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Original Article

Formulation, Development And Evaluation Of Amlodipine Nanosponges For Enhanced Solubility And Immediate Release Tablet

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ABSTRACT

Background: Amlodipine besylate, a BCS class II antihypertensive drug, exhibits poor water solubility leading to limited bioavailability. Nanosponges offer a promising approach to enhance solubility and control drug release. Objective: To formulate and evaluate amlodipine-loaded nanosponges incorporated into immediate release tablets. Methods: Amlodipine nanosponges were prepared using ethyl cellulose and β-cyclodextrin via emulsion solvent diffusion method employing a 3^2 full factorial design. Optimized nanosponges were characterized for particle size, zeta potential, entrapment efficiency, morphology (SEM), and in-vitro drug release. Nanosponges were subsequently formulated into immediate release tablets using crospovidone as superdisintegrant. Results: Optimized nanosponges (F6) showed particle size of 4097 nm, zeta potential -24.3 mV, and entrapment efficiency of 73.87±0.32%. SEM revealed spherical, porous morphology. In-vitro release showed 97.98% drug release at 45 minutes following Higuchi model kinetics (R^2=0.779). Optimized tablets (F3) demonstrated disintegration time of 31 seconds, drug content 99.12±0.82%, and 98.19% drug release at 35 minutes. Conclusion: Amlodipine nanosponges effectively enhanced drug solubility with immediate release characteristics suitable for improved oral delivery.

Keywords: Amlodipine, nanosponges, emulsion solvent diffusion, immediate release tablet, solubility enhancement, β-cyclodextrin.

INTRODUCTION

Hypertension remains a leading global cause of cardiovascular morbidity and mortality [1]. Amlodipine besylate, a dihydropyridine calcium channel blocker, is widely prescribed for hypertension and angina pectoris due to its vasodilatory properties and favorable safety profile [2,3]. However, amlodipine belongs to Biopharmaceutical Classification System (BCS) class II, characterized by low aqueous solubility (0.017 mg/mL) but high permeability, resulting in dissolution rate-limited absorption and variable oral bioavailability (64-90%) [4,5].

Nanotechnology-based drug delivery systems have emerged as promising strategies to overcome solubility limitations of poorly water-soluble drugs [6]. Among these, nanosponges represent a novel class of colloidal carriers consisting of three-dimensional网状 structures with nanometer-sized cavities capable of encapsulating both hydrophilic and lipophilic drug molecules [7,8]. These polymeric nanoparticles offer several advantages including enhanced solubility, controlled release, protection from degradation, and improved bioavailability [9].

Cyclodextrin-based nanosponges have demonstrated particular efficacy in improving solubility of BCS class II drugs through inclusion complex formation [10]. The hydrophobic cavity of β-cyclodextrin encapsulates lipophilic drug molecules, while the hydrophilic exterior ensures aqueous dispersibility [11]. Ethyl cellulose serves as a biocompatible polymer providing structural integrity and controlled release characteristics [12].

Immediate release dosage forms remain the preferred oral delivery system due to patient compliance, cost-effectiveness, and manufacturing simplicity [13].

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Superdisintegrants such as crospovidone facilitate rapid tablet disintegration through water wicking and swelling mechanisms, enabling prompt drug dissolution and absorption [14].

The present study aims to formulate and evaluate amlodipine nanosponges using emulsion solvent diffusion technique, optimize formulation parameters employing factorial design, and develop immediate release tablets with enhanced dissolution characteristics.

MATERIALS AND METHODS:

Materials:

Amlodipine besylate was obtained as a gift sample. Ethyl cellulose (viscosity 10 cP), β-cyclodextrin, polyvinyl alcohol (PVA), dichloromethane, crospovidone, microcrystalline cellulose (Avicel PH101), lactose monohydrate, magnesium stearate, and talc were purchased from commercial sources. All reagents were of analytical grade.

Preformulation Studies:

Solubility determination: Excess amlodipine was added to 10 mL of various solvents (methanol, ethanol 95%, water, 0.1N HCl) in sealed flasks and agitated at 100 rpm for 24 hours at 30±1°C. Samples were filtered, appropriately diluted, and analyzed spectrophotometrically at 238 nm [15].

Melting point: Determined by open capillary method using Thiele's tube.

UV Spectrophotometric analysis: Amlodipine (10 mg) was dissolved in methanol (10 mL) to obtain 1000 µg/mL stock solution. Working solutions (10-50 µg/mL) were prepared and scanned between 200-400 nm using Jasco V-550 spectrophotometer to determine λmax [16].

Calibration curve: Standard solutions of 5-25 ppm were prepared in methanol and absorbance measured at 238 nm.

FTIR spectroscopy: FTIR spectra of pure amlodipine, physical mixtures with excipients, and optimized nanosponges were recorded using Shimadzu IRAffinity-1 spectrometer with KBr pellet method over 400-4000 cm^{-1} [17].

Preparation of Amlodipine Nanosponges:

Nanosponges were prepared by emulsion solvent diffusion method [18]. The organic phase containing amlodipine, ethyl cellulose, and β-cyclodextrin (1:1:1 to 3:2:3 ratios) was dissolved in dichloromethane (8-12 mL). The aqueous phase consisted of PVA (0.5% w/v) in distilled water. The organic phase was slowly added to the aqueous phase under magnetic stirring at 1000 rpm for 2 hours at room temperature. Formed nanosponges were recovered by vacuum filtration, washed with distilled water, and dried at 40°C for 24 hours, then stored in vacuum desiccators [19].

Experimental Design:

A 3^2 full factorial design was employed to optimize nanosponge formulation with independent variables: X_1 (ethyl cellulose ratio: 1, 1.5, 2) and X_2 (dichloromethane volume: 8, 10, 12 mL). Responses evaluated included practical yield, drug content, and % cumulative drug release [20].

Evaluation of Nanosponges:

Production yield: Calculated as percentage of final dried weight relative to total initial solids [21].

Drug content (Entrapment efficiency): Nanosponges (10 mg) were dissolved in pH 6.8 phosphate buffer (10 mL) with sonication, filtered, diluted, and analyzed at 238 nm. Entrapment efficiency = (Actual drug content / Theoretical drug content) × 100 [22].

Particle size and zeta potential: Determined by dynamic light scattering using Malvern Zetasizer at 25°C. Samples were dispersed in distilled water [23].

Surface morphology: Evaluated using scanning electron microscopy (Hitachi X650). Nanosponges were gold-coated under argon atmosphere and examined at 15 kV acceleration voltage [24].

In-vitro drug release: Performed using USP dissolution apparatus type II (paddle) with 900 mL 0.1N HCl at 37±0.5°C, 75 rpm. Samples (5 mL) were withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, and 45 minutes, replaced with fresh medium, filtered, and analyzed at 238 nm [25].

Release kinetics: Data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models using DD Solver software [26].

X-ray diffraction (XRD): Recorded on Bruker D8 Advance diffractometer with scan rate 5°/min over 2θ range 2.5-60°.

Differential scanning calorimetry (DSC): Performed using Perkin-Elmer DSC/7 at heating rate 10°C/min from 30-400°C under nitrogen purge.

Formulation of Immediate Release Tablets:

Immediate release tablets containing amlodipine nanosponges (equivalent to 5 mg drug) were prepared by direct compression method [27]. Formulation composition included: nanosponges (6.2 mg), crospovidone (3-8 mg) as superdisintegrant, Avicel PH101 (1-5 mg) as binder, lactose (q.s. to 200 mg), magnesium stearate (1.5 mg), and talc (2 mg). Powders were blended geometrically and compressed using 8 mm round flat punches on rotary tablet press [28].

Evaluation of Tablets:

Precompression parameters: Bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose were determined for powder blends [29].

Postcompression parameters: Tablets were evaluated for weight variation (20 tablets), hardness (Monsanto hardness tester), thickness (Vernier caliper), friability (Roche friabilator, 25 rpm for 4 minutes), drug content uniformity, disintegration time (USP apparatus in distilled water at 37±2°C), and wetting time [30].

In-vitro dissolution: Performed using USP apparatus type II with 900 mL 0.1N HCl at 37±0.5°C, 75 rpm for 35 minutes. Samples analyzed at 238 nm [31].

Stability Studies:

Optimized formulation was stored at 40±2°C/75±5% RH for 90 days in aluminum foil packs. Samples were evaluated at 0, 30, 60, and 90 days for physical appearance, drug content, disintegration time, and in-vitro drug release as per ICH Q1A(R2) guidelines [32].

Statistical Analysis:

All experiments were performed in triplicate. Results expressed as mean ± standard deviation. Data analyzed using one-way ANOVA with significance level $p<0.05$.

RESULTS AND DISCUSSION:

Preformulation Studies:

Table 1 presents solubility results of amlodipine in various solvents. The drug showed good solubility in methanol (27.81±0.018 mg/mL) and ethanol (26.76±0.021 mg/mL) but was practically insoluble in water (0.017±0.005 mg/mL), confirming its BCS class II classification.

Sr. No.	Solvent	Observation	Solubility (mg/mL)
1	Methanol	Soluble	27.81 ± 0.018
2	Ethanol (95%)	Soluble	26.76 ± 0.021
3	Water	Insoluble	0.017 ± 0.005
4	0.1N HCl	Soluble	27.2 ± 0.025

Table 1: Solubility profile of Amlodipine in various solvents

Melting point was determined as 198-200°C, consistent with reported value (199-200°C), confirming drug purity. UV spectrophotometric analysis revealed λmax at 238 nm in methanol. Calibration curve showed excellent linearity (R^2=0.9955) over 5-25 ppm range following Beer-Lambert's law.

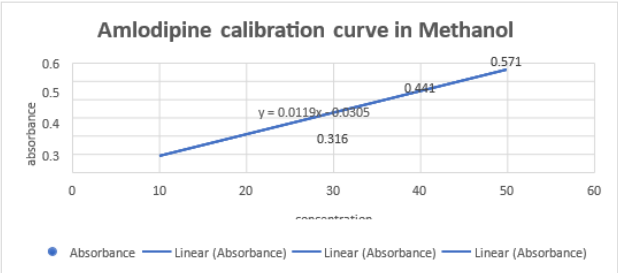

Figure 1: Calibration Curve of Amlodipine

FTIR Compatibility Studies:

FTIR spectra of pure amlodipine showed characteristic peaks at 3299 cm^{-1} (O-H stretching), 1735 cm^{-1} (C=O stretching), 1202 cm^{-1} (C-N stretching), and 789-792 cm^{-1} (C-Cl stretching), The FTIR spectrum of pure amlodipine revealed characteristic absorption bands corresponding to its functional groups. The O-H stretching vibration was observed at 3299 cm^{-1}, falling within the standard range of 3100–3500 cm^{-1}. The C-Cl stretching appeared as peaks at 789 and 792.71 cm^{-1}, consistent with the expected range of 550–850 cm^{-1}. The C=O stretching was noted at 1735 cm^{-1}, which aligns with the standard range of 1750–1500 cm^{-1}. Additionally, the C-N stretching was observed at 1202 cm^{-1} (standard range 1210–1163 cm^{-1}), and the C-H bending appeared at 692 cm^{-1} (standard range 690–515 cm^{-1}). These assignments confirm the structural integrity of the amlodipine sample.

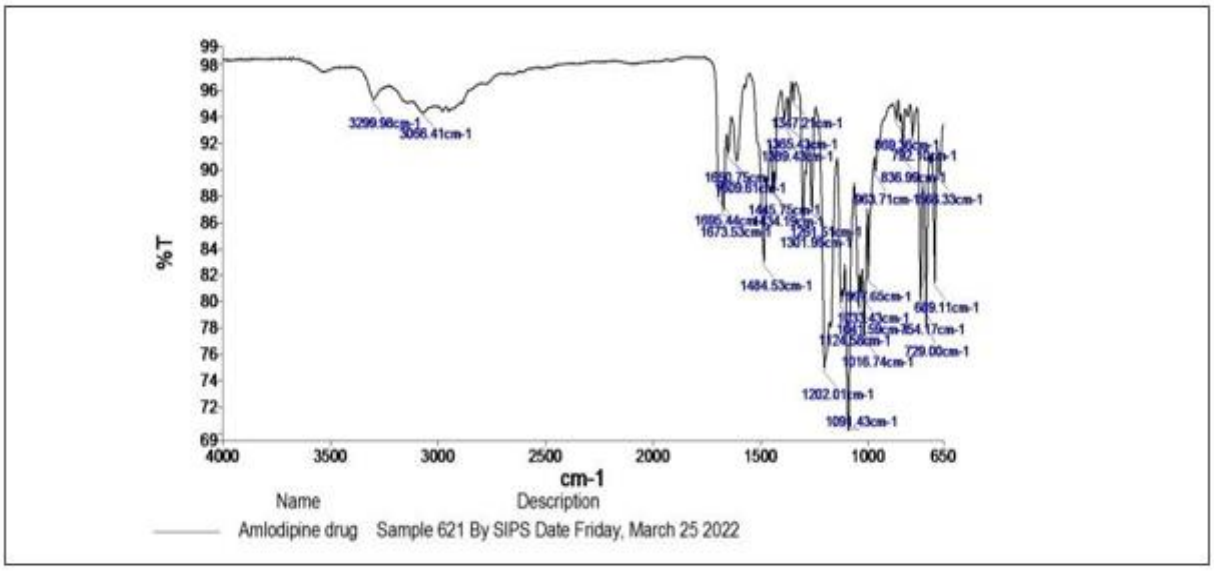

Figure 2: IR of Amlodipine

FTIR results of drug-excipient physical mixtures- No significant shifting of characteristic peaks or appearance of new peaks was observed, indicating absence of chemical interactions between amlodipine and selected polymers (β-cyclodextrin, ethyl cellulose). The drug-excipient compatibility study evaluated physical mixtures of amlodipine with β-cyclodextrin and ethyl cellulose in a 1:1 ratio. FTIR analysis of both mixtures revealed no new peaks and all characteristic peaks of amlodipine were retained, indicating the absence of any chemical interaction between the drug and the selected polymers.

Optimization of Nanosponges:

Nine formulations (F1-F9) were prepared according to 3^2 factorial design. **Table 2** presents the formulation strategy.

Batch	Amlodipine	Ethyl cellulose	β-cyclodextrin	Dichloromethane (mL)
F1	1	1	1	8
F2	1	1.5	1	8
F3	1	2	1	8
F4	1	1	1	10
F5	1	1.5	1	10
F6	1	2	1	10
F7	1	1.5	1	12
F8	1	1.5	1	12
F9	1	2	1	12

Table 2: Formulation strategy for Amlodipine nanosponges

Practical yield ranged from 32.6% to 69.7%, with F6 showing highest yield (69.7%). Drug content ranged from 44.97±0.53% to 73.87±0.32%, with F6 exhibiting maximum entrapment (73.87±0.32%). Higher ethyl cellulose ratio (1:2) and moderate solvent volume (10 mL) favored nanosponge formation and drug incorporation. **Table 7** presents practical yield and drug content for all formulations.

Table 3 shows in-vitro drug release profiles. F6 demonstrated superior release (97.98% at 45 minutes) compared to other formulations. The enhanced release from F6 can be attributed to optimal polymer concentration producing nanosponges with appropriate porosity and reduced crystallinity.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	15.86	15.65	16.25	16.48	14.24	19.21	18.98	15.38	14.13
10	27.31	27.89	28.35	29.43	24.56	29.53	27.14	26.14	25.61
15	45.12	43.67	40.76	43.54	44.87	48.19	45.31	44.87	44.65
20	52.74	56.97	53.87	53.16	53.87	54.54	53.61	51.76	52.64
25	63.96	63.74	65.81	61.65	61.98	66.21	61.32	64.64	63.45
30	76.65	76.98	79.84	79.90	78.14	78.52	76.13	73.19	74.14
35	84.61	84.98	85.79	84.16	81.88	83.20	83.51	81.93	82.93
40	91.81	93.52	93.54	92.13	92.61	91.28	91.51	91.59	92.43
45	94.54	96.43	95.43	98.32	96.64	97.98	95.43	96.32	96.65

Table 3: In-vitro drug release profile of nanosponge formulations (% cumulative drug release)

Characterization of Optimized Nanosponges (F6):

Particle size and zeta potential: Table 7 shows particle size analysis revealed average diameter of 4097 nm (PDI=1.000, intercept=1.41). Zeta potential was -24.3 mV, indicating moderate stability. Values greater than ±25 mV typically indicate good colloidal stability; the obtained -24.3 mV suggests adequate stability for pharmaceutical application.

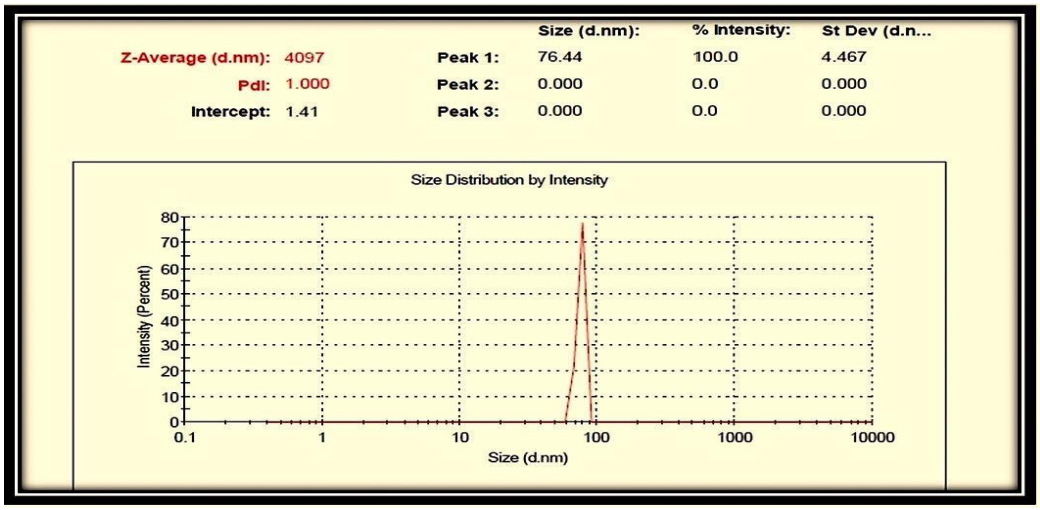

Figure 3: Zeta size distribution of Amlodipine nanosponges

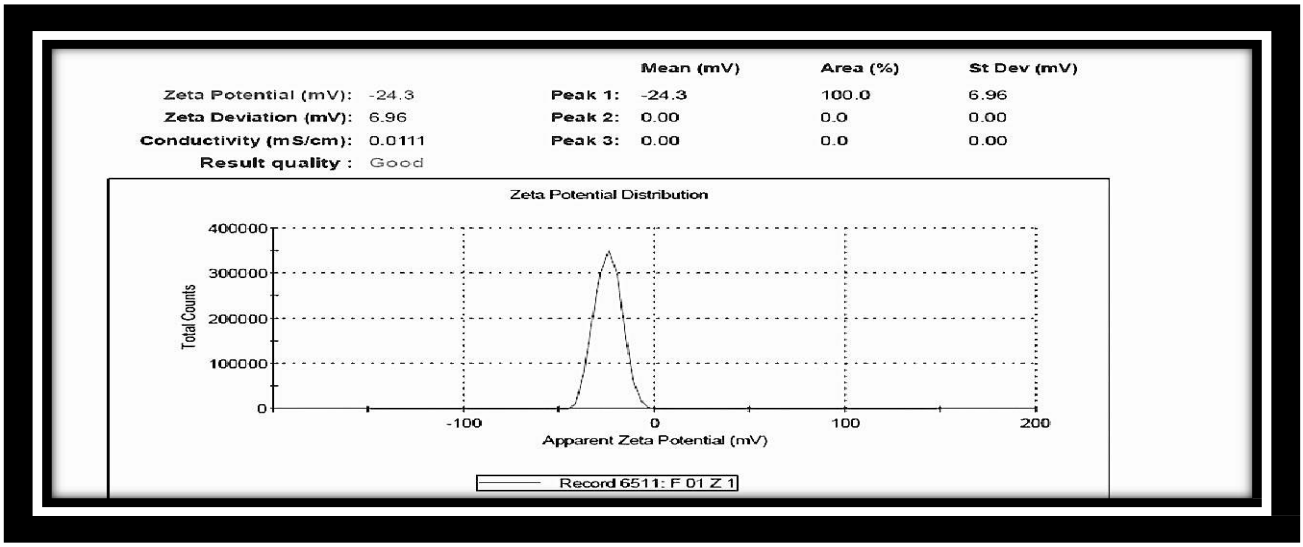

Figure 4: Zeta potential of Amlodipine nanosponges

Parameter	Optimized batch (F6)
Average particle size	4097 nm
PDI value	1.000
Intercept	1.41
Zeta potential	-24.3 mV
Result quality	Good

Table 4: Particle size and zeta potential of optimized nanosponges

SEM analysis: Scanning electron micrographs revealed spherical particles with smooth surface and porous structure. The porous morphology resulted from dichloromethane diffusion during emulsion solvent evaporation, which is characteristic of nanosponge architecture enabling drug encapsulation and release.

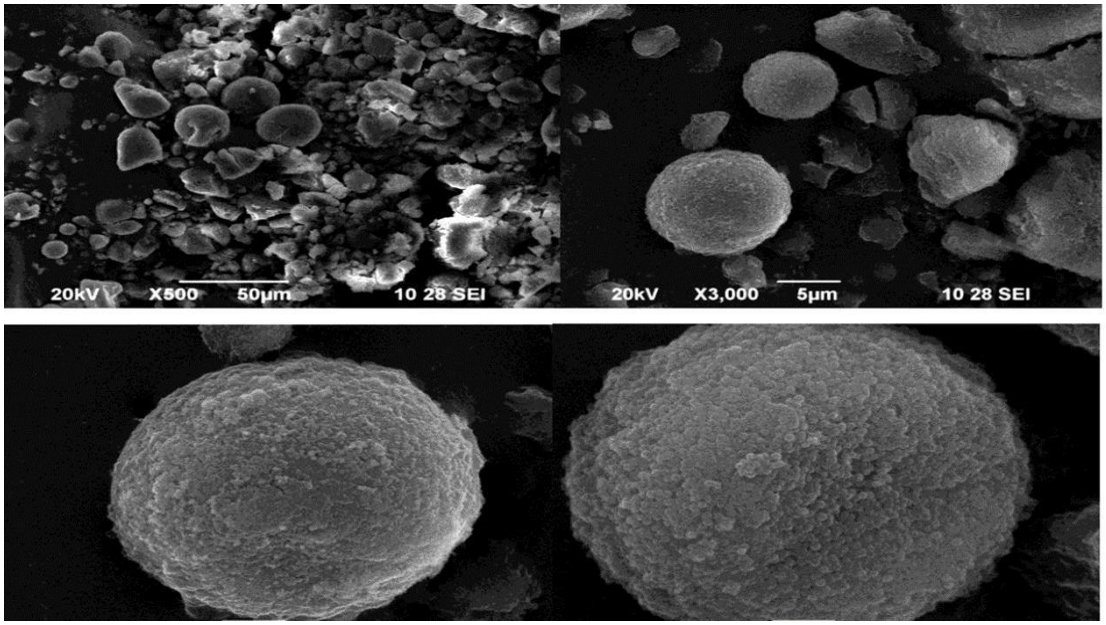

Figure 5: SEM images of Amlodipine nanosponges

XRD analysis: Diffractograms showed reduction in characteristic crystalline peaks of amlodipine in nanosponge formulation compared to pure drug, indicating conversion to amorphous or less crystalline state. This amorphous transformation contributes to enhanced solubility.

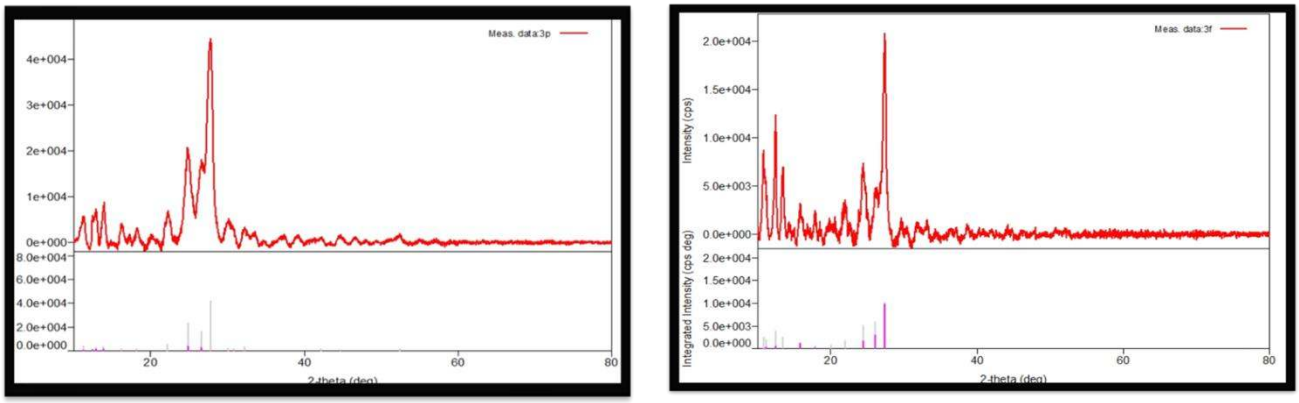

Figure 6: X-RD diffraction of Amlodipine (B) & Amlodipine Nanosponges(A)

DSC analysis: Amlodipine exhibited endothermic peak at 210°C (Tpeak=290°C), which was diminished in nanosponge complex, suggesting molecular dispersion of drug within polymer matrix and potential protection from thermal degradation.

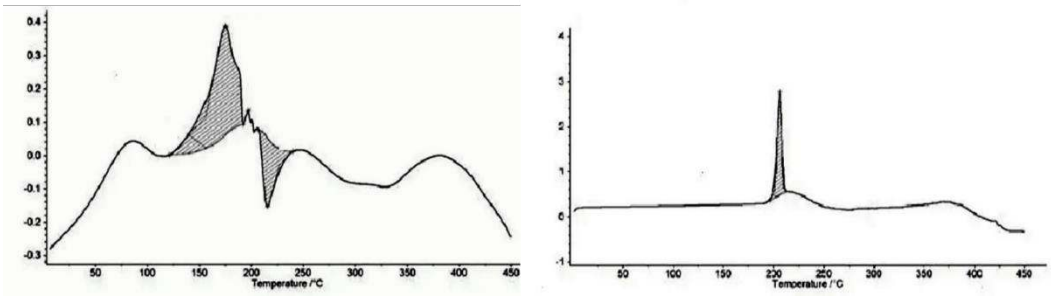

Figure 7 : DSC of Amlodipine (A) & Amlodipine Nanosponges (B)

Release Kinetics;

Table 5 presents kinetic model fitting parameters for F6 formulation. The Higuchi model showed best fit (R^2=0.779) indicating diffusion-controlled drug release from matrix system. Korsmeyer-Peppas model exponent (n=0.6022) suggested anomalous (non-Fickian) transport mechanism, where drug release is governed by combination of diffusion and polymer relaxation.

Model	Equation	R^2 Value
Zero order	y = 2.9936x + 17.723	0.9099
First order	y = -0.0014x + 1.4349	0.0012
Higuchi	y = 0.1438x - 1.4184	0.7790
Korsmeyer-Peppas	y = 0.6022x - 1.4871	0.8900

Table5: Kinetic model fitting parameters for F6 nanosponges

Immediate Release Tablet Evaluation:

Precompression parameters: Table 6shows powder blend properties. Angle of repose ranged 25.07-29.96°, indicating good flow. Carr's index (12-14.79%) and Hausner's ratio (1.14-1.20) confirmed acceptable compressibility for direct compression.

Batch	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Angle of repose (θ)	Hausner's ratio
F1	0.59	0.75	12.00	25.25	1.20
F2	0.63	0.73	13.69	26.27	1.15
F3	0.60	0.70	14.79	27.65	1.16
F4	0.61	0.71	13.08	26.32	1.16
F5	0.62	0.71	12.67	28.42	1.15
F6	0.64	0.74	13.51	29.96	1.16
F7	0.63	0.72	12.50	25.07	1.14

F8	0.66	0.76	13.15	26.56	1.15
F9	0.64	0.75	14.66	27.60	1.17

Table 6: Precompression parameters of tablet powder blends

Table 7 presents drug content uniformity. All formulations showed content between 73.98-99.12%, with F3 exhibiting highest drug content (99.12±0.82%), meeting pharmacopoeial specifications (85-115%).

Batch	Practical yield (%)	Drug content (%)	% Drug Content (SD±)	Disintegration Time (seconds)
F1	32.6	44.97 ± 0.53	83.3 ± 0.63	42
F2	42	50.33 ± 0.16	84.7 ± 0.41	51
F3	59	50.76 ± 0.15	99.12 ± 0.82	31
F4	32.3	67.81 ± 0.51	86.53 ± 0.31	55
F5	41.8	71.44 ± 0.91	91.7 ± 0.37	34
F6	69.7	73.87 ± 0.32	83.97 ± 0.27	38
F7	53.8	60.43 ± 0.41	94.12 ± 0.41	45
F8	41.5	63.87 ± 0.31	73.98 ± 0.21	30
F9	51.8	61.23 ± 0.41	79.49 ± 0.43	32

Table 7: Practical yield and drug content of nanosponge formulations, Drug content of immediate release tablets and Disintegration time

Disintegration time: Table 7 shows disintegration times ranged 30-55 seconds. F3 demonstrated fastest disintegration (31 seconds), attributed to optimal crospovidone concentration (8 mg) which promotes rapid water uptake and swelling.

Table 8 presents in-vitro drug release from tablets. F3 showed maximum release (99.19% at 35 minutes), confirming immediate release characteristics as per USP criteria (>85% in 30 minutes).

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	43.65	43.89	40.75	43.16	44.76	48.84	45.73	44.32	45.32
10	51.65	56.85	53.65	54.75	53.85	56.63	53.75	55.73	54.52
15	63.65	65.64	64.91	69.42	63.82	65.81	64.14	65.92	65.94
20	77.93	77.81	80.41	81.43	80.13	76.25	77.63	74.73	78.31
25	84.81	84.93	84.51	85.31	84.81	84.81	84.71	84.74	86.81

30	91.54	91.85	91.64	94.74	93.83	92.31	91.65	91.96	93.61
35	94.64	95.69	99.19	98.19	98.53	97.64	95.63	96.52	96.18

Table 8: In-vitro drug release profile of immediate release tablets (% CDR)

Table 9 summarizes postcompression parameters. All formulations complied with pharmacopoeial specifications for weight variation (±5%), hardness (3-5 kg/cm²), friability (<1%), and thickness uniformity.

Batch	Weight (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Wetting time (sec)
F1	202.3±0.15	3.4	3.2	0.69	40
F2	202.2±0.66	3.7	3.1	0.71	48
F3	198.9±0.30	3.2	2.7	0.68	36
F4	200.6±0.23	3.6	2.9	0.79	39
F5	202.1±0.18	4.2	2.7	0.74	51
F6	201.3±0.26	3.9	2.7	0.91	54
F7	202.4±0.13	3.3	3.2	0.86	48
F8	198.6±0.30	3.6	2.9	0.75	56
F9	199.2±0.29	3.7	2.7	0.79	55

Table 9: Post compression evaluation parameters of immediate release tablets

Table 10 shows comparative dissolution between optimized formulation (F3) and marketed product (Stamlo 2.5, Dr. Reddy's). Optimized formulation showed faster release (98.26% at 15 minutes) compared to marketed tablet (98.48% at 30 minutes), demonstrating improved dissolution rate attributed to nanosponge-mediated solubility enhancement.

Time (min)	Marketed tablet (% CDR)	Optimized batch F3 (% CDR)
0	0	0
5	17.58	45.89
10	32.16	88.65
15	46.87	98.26
20	69.66	-
25	83.94	-
30	98.48	-

Table 10: Comparative drug release of optimized batch vs marketed formulation

Stability Studies:

Table 11 presents stability data at 40±2°C/75±5% RH over 90 days. Optimized formulation showed no significant change in physical appearance, drug content (98.43%), drug release (99.59%), or disintegration time (61 sec), indicating good stability under accelerated conditions.

Evaluation parameter	Initial	After 1 month	After 2 months	After 3 months
Physical evaluation	White, round	No change	No change	No change
% Drug content	99.12	99.07	98.96	98.43
% Drug release	99.19	99.15	99.08	99.59
Disintegration time (sec)	31	34	52	61
Weight (mg)	198.9	199.2	199.5	200.0

Table 11: Stability study results of optimized formulation

DISCUSSION:

The successful formulation of amlodipine nanosponges using emulsion solvent diffusion method demonstrated significant improvement in drug solubility and release characteristics. The selection of ethyl cellulose and β-cyclodextrin as polymers proved optimal, as hydrophilic polymers alone yielded poor nanosponge formation. The combination of hydrophobic ethyl cellulose providing structural integrity and β-cyclodextrin enabling inclusion complexation created synergistic effect on drug entrapment.

FTIR studies confirmed no chemical incompatibility between drug and polymers, maintaining therapeutic efficacy. The shift from crystalline to amorphous state observed in XRD and DSC analyses explains enhanced dissolution, as amorphous forms have higher free energy and improved wettability compared to crystalline counterparts.

The Higuchi model fit (R^2=0.779) indicates diffusion-controlled release mechanism, while Korsmeyer-Peppas exponent (n=0.6022) suggests anomalous transport combining Fickian diffusion and polymer relaxation. This biphasic release pattern is desirable for maintaining therapeutic concentrations.

Incorporation of crospovidone as superdisintegrant in tablet formulation produced rapid disintegration (<31 seconds) due to its high swelling capacity and water wicking properties. The direct compression method ensured manufacturing simplicity and reproducibility, crucial for scale-up.

Comparison with marketed formulation revealed superior dissolution profile of optimized tablets, achieving complete release within 15 minutes versus 30 minutes for commercial product. This enhanced performance can be attributed to increased surface area and reduced crystallinity achieved through nanosponge technology.

CONCLUSION

Amlodipine nanosponges were successfully prepared by emulsion solvent diffusion method using ethyl cellulose and β-cyclodextrin. The 3^2 factorial design optimization identified F6 as optimal formulation with 69.7% yield, 73.87% drug entrapment, particle size 4097 nm, and zeta potential -24.3 mV. SEM revealed spherical porous morphology. In-vitro release (97.98% at 45 minutes) followed Higuchi kinetics with anomalous diffusion mechanism.

Immediate release tablets containing optimized nanosponges with crospovidone (8 mg) as superdisintegrant exhibited rapid disintegration (31 seconds) and complete drug release (99.19% at 35 minutes), outperforming marketed formulation. Stability studies confirmed formulation integrity under accelerated conditions.

The developed nanosponge-based immediate release tablet offers promising approach for enhancing

solubility and dissolution of BCS class II drugs, potentially improving oral bioavailability and therapeutic efficacy of amlodipine for hypertension management.

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