RESEARCH PAPER

Nanotechnology-Driven Orodispersible Tablets of Isradipine: Enhancing Dissolution, Stability and Therapeutic Efficiency

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Received: 12th Mar, 2026 | **Revised:** 24th Mar, 2026 | **Accepted:** 14th Apr, 2026 | **Available Online:** 30th Apr, 2026

ABSTRACT

The present study aimed to develop and optimize oral disintegrating tablets (ODTs) of Isradipine using chitosan (CS) nanoparticles to enhance solubility, dissolution rate, and patient compliance in hypertension management. Isradipine, a Biopharmaceutics Classification System (BCS) class II drug, exhibits poor aqueous solubility, leading to variable bioavailability. To overcome this limitation, Isradipine-loaded CS nanoparticles were prepared using the ionotropic external gelation technique. The prepared nanoparticles showed desirable characteristics, including nanoscale particle size (115–420 nm), high encapsulation efficiency (65.75%–90.15%), and improved drug loading. A significant enhancement in solubility (~10-fold) was observed compared to the pure drug. The optimized nanoparticle formulation was further incorporated into ODTs using the direct compression method. A 2^3 full factorial design was employed to study the effect of critical formulation variables, namely croscarmellose sodium (CCS), microcrystalline cellulose (MCC), and compression force, on disintegration time (DT) and drug release (DR). The developed ODTs exhibited satisfactory physicochemical properties, including uniform weight, adequate hardness, low friability (<1%), and rapid disintegration (12–75 seconds). Statistical analysis revealed that CCS significantly reduced DT and enhanced DR, whereas MCC concentration and compression force showed an inverse effect on drug release. The optimized formulation demonstrated more than 85–95% drug release within 30 minutes, compared to significantly lower release from pure drug tablets. Overall, the study highlights that nanoparticle-based ODTs of Isradipine offer a promising strategy to improve solubility, dissolution, and patient compliance. This approach may serve as an effective alternative to conventional dosage forms, particularly for geriatric patients with swallowing difficulties.

Keywords: Isradipine; Oral disintegrating tablets; Chitosan nanoparticles; Hypertension; Solubility enhancement; Factorial design; Drug release; Patient compliance

How to cite this article: Kumar A, Maharana SK, Khan A, Jadhav SM, Kumar S, Saxena S, Sharma D. Nanotechnology-Driven Orodispersible Tablets of Isradipine: Enhancing Dissolution, Stability and Therapeutic Efficiency. Int J Drug Deliv Technol. 2026;16(39s): 859-870. DOI: 10.25258/ijddt.16.39s.106

Source of support: Nil.

Conflict of interest: None

INTRODUCTION:

Hypertension is a chronic cardiovascular disorder characterized by persistently elevated arterial blood pressure, which can lead to severe complications such as stroke, myocardial infarction, heart failure, and renal impairment if left untreated. Common clinical manifestations may include headache, dizziness, palpitations, and in many cases, patients remain asymptomatic, making it a "silent disease." Hypertension can affect both adult and geriatric populations, with a higher prevalence observed in elderly patients due to age-related vascular changes.

Isradipine (ISR) is a dihydropyridine calcium channel blocker widely used as an antihypertensive agent. It exerts its pharmacological action by inhibiting calcium ion influx into vascular smooth muscle cells, leading to

vasodilation and a consequent reduction in blood pressure. It is indicated in the management of mild to moderate hypertension and may also be used in certain cases of angina pectoris. However, in geriatric patients, conventional dosage forms such as tablets and capsules may present difficulties in swallowing, thereby affecting patient adherence. Moreover, Isradipine is classified as a Biopharmaceutics Classification System (BCS) class II drug, exhibiting low aqueous solubility and high permeability, which may result in variable oral bioavailability. Therefore, an optimized formulation is required to enhance its dissolution profile and therapeutic efficacy.

In recent years, nanoparticle engineering approaches have gained significant attention in pharmaceutical research for improving the solubility and bioavailability of poorly water-soluble drugs. By reducing the particle size of Isradipine from the micron to nanometer range, there is a substantial increase in surface area, which enhances the dissolution rate and, consequently, drug absorption. Nanoparticle-based drug delivery systems can be formulated either as standalone particles or in combination with suitable pharmaceutical excipients to achieve improved performance.

Optimization of oral drug delivery systems for geriatric patients remains a challenging task. A significant proportion of elderly individuals experience dysphagia, which limits their ability to take conventional solid dosage forms. In this context, oral fast disintegrating tablets (FDTs) containing Isradipine nanoparticles represent an innovative drug delivery approach. These formulations disintegrate rapidly in the oral cavity without the need for water, thereby improving ease of administration and patient compliance. Additionally, FDTs offer advantages such as rapid onset of action, enhanced bioavailability, and better acceptability among elderly, bedridden, and non-cooperative patients.

Hence, the aim of the present study was to develop oral fast disintegrating tablets containing Isradipine nanoparticles for the effective management of hypertension, with a focus on improving patient compliance and therapeutic outcomes in geriatric patients.

MATERIALS AND METHODS:

Materials:

Isradipine (ISR) was procured from Sun Pharmaceutical Industries Ltd. (Mumbai, India). Chitosan (CS), microcrystalline cellulose (MCC), lactose, aerosil, magnesium stearate, and croscarmellose sodium (CCS) were obtained from Himedia Laboratories Pvt. Ltd. (Mumbai, India). Tripolyphosphate (TPP) and glacial acetic acid were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India).

Methods:

Preparation of Isradipine–Chitosan Nanoparticles by Ionotropic External Gelation Technique:

Isradipine-loaded chitosan (CS) nanoparticles were prepared using the ionotropic external gelation method. CS was dissolved in an aqueous solution of acetic acid under continuous stirring at room temperature. The concentration of acetic acid in the medium was maintained at 1.5 times higher than that of CS to ensure complete solubilization. Tween-80 (1.5% v/v) was incorporated into the clear CS solution as a surfactant to stabilize the emulsion system.

Isradipine was dissolved in an organic solvent (methanol), and this organic phase was added dropwise into the aqueous CS solution under constant stirring to form an oil-in-water (o/w) emulsion. Stirring was continued for an additional 5 minutes following complete addition to ensure uniform dispersion.

Subsequently, cross-linking of the nanoparticles was achieved by the dropwise addition of tripolyphosphate (TPP) solution of varying concentrations into the emulsion under continuous stirring. The system was then kept undisturbed overnight at room temperature to allow complete evaporation of the organic solvent. The formation of nanoparticles occurred due to electrostatic interaction between the negatively charged phosphate groups of TPP and the positively charged amino groups of CS.

The formed nanoparticles were separated by centrifugation at 15,000 rpm for 30 minutes at −10 °C using a cooling centrifuge. The collected supernatant was analyzed for free Isradipine content using a UV–visible spectrophotometer. The prepared Isradipine-loaded CS nanoparticles were further characterized, and the optimized formulation was selected for the development of oral dispersible tablets (ODTs) intended for the management of hypertension. Table 1 presents the composition of different nanoparticle formulations.

Table 1. Isradipine–Chitosan (ISR–CS) Nanoparticle Formulations

Batch	CS (% w/v)	TPP (% w/v)
F1	0.30	0.10
F2	0.30	0.20
F3	0.60	0.15
F4	0.60	0.30

Abbreviations: Isradipine (ISR), chitosan (CS), tripolyphosphate (TPP).

2³ Full Factorial Design for Development of Isradipine ODT:

Statistical optimization of the experimental design was carried out using Design-Expert (Version 11, Stat-Ease Inc., USA). A three-factor, two-level (2^3) full factorial design was employed to develop a second-order polynomial model for the formulation of oral disintegrating tablets (ODTs) of Isradipine intended for hypertension management.

Dependent Variables	Response
Y_1	Disintegration time (DT, sec)
Y_2	Drug release (%DR at 30 min)

The concentration of croscarmellose sodium (CCS, A), microcrystalline cellulose (MCC, B), and compression force (C) were selected as independent variables, whereas disintegration time (DT; Y_1) and cumulative in vitro drug release at 30 min (DR; Y_2) were considered as dependent variables. The levels of the independent variables were selected based on preliminary trials and are summarized in Table 2.

A 2^3 factorial design was utilized to systematically evaluate the main effects, as well as interaction effects, of formulation and process variables on the responses. Various mathematical models, including linear, two-factor interaction (2FI), and quadratic models, were generated and analyzed. The suitability of the model was assessed using statistical parameters such as adjusted R^2, predicted R^2, model F-value, and P-value. A model was considered significant when the P-value was less than 0.05, with a good agreement between adjusted R^2 and predicted R^2 (difference < 0.2). Additionally, the Predicted Residual Error Sum of Squares (PRESS) value was used as an indicator of model fitness, where a lower value indicated better predictability.

Response surface methodology (RSM) was applied to generate contour plots and three-dimensional response surface plots to visualize the effect of independent variables on DT and drug release. The developed polynomial equations were interpreted based on the magnitude and sign of coefficients to understand the influence of variables and their interactions.

The optimized formulation was selected based on the criteria of minimum disintegration time and maximum drug release, ensuring rapid onset of action and improved bioavailability of Isradipine ODTs for effective hypertension management. Analysis of variance (ANOVA) was performed to validate the statistical significance of the model and the formulation variables.

Table 2. Variables and Their Levels for Optimization of Isradipine ODT

Independent Variables	Low Level (−1)	High Level (+1)
A = CCS concentration (%)	3	7
B = MCC concentration (%)	15	35
C = Compression force (kN)	3	6

Abbreviations: Isradipine (ISR), croscarmellose sodium (CCS), microcrystalline cellulose (MCC), disintegration time (DT), drug release (DR).

Preparation of Isradipine ODTs by Direct Compression Method:

Oral disintegrating tablets (ODTs) of Isradipine were prepared using the direct compression technique. All excipients were accurately weighed and passed through sieve no. 60 to ensure uniform particle size distribution. The sieved ingredients were then blended thoroughly using geometric dilution to achieve a homogeneous powder mixture.

Optimized Isradipine-loaded chitosan (CS) nanoparticles were accurately weighed and incorporated into the above powder blend. The final mixture was lubricated with magnesium stearate and glidant (aerosil) and mixed gently to avoid segregation. The prepared blend was then directly compressed into tablets using a 10 mm flat-faced punch on a rotary tablet compression machine to obtain tablets with an average weight of 120 mg. Compression force was adjusted according to the factorial design batches to achieve desirable hardness and rapid disintegration characteristics.

EVALUATION OF ISRADIPINE-LOADED CHITOSAN NANOPARTICLES:

Percentage Yield:

Isradipine-loaded chitosan (CS) nanoparticles were collected and weighed accurately after drying. The percentage yield was calculated using the following equation:

$$\%\,\text{yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100 \quad (1)$$

Drug Entrapment Efficiency and Drug Loading:

The prepared nanoparticles were separated by centrifugation, and the amount of non-entrapped (free) drug present in the supernatant was determined using a UV–visible spectrophotometer at λmax 326 nm for Isradipine.

Drug loading (DL) and encapsulation efficiency (EE) were calculated using the following equations:

$$\%DL = \frac{\text{Total drug} - \text{free drug}}{\text{Nanoparticle weight}} \times 100$$

$$\%EE = \frac{\text{Total drug} - \text{free drug}}{\text{Total drug amount}} \times 100$$

Phase Solubility Study of Isradipine and ISR–CS Nanoparticles:

An excess amount of pure Isradipine was added to 5 mL of distilled water to obtain a saturated solution. Similarly, saturated solutions of Isradipine-loaded CS nanoparticles were prepared by dispersing excess nanoparticles in distilled water. The samples were shaken mechanically for 24 hours at 37 ± 0.5°C, followed by centrifugation at 10,000 rpm for 5 minutes. The supernatant was suitably diluted, and absorbance was measured at 326 nm using a UV spectrophotometer. The solubility of Isradipine in each sample was calculated and compared to evaluate enhancement in solubility due to nanoparticle formulation.

Particle Size Distribution Analysis

Particle size and size distribution of Isradipine-loaded CS nanoparticles were determined using the laser diffraction method with a Malvern particle size analyzer (Malvern Instruments, UK). Nanoparticles were dispersed in distilled water, and measurements were carried out at 25°C with a scattering angle of 90°.

Scanning Electron Microscopy (SEM)

Surface morphology of the nanoparticles, including characteristic, surface texture, and structural characteristics, was examined using scanning electron microscopy (SEM). The samples were mounted on aluminum stubs, coated with a thin layer of gold, and analyzed under appropriate accelerating voltage to observe the characteristic and surface features of the nanoparticles.

Table 3. Evaluation of Isradipine–Chitosan (ISR–CS) Nanoparticles

Batch	Yield (%)	EE (%)	DL (%)	Particle Size (nm)	Solubility (mg/L)
F1	78.40	65.75	11.80	420	310
F2	84.10	74.90	15.20	290	465
F3	91.25	83.40	19.85	210	680
F4	96.80	90.15	24.60	115	920

Abbreviations: *Isradipine (ISR), chitosan (CS), encapsulation efficiency (EE), drug loading (DL), particle size distribution (PSD).*

EVALUATION OF ISRADIPINE ODTS:

Weight Variation Test

Weight variation was determined by weighing 20 tablets individually, and the average weight was calculated. Each tablet weight was compared with the average weight, and the percentage deviation was determined. The tablets complied with pharmacopeial specifications if not more than two tablets deviated from the permissible limit and none deviated by more than twice the specified percentage limit, as per United States Pharmacopeia guidelines.

Uniformity of Thickness and Diameter:

The thickness and diameter of ten tablets were measured using a Vernier caliper at three different positions. The results were expressed as mean ± standard deviation, ensuring uniformity in tablet thickness and mechanical consistency.

Hardness:

Tablet hardness was measured using a Monsanto hardness tester. The mean hardness was calculated for each batch and expressed in kg/cm². Hardness reflects the mechanical strength of tablets and their ability to withstand handling during packaging and transportation.

Friability:

Friability was evaluated using a Roche friabilator. Pre-weighed tablets were subjected to 100 revolutions, and the percentage weight loss was calculated. A friability value of less than 1% was considered acceptable. Achieving low friability in orally disintegrating tablets is challenging due to their porous structure and rapid disintegration characteristics.

Disintegration Test:

The disintegration test was performed on six tablets using a standard disintegration apparatus. Phosphate buffer (pH 6.8, 900 mL) maintained at 37 ± 0.5°C was used as the medium. The time required for complete disintegration of the tablet, with no visible mass remaining, was recorded in seconds. Rapid disintegration is a key quality attribute for ODTs of Isradipine to ensure quick onset of action in hypertension management.

Dissolution Test:

In vitro dissolution studies were carried out using USP Apparatus Type II (paddle method) at 50 rpm. The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. Samples were withdrawn at predetermined time intervals, filtered, and analyzed using a UV–visible spectrophotometer at λmax 326 nm for Isradipine. The cumulative percentage drug release was calculated to assess the release profile and performance of the formulated ODTs.

RESULTS:

Isradipine-Loaded Chitosan (ISR–CS) Nanoparticles:

Yield of ISR–CS Nanoparticles:

The prepared nanoparticles were collected and accurately weighed. The percentage yield was found to be satisfactory, ranging from 78.40% to 96.80% of the total solid content used during formulation (Table 4). No significant variation in yield was observed among different batches, indicating reproducibility of the method. Minimal loss of nanoparticles was noted during high-speed centrifugation at controlled cooling conditions (−10°C).

The results demonstrated that increasing the concentration of both chitosan (CS) and tripolyphosphate (TPP) led to a proportional increase in nanoparticle yield. This may be attributed to the formation of a denser polymeric network and enhanced ionic cross-linking between CS and TPP, which reduced material loss during processing.

Encapsulation Efficiency (EE) and Drug Loading (DL):

The percentage drug loading (DL) of nanoparticles ranged from 11.80% to 24.60%, while encapsulation efficiency (EE) varied between 65.75% and 90.15% (Table 3). Both DL and EE were significantly influenced by the concentration of polymer and cross-linking agent.

Lower EE observed in some batches may be due to partial drug diffusion into the external phase during preparation. However, increasing CS concentration improved drug entrapment due to enhanced matrix formation. Similarly, higher TPP concentration promoted stronger ionic gelation, resulting in improved encapsulation.

Among all batches, F4 exhibited the highest EE and DL, whereas F1 showed the lowest values. Overall, a direct relationship was observed between CS/TPP concentration and both EE and DL, confirming efficient entrapment of Isradipine within the nanoparticulate system.

Particle Size Distribution Study:

The particle size of ISR–CS nanoparticles was found to be in the range of 115–420 nm (Table 3), confirming successful formation of nanosized particles. Particle size plays a critical role in determining dispersion stability and dissolution behavior.

Smaller particles possess a higher surface area, which enhances dissolution but also increases the tendency for aggregation. The inclusion of surfactant (Tween-80) effectively minimized aggregation by stabilizing the nanoparticle dispersion.

The results indicated that increasing the concentration of CS and TPP led to a reduction in particle size, likely due to stronger cross-linking and formation of compact nanoparticles. The optimized batch exhibited a low polydispersity index (~0.28), indicating a relatively narrow and uniform particle size distribution.

Overall, the study confirmed that the developed Isradipine-loaded chitosan nanoparticles possessed desirable physicochemical properties suitable for further formulation into oral disintegrating tablets for hypertension management.

Phase Solubility Study:

According to the Biopharmaceutics Classification System (BCS), Isradipine is classified as a Class II drug, characterized by low aqueous solubility and high permeability. It exhibits poor water solubility with a log P value of approximately 2.1–2.3, which contributes to its variable oral bioavailability.

The intrinsic aqueous solubility of pure Isradipine was determined and found to be ~85 ± 4 mg/L, which is consistent with reported literature values. To overcome this limitation, Isradipine-loaded chitosan (CS) nanoparticles were developed using the ionotropic gelation technique.

Due to the formation of nanoparticles in the size range of 115–420 nm, a significant enhancement in solubility was observed. All nanoparticle formulations showed improved solubility compared to the pure drug. The maximum solubility was observed in batch F4 (920 ± 5 mg/L), as presented in Table 3. This represents a substantial increase compared to the pure drug, confirming the effectiveness of nanoparticle engineering in solubility enhancement (Figure 1A).

The improvement in solubility can be attributed to the reduction in particle size, which increases the surface area available for dissolution. As particle size decreases, the surface area-to-volume ratio increases, leading to enhanced interaction of drug particles with the dissolution medium.

This phenomenon is well explained by the principles of dissolution kinetics under the Noyes–Whitney equation, which states that the dissolution rate is directly proportional to the surface area of the drug. When particle size is reduced from the micrometer to nanometer range, the surface area increases dramatically, resulting in faster dissolution and improved solubility.

Nanoparticles are typically defined as discrete pharmaceutical entities with dimensions below 1 µm. It is estimated that a significant proportion of newly developed drug molecules suffer from poor aqueous solubility, posing formulation challenges. In such cases, nanoparticle-based drug delivery systems provide an effective strategy to enhance solubility, dissolution rate, and ultimately bioavailability.

Thus, the marked increase in solubility of Isradipine from ~85 mg/L to ~920 mg/L demonstrates the potential of chitosan-based nanoparticle systems in improving the therapeutic performance of poorly soluble antihypertensive drugs.

Morphological Characterization of Nanoparticles:

The morphological characteristics of Isradipine-loaded chitosan (CS) nanoparticles were examined using field emission scanning electron microscopy (FE-SEM), and the representative micrograph is shown in Figure 1B.

The obtained nanoparticles exhibited a uniform spherical shape with a smooth and homogeneous surface morphology. No visible cracks, surface irregularities, or signs of erosion were observed. The surface appeared compact and non-porous, indicating effective ionic cross-linking between chitosan and tripolyphosphate (TPP).

Additionally, the nanoparticles were found to be well-dispersed and discrete, with minimal aggregation, suggesting effective stabilization during formulation. The absence of surface pores and the uniform size distribution further confirm the formation of stable and structurally intact nanoparticles.

The optimized formulation demonstrated desirable morphological properties suitable for enhancing solubility and improving the performance of Isradipine in oral drug delivery for hypertension management.

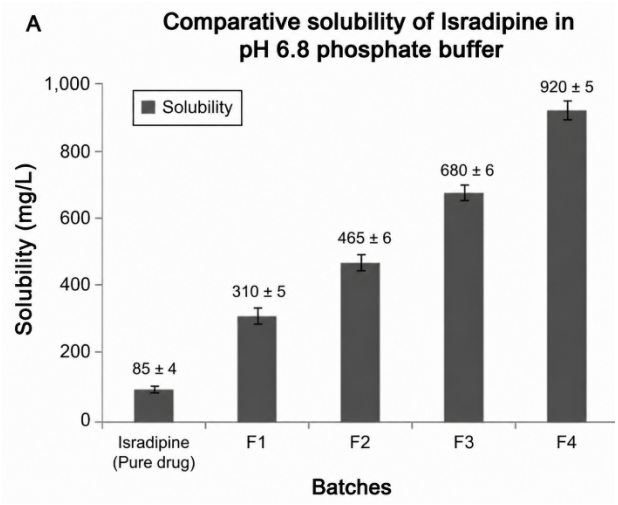


Figure 1. Solubility profile and surface morphology of Isradipine nanoparticles.

Notes: (A) Comparative solubility of Isradipine-loaded chitosan (CS) nanoparticles and pure Isradipine in pH 6.8 phosphate buffer, showing a significant enhancement in solubility with nanoparticle formulations (F1–F4). (B) Field emission scanning electron microscopy (FE-SEM) image of Isradipine-loaded CS nanoparticles, illustrating spherical shape, smooth surface morphology, and uniform particle distribution without aggregation.

ODT Containing Isradipine Nanoparticles:

Physical Evaluation of Tablets

Oral disintegrating tablets (ODTs) of Isradipine were prepared by the direct compression method. To enhance the solubility and dissolution rate of Isradipine, Isradipine–chitosan (ISR–CS) nanoparticles were incorporated into the tablet formulation. As discussed earlier, these nanoparticles significantly improved the solubility of the drug and were therefore selected for ODT development. The physical evaluation parameters of all formulation batches are presented in Table 4.

The tablets were compressed using a 10 mm round flat punch, and the diameter of all tablets was found to be nearly uniform with minimal variation, ranging from 9.8 ± 0.3 mm to 10.2 ± 0.4 mm. The average tablet weight was maintained at 120 mg, with all batches falling within the acceptable range of 118 ± 2 mg to 122 ± 2 mg, indicating good weight uniformity.

Tablets were compressed at two different compression forces (3 kN and 6 kN), which significantly influenced hardness and thickness. Tablets compressed at 6 kN exhibited higher hardness values ranging from 2.2 ± 0.2 to 3.1 ± 0.3 kg/cm², whereas tablets compressed at 3 kN showed comparatively lower hardness values (1.5 ± 0.2 to 1.9 ± 0.2 kg/cm²). This confirms a direct

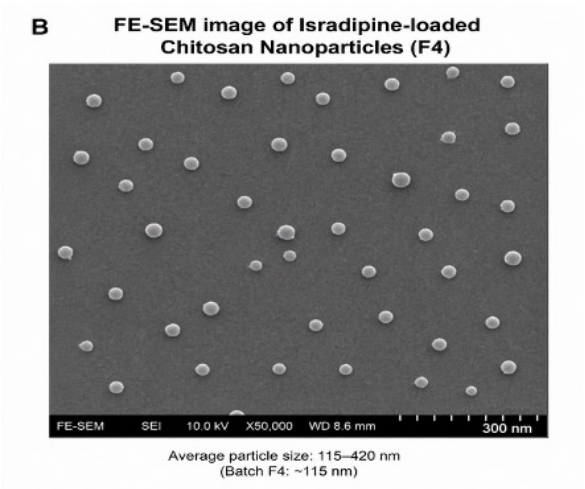
relationship between compression force and tablet hardness. An inverse relationship was observed for thickness. Tablets compressed at lower compression force (3 kN) showed higher thickness (3.0 ± 0.2 mm to 3.6 ± 0.3 mm), while those compressed at higher force (6 kN) exhibited reduced thickness (2.4 ± 0.2 mm to 2.8 ± 0.2 mm).

All formulation batches demonstrated acceptable friability values (<1%), indicating adequate mechanical strength despite the fast disintegrating nature of ODTs.

Overall, the results confirm that all Isradipine ODT formulations met pharmacopeial requirements and exhibited suitable physical characteristics, making them promising candidates for improving patient compliance, particularly in geriatric hypertensive patients.

Table 4. Evaluation Parameters for Isradipine ODTs

Batch	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)	DT (sec)
F1	120 ± 2	3.2 ± 0.2	10.0 ± 0.2	2.3 ± 0.2	0.9	42
F2	121 ± 3	3.3 ± 0.2	9.9 ± 0.1	2.0 ± 0.2	0.7	28
F3	119 ± 2	3.1 ± 0.1	10.1 ± 0.2	2.5 ± 0.2	0.8	55
F4	118 ± 2	3.4 ± 0.2	10.0 ± 0.2	1.9 ± 0.2	0.8	35
F5	122 ± 2	3.5 ± 0.3	9.8 ± 0.2	1.8 ± 0.2	0.7	18
F6	120 ± 1	2.6 ± 0.2	10.1 ± 0.1	3.1 ± 0.3	0.4	75
F7	119 ± 2	2.8 ± 0.2	9.9 ± 0.2	2.7 ± 0.2	0.5	65
F8	121 ± 3	3.6 ± 0.3	10.0 ± 0.2	1.6 ± 0.2	0.6	12



DISCUSSION:

Oral disintegrating tablets (ODTs) of Isradipine were developed with the objective of improving patient compliance, particularly in geriatric patients suffering from hypertension who may experience difficulty in swallowing conventional dosage forms. The solubility limitation of Isradipine, a BCS Class II drug, was addressed through the formulation of chitosan (CS) nanoparticles.

The prepared Isradipine-loaded CS nanoparticles exhibited desirable physicochemical characteristics, including spherical shape, smooth surface morphology, and free-flowing nature, with particle sizes in the nanometer range (minimum ~115 nm). Additionally, high encapsulation efficiency (EE) and drug loading (DL) were achieved. The reduction in particle size significantly enhanced the surface area, leading to improved solubility of Isradipine. Notably, the solubility of the drug was enhanced by approximately 10–11 fold compared to the pure drug. These findings highlight the effectiveness of nanoparticle engineering in overcoming solubility-related challenges.

Following successful nanoparticle optimization, the best-performing batch (F4) was selected for incorporation into tablet formulations. ODTs were prepared using the direct compression method with microcrystalline cellulose (MCC 101) as a directly compressible diluent. The developed tablets exhibited satisfactory pharmaceutical properties, including uniform shape, acceptable thickness, adequate hardness, minimal weight variation, low friability, and rapid disintegration time (DT). All evaluation parameters complied with pharmacopeial limits.

Croscarmellose sodium (CCS) played a crucial role as a superdisintegrant in achieving rapid tablet disintegration at salivary pH. Statistical analysis using factorial design confirmed that all independent

variables significantly influenced DT and in vitro drug release (DR).

The dissolution studies revealed a marked improvement in drug release from nanoparticle-based ODTs. Tablets containing Isradipine-loaded CS nanoparticles exhibited more than 85–90% drug release within 30 minutes, whereas tablets containing pure Isradipine showed comparatively lower release (~35–40%). This substantial enhancement in dissolution rate can be attributed to the reduced particle size and increased surface area of the nanoparticles.

The developed Isradipine ODTs incorporating CS nanoparticles demonstrated significant improvement in solubility, dissolution rate, and tablet performance. These findings suggest that such a formulation approach can serve as a promising and patient-friendly drug delivery system for the effective management of hypertension, particularly in geriatric populations.

Statistical Analysis of Disintegration Time (DT):

The in vitro disintegration time (DT) of oral disintegrating tablets (ODTs) of Isradipine was evaluated using phosphate buffer (pH 6.8), simulating salivary conditions (pH 6.2–7.4). The prepared tablets exhibited DT in the range of 12 to 75 seconds (Table 5), confirming their fast disintegrating nature and suitability for rapid drug release.

The polynomial equation generated for DT (Y_1) is as follows:

$$Y1=+45.63-19.38A+4.38B+9.38C \quad (4$$

where Y_1 represents disintegration time, A is the concentration of croscarmellose sodium (CCS), B is the concentration of microcrystalline cellulose (MCC), and C is the compression force.

Table 5. Formulation of Isradipine ODT Using 2^3 Full Factorial Design

Batches	A	B	C	Y_1 (DT, sec)	Y_2 (% DR at 30 min)
F1	−1	−1	−1	42	84.20
F2	+1	−1	+1	28	90.10
F3	−1	+1	−1	55	80.45
F4	+1	+1	+1	35	88.75
F5	+1	+1	−1	18	94.30
F6	−1	+1	+1	75	76.80
F7	−1	−1	+1	65	82.10
F8	+1	−1	−1	12	97.60

Notes:

A = CCS concentration (%), B = MCC concentration (%), C = compression force (kN),

Y_1 = Disintegration time (DT), Y_2 = Percentage drug release (% DR at 30 min).

Abbreviations: *Isradipine (ISR), croscarmellose sodium (CCS), microcrystalline cellulose (MCC), oral disintegrating tablets (ODT), disintegration time (DT), drug release (DR).*

The model F-value (~385.40) indicates that the model is statistically significant. The negative coefficient of A demonstrates that increasing CCS concentration decreases DT (antagonistic effect), whereas the positive coefficients of B and C indicate that increasing MCC concentration and compression force leads to an increase in DT (synergistic effect).

The selected model for DT was a two-factor interaction (2FI) model. The correlation coefficient ($R^2 \approx 0.995$) indicates excellent agreement between predicted and observed values. The model P-value ($P < 0.0001$) confirms statistical significance. All three independent variables showed significant effects on DT: A ($P < 0.0001$), B ($P \approx 0.003$), and C ($P < 0.0001$).

Croscarmellose sodium (CCS), a well-known superdisintegrant, played a critical role in reducing DT. As its concentration increased, DT decreased significantly (from ~75 seconds to ~12 seconds). This is attributed to its swelling and wicking mechanisms, which promote rapid water uptake and tablet disintegration.

Microcrystalline cellulose (MCC 101), used as a diluent with good compressibility, exhibited a positive effect on DT. Increasing MCC concentration resulted in increased DT, likely due to the formation of a more compact tablet matrix, which slows water penetration.

Compression force also had a significant impact on DT. As compression force increased from 3 kN to 6 kN, DT increased due to the formation of harder, less porous tablets that resist rapid penetration of the dissolution medium. The statistical analysis demonstrates that CCS concentration is the most influential factor in achieving rapid disintegration, while MCC concentration and compression force must be carefully optimized to balance tablet strength and disintegration performance for effective hypertension management.

Table 6. Summary of Results of Regression Analysis for Responses (Y_1 and Y_2) of Isradipine ODT

Models	R^2	Adjusted R^2	Predicted R^2	Standard Deviation	PRESS	Remarks
Response						

Y_1 (DT)						
Linear	0.8254	0.8130	0.6425	3.10	30.45	
2FI	**0.9950**	**0.9928**	**0.9855**	**1.60**	**18.20**	Suggested
Quadratic	0.9102	0.8825	0.8401	2.10	25.80	
Cubic	0.9320	0.9010	0.8705	2.80	40.10	
Response Y_2 (% DR)						
Linear	0.7025	0.6508	0.7102	3.20	14.80	
2FI	**0.9875**	**0.9789**	**0.9520**	**1.20**	**16.40**	Suggested
Quadratic	0.9150	0.8905	0.8652	2.80	12.50	
Cubic	0.9402	0.9054	0.8803	3.60	18.90	

Regression Equations of the Fitted Models

For Disintegration Time (Y_1):

$Y1=+38.75-17.20A+5.10B+8.60C$

For Drug Release (Y_2):

$Y2=+88.40+5.85A-2.30B-3.50C$

Note: The bold values indicate the parameters of the suggested (best-fit) model.

Abbreviations: *Isradipine (ISR), DT – Disintegration Time, DR – Drug Release, PRESS – Predicted Residual Error Sum of Squares.*

The model summary statistics (Table 6) indicated that the 2FI model was the best fit, with a high correlation coefficient ($R^2 \approx 0.995$), good agreement between adjusted and predicted R^2 values, and a low PRESS value. The model F-value (~385.40) and $P < 0.0001$ confirmed that the model is statistically significant.

Table 7. ANOVA of Models for Responses (Y_1 and Y_2) of Isradipine ODT

Source	DF	Sum of Squares	Mean Square	F-value	P-value
Model for Y_1 (DT)					
Model	3	3520.40	1173.47	385.40	**<0.0001**
A (CCS)	1	2750.25	2750.25	902.10	**<0.0001**
B (MCC)	1	165.30	165.30	54.20	**0.0030**
C (Compression force)	1	604.85	604.85	198.75	**<0.0001**
Model for Y_2 (% DR)					
Model	3	452.60	150.87	132.40	**<0.0001**
A (CCS)	1	320.45	320.45	281.30	**<0.0001**
B (MCC)	1	42.20	42.20	37.05	**0.0045**
C (Compression force)	1	89.95	89.95	78.60	**0.0010**

Note: The bold values indicate statistically significant terms of the suggested model.

Abbreviations: *ANOVA – Analysis of Variance; DF – Degrees of Freedom; DT – Disintegration Time; DR – Drug Release; Isradipine (ISR); CCS – Croscarmellose sodium; MCC – Microcrystalline cellulose*.

The analysis of variance (ANOVA) results (Table 7) demonstrated that all independent variables significantly affected DT. Among them, CCS concentration (A) showed the most significant effect ($P < 0.0001$), followed by compression force (C) and MCC concentration (B).

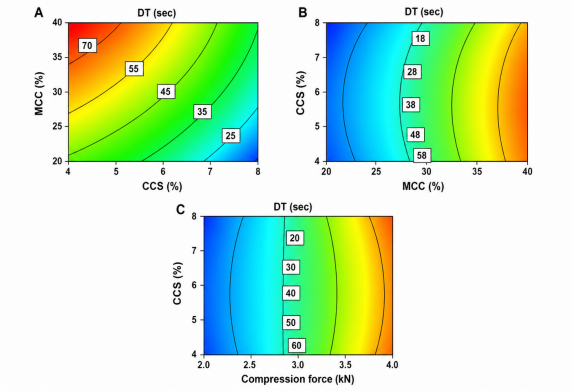


Figure 2. Contour plots showing effect of independent variables on dependent variable (DT) of Isradipine ODTs

Notes:(A) Contour plot showing the effect of croscarmellose sodium (CCS) on the disintegration time (DT) of Isradipine tablets. (B) Contour plot showing the effect of microcrystalline cellulose (MCC) on the DT of tablets.

(C) Contour plot showing the effect of compression force on the DT of tablets.

Abbreviations: *CCS – Croscarmellose sodium; DT – Disintegration time; MCC – Microcrystalline cellulose; ODT – Oral disintegrating tablets.*

From the contour plots and 3D response surface plots (Figure 2A–C), the following observations were made: Effect of CCS (Figure 2A): Increasing CCS concentration significantly reduced DT (from ~75 sec to ~12 sec) due to its swelling and wicking action, which enhances water uptake and promotes rapid tablet disintegration.

Effect of MCC (Figure 2B): Increasing MCC concentration resulted in increased DT, likely due to the formation of a denser matrix that slows water penetration.

Effect of Compression Force (Figure 2C): Higher compression force increased DT, as harder and less porous tablets resist penetration of the dissolution medium.

The contour plots clearly illustrated the interaction effects between variables, confirming that low MCC concentration, high CCS concentration, and lower compression force favor rapid disintegration.

Statistical Analysis of Drug Release (DR):

The in vitro drug release (DR) study of directly compressed oral disintegrating tablets (ODTs) of Isradipine was carried out in phosphate buffer (pH 6.8) to simulate salivary conditions. All formulation batches exhibited more than 80% drug release within 15 minutes, as shown in **Figure 3.** The overall drug release ranged from 76.80% to 97.60% (Table 4), indicating rapid dissolution behavior.

The polynomial equation for drug release (Y_2) is expressed as:

$$Y2=+87.22+6.13A-2.04B-3.08C$$

where A represents CCS concentration, B represents MCC concentration, and C represents compression force.

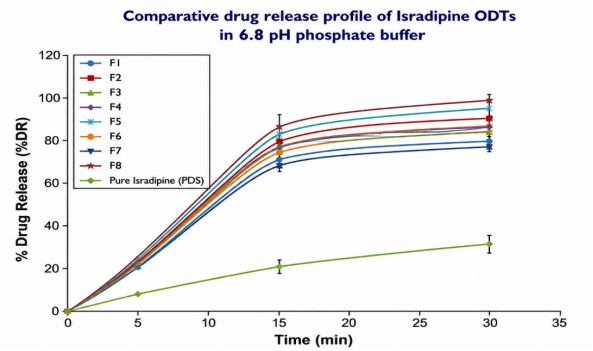


Figure 3. Comparative drug release profile of all tablets containing Isradipine-loaded CS nanoparticles and pure Isradipine in pH 6.8 phosphate buffer

Abbreviations: *Isradipine (ISR); CS – chitosan; DR – drug release; min – minute.*

The model F-value (~132.40) indicates that the model is statistically significant. A positive coefficient of A suggests a synergistic effect (increase in drug release), whereas negative coefficients of B and C indicate antagonistic effects (decrease in drug release). The suggested model for Y_2 was found to be 2FI, as shown in Table 6.

The correlation coefficient ($R^2 \approx 0.9875$) demonstrated a good fit of the model, while the P-value (<0.0001) confirmed statistical significance. All independent variables showed significant influence on drug release: A (CCS, $P < 0.0001$), B (MCC, $P \approx 0.0057$), and C (compression force, $P \approx 0.0012$), as presented in Table 7.

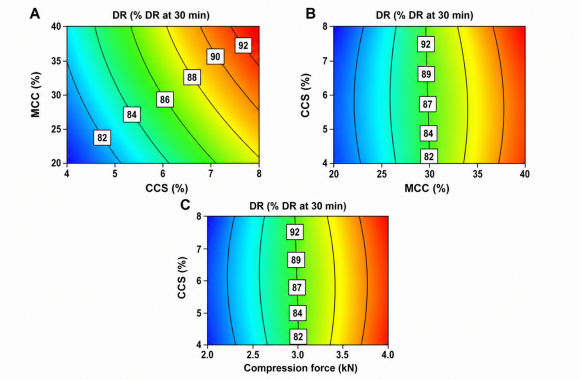


Figure 4. Contour plots showing effect of independent variables on dependent variable (DR) of Isradipine ODTs

Notes: (A) Contour plot showing the effect of croscarmellose sodium (CCS) on the drug release (DR) of Isradipine tablets. (B) Contour plot showing the effect of microcrystalline cellulose (MCC) on the DR of tablets.

(C) Contour plot showing the effect of compression force on the DR of tablets.

Abbreviations: *CCS – Croscarmellose sodium; DR – Drug release; MCC – Microcrystalline cellulose; ODT – Oral disintegrating tablets*.

Croscarmellose sodium (CCS) played a crucial role in enhancing drug release due to its superdisintegrant properties. As the concentration of CCS increased, rapid tablet disintegration occurred, leading to faster drug release. This effect is clearly observed in Figure 4A, where drug release increased significantly with increasing CCS concentration. The swelling and wicking mechanism of CCS facilitated rapid tablet disintegration and immediate drug availability.

Another important factor contributing to enhanced drug release was the incorporation of Isradipine-loaded chitosan nanoparticles. Due to reduced particle size and increased surface area, the solubility of Isradipine was significantly improved, resulting in faster dissolution. In contrast, tablets prepared with pure drug (without nanoparticles) showed significantly lower drug release (~35–40% within 30 minutes).

Microcrystalline cellulose (MCC 101) showed a statistically significant negative effect on drug release ($P = 0.0057$). As MCC concentration increased (20% to 40%), drug release decreased, as shown in Figure 4B. This may be attributed to the formation of a denser matrix, which slows penetration of dissolution medium.

Similarly, compression force exhibited a negative influence on drug release. As compression force increased, tablet hardness increased and porosity decreased, resulting in reduced drug release, as illustrated in Figure 4C.

Overall, the statistical analysis confirms that CCS is the most influential factor for enhancing drug release, while MCC concentration and compression force must be optimized to achieve a balance between mechanical strength and rapid dissolution. The developed Isradipine ODTs demonstrated significantly improved dissolution performance, making them a promising formulation for effective management of hypertension.

CONCLUSION:

Oral disintegrating tablets (ODTs) of Isradipine incorporating chitosan (CS) nanoparticles were successfully developed using the direct compression method. The nanoparticle-based approach proved to be an effective strategy for enhancing the solubility and dissolution rate of this BCS Class II drug.

The formulated Isradipine-loaded CS nanoparticles exhibited desirable physicochemical properties, including nanoscale particle size, high encapsulation efficiency, and improved aqueous solubility, which significantly contributed to enhanced drug release. The optimized nanoparticles were effectively incorporated into ODTs, which demonstrated acceptable pharmaceutical characteristics such as uniform weight, adequate hardness, low friability, and rapid disintegration.

The developed ODTs showed markedly improved in vitro drug release compared to conventional formulations, highlighting the advantage of nanoparticle incorporation. This formulation approach offers a promising and patient-friendly drug delivery system, particularly for geriatric patients with hypertension who may experience difficulty in swallowing conventional dosage forms.The study establishes that ODTs containing Isradipine-loaded chitosan nanoparticles represent a potential and efficient strategy for improving bioavailability and patient compliance in hypertension management.

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