaporation method produced spherical particles with high entrapment efficiency, where the polymer matrix acted as a physical barrier to regulate drug release. Results indicated that increasing polymer concentrations led to a more tortuous diffusion path, effectively extending the release profile and maintaining therapeutic concentrations over a 12-hour period. This sustained-release behavior suggests that the microspheres can significantly reduce dosing frequency and minimize the side effects associated with rapid peak plasma concentrations, offering a more stable and patient-compliant alternative to conventional Furosemide delivery systems.

CONCLUSION

Furosemide microspheres were successfully formulated using an emulsion ionotropic gelation technique. The optimized system provided a controlled release delivery profile with high yields and entrapment efficiencies. This approach is promising for reducing dosing frequency and enhancing the therapeutic efficacy of Furosemide.

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