Formulation And Evaluation of Polymeric Nanoparticles of Nifedipine for Enhanced Solubility, Dissolution and Oral Bioavailability

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***Abstract*—The present study focused on the development and evaluation of polymeric nanoparticles of nifedipine to enhance its solubility, dissolution rate, stability, and oral bioavailability. Nifedipine, a poorly water-soluble antihypertensive drug belonging to Biopharmaceutics Classification System (BCS) Class II, exhibits low bioavailability owing to poor aqueous solubility. To overcome this limitation, polymeric nanoparticles were prepared by the ionic gelation (ionotropic gelation) method using chitosan and sodium alginate as biodegradable polymers and sodium tripolyphosphate (TPP) as a cross-linking agent. Eight nanoparticle batches (F1-F8) were evaluated for particle size, polydispersity index (PDI), zeta potential and drug entrapment efficiency; Fourier Transform Infrared (FTIR) spectroscopy confirmed drug-excipient compatibility, and Differential Scanning Calorimetry (DSC) indicated retention of drug crystallinity. The optimized nanoparticle batch (F6) was incorporated into Tablets (F1-F7) and evaluated for pre- and post-compression parameters including thickness, hardness, weight variation, friability, drug content, disintegration time and in vitro drug release. Batch F4 exhibited the maximum cumulative drug release (98.6 ± 0.4% at 12 h) with acceptable mechanical and stability characteristics, and was selected as the optimized formulation. Stability studies conducted as per ICH guidelines confirmed that the optimized formulation remained sTable over a three-month period. The study concludes that a polymeric nanoparticle-based drug delivery system markedly improves the dissolution rate and therapeutic performance of poorly soluble drugs such as nifedipine and represents a promising strategy for oral antihypertensive therapy.**

***Index Terms*—Nifedipine; Polymeric Nanoparticles; Ionotropic Gelation; Chitosan; Sodium Alginate; Sustained Release; Bioavailability Enhancement; Drug Delivery System; Dissolution Rate; BCS Class II.**

I. INTRODUCTION

The oral route of drug administration remains the most widely accepted and preferred method of drug delivery owing to its simplicity, convenience, cost-effectiveness and high level of patient compliance [1,2]. Oral dosage forms such as Tablets, capsules and suspensions are easy to administer, non-invasive and suitable for long-term therapy, which makes oral delivery the first choice in pharmaceutical development and clinical practice [3-5]. Despite these advantages, oral drug delivery faces a significant challenge in the form of poor aqueous solubility. Nearly 40% of newly developed drug candidates are poorly water-soluble, which severely limits their therapeutic effectiveness [6-8]. Poor solubility leads to low dissolution rates in gastrointestinal fluids, resulting in inadequate drug absorption and reduced bioavailability [9]. Since drug absorption after oral administration depends primarily on dissolution in gastrointestinal fluids and permeability across the intestinal membrane, dissolution becomes the rate-limiting step for poorly soluble drugs [10,11]. The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes based on their aqueous solubility and intestinal permeability [13]. Among these, BCS Class II drugs, which possess low solubility but high permeability, pose considerable formulation challenges; enhancement of their dissolution rate significantly improves bioavailability [14-16]. Various strategies including particle size reduction, solid dispersion, surfactant use, complexation, lipid-based systems and nanoparticle-based drug delivery have been developed to overcome these limitations, of which nanotechnology-based

approaches have attracted particular attention for their ability to improve dissolution, enhance absorption and provide controlled drug release [6,9,15,16].Nifedipine, a dihydropyridine calcium channel blocker widely used in the management of hypertension and angina, is a BCS Class II drug that exhibits poor aqueous solubility and consequently erratic and incomplete oral bioavailability. Conventional nifedipine formulations therefore show variable therapeutic response. Polymeric nanoparticles composed of biodegradable and biocompatible polymers such as chitosan and sodium alginate offer an attractive platform to overcome these limitations because they provide increased surface area, controlled/sustained drug release, improved stability and enhanced mucoadhesion, thereby improving the extent and consistency of drug absorption [17-20]. Chitosan, a cationic polysaccharide, and sodium alginate, an anionic polysaccharide, undergo ionotropic gelation in the presence of a polyanionic cross-linking agent such as sodium tripolyphosphate (TPP) to form nanoparticles without the use of harsh organic solvents or high shear/heat, making the method particularly suiTable for encapsulating labile drug molecules [18,19].In view of the above, the present study was undertaken to formulate and characterize chitosan-sodium alginate nanoparticles of nifedipine by the ionotropic gelation technique, to incorporate the optimized nanoparticles into a Tablet dosage form, and to evaluate the resulting formulation for physicochemical properties, in vitro drug release and short-term stability, with the overall objective of improving the solubility, dissolution rate and oral bioavailability of nifedipine.

II. MATERIALS AND METHODS

A. Materials

Nifedipine was obtained ex gratia from Wockhardt Pvt. Ltd., Aurangabad. Chitosan and sodium alginate were procured from Rajesh Chemicals, Nagpur. Polyvinyl alcohol (PVA) and Tween 80 were obtained from Ozone International Ltd., Mumbai, and sodium tripolyphosphate (TPP) was procured from ACS Pharmaceuticals, Pune. All other chemicals and reagents used were of analytical grade.

Table 1 Materials used and their category

Material	Category	Source
Nifedipine	Active pharmaceutical ingredient	Wockhardt Pvt. Ltd., Aurangabad
Chitosan	Polymer	Rajesh Chemicals, Nagpur
Sodium alginate	Polymer	Rajesh Chemicals, Nagpur
Polyvinyl alcohol (PVA)	Stabilizer	Ozone International Ltd., Mumbai
Tween 80	Surfactant	Ozone International Ltd., Mumbai
Sodium tripolyphosphate (TPP)	Cross-linking agent	ACS Pharmaceuticals, Pune
Ethanol	Solvent	Aglo Pharmaceuticals, Pune
Mannitol	Cryoprotectant	Ozone International Ltd., Mumbai

B. Preformulation Studies

Preformulation studies were carried out to characterize the physicochemical properties of nifedipine prior to formulation. Organoleptic properties (colour, odour, appearance and texture) were assessed by visual and sensory examination. Solubility was determined in distilled water, methanol, ethanol and phosphate buffer pH 6.8 by shaking excess drug with each solvent for 24 h and analysing the filtrate spectrophotometrically. Melting point was determined by the capillary tube method. The wavelength of maximum absorbance (λmax) was determined by scanning a methanolic drug solution between 200-400 nm using a UV-Visible spectrophotometer. Drug-excipient compatibility was assessed by FTIR spectroscopy (KBr pellet method) and Differential Scanning Calorimetry (DSC) of the pure drug and drug-excipient physical mixtures.

C. Preparation of Nifedipine Nanoparticles

Nifedipine-loaded chitosan-sodium alginate nanoparticles were prepared by the ionotropic gelation technique. Briefly, accurately weighed sodium alginate was dissolved in distilled water under continuous magnetic stirring to obtain a clear solution, while chitosan was separately dissolved in 1% v/v acetic acid and the pH adjusted to 5.0-5.5 with sodium

hydroxide solution. Nifedipine, dissolved in a small quantity of ethanol, was incorporated into the sodium alginate solution under stirring. A calcium chloride solution containing TPP was added dropwise into the drug-polymer dispersion under high-speed stirring, followed by slow addition of the chitosan solution, resulting in nanoparticle formation through ionic cross-linking between the positively charged chitosan and the negatively charged alginate/TPP. The resulting dispersion was ultrasonicated for 10-15 min to reduce particle size, centrifuged at 15,000 rpm for 30 min, washed with distilled water to remove unentrapped drug, and freeze-dried (lyophilized) for further evaluation. Eight batches (F1-F8) were prepared by varying the concentration of chitosan (50-225 mg) while keeping the concentrations of nifedipine (20 mg), sodium alginate (25 mg), PVA (20 mg), Tween 80 (10 mg) and TPP (15 mg) constant, as summarised in Table 2.

Table 2 Composition of nifedipine nanoparticle formulations (f1-f8, mg)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Nifedipine	20	20	20	20	20	20	20	20
Chitosan	50	75	100	125	150	175	200	225
Sodium alginate	25	25	25	25	25	25	25	25
PVA	20	20	20	20	20	20	20	20
Tween 80	10	10	10	10	10	10	10	10
TPP	15	15	15	15	15	15	15	15
Mannitol	25	25	25	25	25	25	25	25
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

D. Characterization of Nanoparticles

Particle size and polydispersity index (PDI) were determined by dynamic light scattering (DLS) using a Zetasizer. Zeta potential was measured on the same instrument to assess colloidal stability; absolute values greater than 30 mV are generally considered indicative of good physical stability. Drug entrapment efficiency was determined by centrifuging the nanoparticle suspension at high speed, estimating the free (unentrapped) drug in the supernatant by UV-Visible spectrophotometry at λmax, and calculating entrapment efficiency as: Entrapment Efficiency (%) = [(Total drug − Free drug) / Total drug] × 100. Surface morphology of the optimized batch was examined by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM).

E. Preparation of Nifedipine Nanoparticle Tablets

The optimized nanoparticle batch was incorporated into Tablets by direct compression. Seven Tablet formulations (F1-F7) were prepared by blending nifedipine nanoparticles (equivalent to 50 mg) with microcrystalline cellulose, superdisintegrant, glidant and lubricant in varying ratios, followed by sieving, blending, lubrication, and compression on a rotary Tablet punching machine. The compressed Tablets were stored in airtight containers for further evaluation.

F. Evaluation of Tablets

The prepared Tablets were evaluated for appearance (visual inspection for colour, shape, surface texture and defects); thickness (digital Vernier caliper, n = 10); hardness (Monsanto/Pfizer hardness tester, kg/cm²); weight variation (20 Tablets weighed individually as per IP limits: ±7.5% for average weight 80-250 mg); friability (Roche friabilator, 100 revolutions at 25 rpm, acceptance <1%); drug content uniformity (UV-Visible spectrophotometry at λmax, acceptance 95-105% of label claim); and disintegration time (USP disintegration apparatus, 37 ± 0.5 °C).

G. In Vitro Drug Release Study

In vitro drug release was carried out using USP Dissolution Apparatus II (paddle type) in 900 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C and stirred at 50 rpm. Aliquots were withdrawn at predetermined time intervals, replaced with an equal volume of fresh medium, and analysed spectrophotometrically. Cumulative percentage drug release was calculated as: Cumulative Drug Release

(%) = (Amount of drug released / Total drug in formulation) × 100.

H. Stability Studies

Stability studies were performed on the optimized formulation as per ICH guidelines. Samples were stored under refrigerated condition (4 ± 2 °C) and room temperature (25 ± 2 °C), and the optimized Tablet batch was additionally evaluated at accelerated conditions over 1 and 3 months for appearance, hardness, drug content and in vitro drug release.

III. RESULTS AND DISCUSSION

A. Preformulation Studies

Nifedipine was obtained as a yellow, odourless crystalline powder with a smooth texture, consistent with standard specifications and confirming the purity of the sample used. The drug was found to be practically insoluble in water, freely soluble in methanol, soluble in ethanol, and slightly soluble in phosphate buffer pH 6.8 (Table 3), confirming its classification as a poorly water-soluble (BCS Class II) drug and justifying the need for nanoparticle-based formulation to enhance dissolution. The melting point of nifedipine was found to be 172-174 °C, in agreement with the reported official range and indicating absence of major impurities.

Table 3 Preformulation characterization of nifedipine

Parameter	Observation
Colour	Yellow
Odour	Odourless
Appearance	Crystalline powder
Solubility - Water	Practically insoluble
Solubility - Methanol	Freely soluble
Solubility - Ethanol	Soluble
Solubility - Phosphate buffer pH 6.8	Slightly soluble
Melting point	172-174 °C

UV scanning of nifedipine in methanol showed maximum absorbance at 238 nm (Fig. 1), consistent with reported literature values; this wavelength was subsequently used for all quantitative estimations.

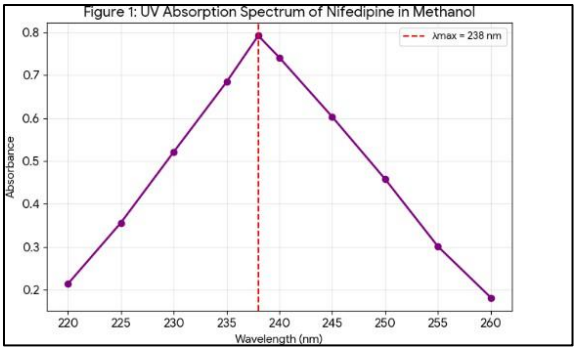

Fig. 1. UV absorption spectrum of nifedipine in methanol (λmax = 238 nm)

FTIR spectra of the pure drug and drug-excipient physical mixtures (Fig. 2) showed retention of all characteristic nifedipine peaks — N-H stretching (3320-3350 cm^{-1}), ester C=O stretching (1680-1700 cm^{-1}), NO2 stretching (1520-1540 cm^{-1}) and C-O stretching (1200-1250 cm^{-1}) — with no shift or disappearance of peaks, confirming the absence of chemical interaction and compatibility of nifedipine with chitosan, sodium alginate, PVA, Tween 80 and TPP.

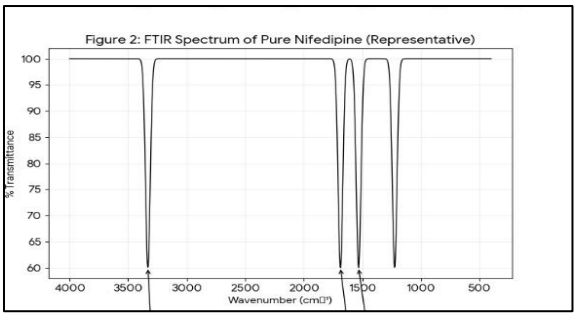

Fig. 2. FTIR spectrum of pure nifedipine

DSC thermograms (Fig. 3) of pure nifedipine showed a sharp endothermic peak at 173 °C corresponding to its melting point, confirming its crystalline nature. The formulation mixture exhibited a slightly broadened endothermic peak at 171-172 °C with retention of the characteristic peak, indicating minor loss of crystallinity due to molecular dispersion of the drug within the polymer matrix during nanoparticle formation, without evidence of drug-excipient interaction or instability.

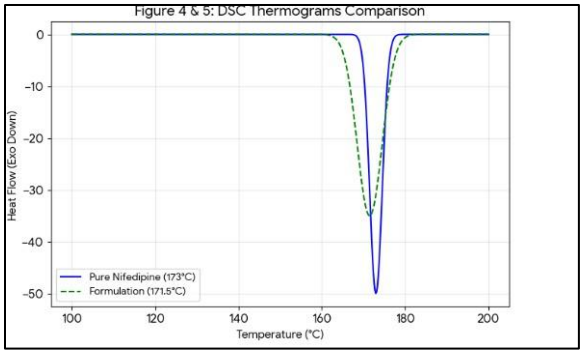

Fig. 3. DSC thermogram of pure nifedipine and nifedipine formulation

B. Characterization of Nanoparticles

Particle size of the nanoparticle batches (F1-F8) ranged from 145 ± 2.1 nm to 320 ± 4.2 nm (Table 4). Particle size increased progressively with increasing chitosan concentration, attribuTable to the higher viscosity of the polymeric dispersion at higher polymer loading, which reduces the efficiency of ultrasonic size reduction. The polydispersity index (PDI) decreased from batch F1 to F6 (0.221) and thereafter increased in F7 and F8, indicating that an intermediate polymer concentration produced the most uniform nanoparticle population; batch F6 exhibited the narrowest size distribution among all batches (Fig. 4).

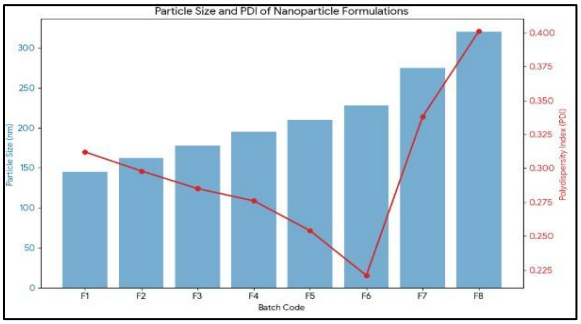

Fig. 4. Particle size and polydispersity index (PDI) of nanoparticle formulations F1-F8

Table 4 Particle size, pdi, zeta potential and entrapment efficiency of nanoparticle formulations (f1-f8)

Batch	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
F1	145 ± 2.1	0.312	-18.5	62.4 ± 1.2
F2	162 ± 1.8	0.298	-20.1	67.8 ± 1.5
F3	178 ± 2.5	0.285	-22.4	72.5 ± 1.3
F4	195 ± 3.1	0.276	-24.3	76.9 ± 1.6
F5	210 ± 2.8	0.254	-26.2	81.4 ± 1.4
F6	228 ± 2.2	0.221	-29.8	88.2 ± 1.1
F7	275 ± 3.5	0.338	-31.4	84.5 ± 1.8
F8	320 ± 4.2	0.401	-33.2	80.3 ± 1.9

All formulations exhibited negative zeta potential values, ranging from -18.5 mV (F1) to -33.2 mV (F8), owing to the anionic surface characteristics imparted by sodium alginate and TPP; the increasing magnitude of zeta potential with polymer concentration reflects greater electrostatic repulsion and hence improved colloidal stability at higher cross-linking. Drug entrapment efficiency increased from 62.4% (F1) to a maximum of 88.2% (F6) with increasing chitosan concentration, due to more extensive polymeric cross-linking and matrix formation limiting drug loss, and then declined in F7 and F8, possibly due to increased viscosity restricting drug incorporation during nanoparticle formation. Based on the optimum particle size, narrowest PDI, satisfactory zeta potential and maximum entrapment efficiency, batch F6 was selected as the optimized nanoparticle formulation for incorporation into the Tablet dosage form.

C. Evaluation of Nanoparticle Tablets (F1-F7)

All Tablet formulations were yellow, round, and showed a smooth surface free from cracks, capping or mottling. Thickness ranged from 3.12 ± 0.03 mm to 3.35 ± 0.04 mm and hardness from 3.5 ± 0.2 to 5.4 ± 0.2 kg/cm², both increasing with increasing polymer concentration and remaining within accepTable pharmacopeial limits. Weight variation of all batches (179.2-180.5 mg) complied with IP limits (±7.5% for Tablets of 80-250 mg), and friability values were below 1% (0.49-0.86%) for all batches, indicating adequate mechanical strength. Drug content of all formulations ranged from 95.4% to 99.2%, within the accepTable pharmacopeial range of 95-105% of label claim, confirming uniform drug distribution. Disintegration time increased with polymer concentration (5.2 min for F1 to 9.3 min for F7), consistent with formation of a stronger, more cohesive polymeric matrix at higher polymer loading.

Table 5 post-compression evaluation parameters of nifedipine nanoparticle tablets (f1-f7)

Batch	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)	Disintegration Time (min)
F1	3.12 ± 0.03	3.5 ± 0.2	0.86	95.4 ± 0.6	5.2 ± 0.3
F2	3.18 ± 0.02	3.8 ± 0.1	0.79	96.8 ± 0.5	5.8 ± 0.2
F3	3.20 ± 0.04	4.1 ± 0.2	0.71	97.9 ± 0.4	6.4 ± 0.3
F4	3.24 ± 0.03	4.5 ± 0.1	0.63	99.2 ± 0.3	7.1 ± 0.2
F5	3.28 ± 0.02	4.8 ± 0.2	0.58	98.7 ± 0.4	7.8 ± 0.3
F6	3.31 ± 0.03	5.1 ± 0.1	0.54	97.6 ± 0.5	8.5 ± 0.2
F7	3.35 ± 0.04	5.4 ± 0.2	0.49	96.9 ± 0.6	9.3 ± 0.4

D. In Vitro Drug Release and Optimization

Cumulative in vitro drug release at 12 h ranged from 82.4% (F1) to 98.6% (F4) (Table 6). Drug release increased from F1 to F4 with increasing polymer concentration owing to improved nanoparticle entrapment and matrix formation, but decreased progressively from F4 to F7 at still higher polymer levels, most likely because excessive polymer content produced a denser, more rate-limiting matrix that retarded drug diffusion despite higher entrapment. Formulation F4 therefore provided the best balance between controlled matrix formation and drug release and exhibited the maximum cumulative release with a controlled-release profile; it was accordingly selected as the optimized Tablet formulation, in addition to showing excellent drug content uniformity, acceptable hardness/friability, and a suitable disintegration time.

Table 6 Cumulative in vitro drug release (%) of tablet formulations f1-f7 at 12 h

Batch	F1	F2	F3	F4	F5	F6	F7
Drug release at 12 h (%)	82.4 ± 0.8	85.9 ± 0.7	89.5 ± 0.6	98.6 ± 0.4	95.8 ± 0.5	91.7 ± 0.6	88.2 ± 0.7

E. Stability Studies

The optimized formulation (F4) was subjected to stability testing as per ICH guidelines under refrigerated (4 ± 2 °C) and room temperature (25 ± 2 °C) conditions. As shown in Table 7, no significant changes were observed in appearance, hardness, drug content or in vitro drug release over three months; hardness decreased marginally from 4.5 ± 0.1 to 4.4 ± 0.2 kg/cm², drug content from 99.2 ± 0.3% to 98.6 ± 0.5%, and drug release from 98.6 ± 0.4% to 97.8 ± 0.6%. These minor variations were within accepTable limits, confirming that the optimized nifedipine nanoparticle Tablet formulation is physically and chemically sTable and suiTable for further development.

Table 7 Stability study data of optimized formulation (f4)

Parameter	Initial	After 1 Month	After 3 Months
Appearance	Uniform	No change	No change
Hardness (kg/cm²)	4.5 ± 0.1	4.4 ± 0.1	4.4 ± 0.2
Drug content (%)	99.2 ± 0.3	98.9 ± 0.4	98.6 ± 0.5
Drug release (%)	98.6 ± 0.4	98.1 ± 0.5	97.8 ± 0.6

IV. CONCLUSION

Nifedipine nanoparticles were successfully prepared by the ionotropic gelation technique using chitosan and sodium alginate as biodegradable polymers and sodium tripolyphosphate as a cross-linking agent. FTIR and DSC studies confirmed the absence of significant drug-excipient interaction and retention of drug crystallinity. Among the eight nanoparticle batches, F6 exhibited the optimum particle size, narrowest polydispersity index, satisfactory zeta potential and maximum drug entrapment efficiency. On incorporation into Tablets, formulation F4 demonstrated the best combination of physicochemical properties, maximum cumulative in vitro drug release (98.6 ± 0.4% at 12 h) and satisfactory stability under ICH storage conditions. The study demonstrates that polymeric nanoparticle-based Tablet formulations can effectively enhance the dissolution rate and, by extension, the oral bioavailability of poorly water-soluble drugs such as nifedipine, and represent a promising strategy for improving therapeutic efficacy and patient compliance in the management of hypertension. Further work involving in vivo pharmacokinetic evaluation and

scale-up studies is recommended to confirm the clinical translational potential of this formulation.

V. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, financial or otherwise, related to this study.

VI. SOURCE OF FUNDING

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