RESEARCH PAPER

Design, optimization, and in vitro characterization of fast-dissolving tablets of nifedipine using response surface methodology

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ABSTRACT

Fast-dissolving tablets (FDTs) offer improved patient compliance and rapid drug release, particularly for poorly water-soluble antihypertensive agents such as nifedipine. Optimization of such formulations requires a systematic approach to balance disintegration, dissolution, and mechanical properties. Nifedipine FDTs were developed using a spray-drying approach followed by compression. Response surface methodology was applied using central composite design (CCD) for nifedipine. Key formulation variables were optimized against critical quality attributes, including disintegration time, wetting time, and in vitro drug release. Tablets were evaluated for physicochemical properties, dissolution, and solid-state characterization (ATR, DSC, XRD). Optimized formulations demonstrated rapid disintegration (<120 s), reduced wetting time, and enhanced dissolution profiles. Nifedipine showed improved solubility in ethanol (9.25 ± 2.08 mg/mL) compared to aqueous media. DoE models showed statistically significant effects of formulation variables on responses ($p < 0.05$). Solid-state studies confirmed compatibility between the drug and excipients without significant interaction. DoE-guided formulation strategies successfully developed fast-dissolving nifedipine tablets with enhanced in vitro performance, supporting their potential for improved oral delivery of poorly soluble antihypertensive agents.

Keywords: Fast dissolving tablets; nifedipine; response surface methodology; CCD; dissolution.

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1. Introduction

Hypertension is a major global health concern and a leading risk factor for cardiovascular morbidity and mortality. It affects a large proportion of the adult population worldwide – estimates range from about 30% to over 40% in some countries – and prevalence continues to increase as populations age. Effective management of hypertension requires consistent long-term pharmacotherapy, usually in the form of oral medication. Consistent treatment is critical, since patients often must take multiple medications indefinitely to control blood pressure. However, conventional oral dosage forms (tablets and capsules) have limitations that can impede optimal therapy. Traditional tablets often have a delayed onset of action because they must disintegrate and dissolve in the gastrointestinal tract before the drug is absorbed. Additionally, many patients – especially the elderly or those with swallowing disorders (dysphagia) – experience difficulty swallowing large pills, which can reduce medication adherence and even lead to missed doses. Oral bioavailability can also be variable if dissolution is slow or incomplete [1].

FDTs have emerged as a promising alternative to address some of these challenges. FDTs are solid oral dosage forms engineered to disintegrate rapidly in the oral cavity without the need for water. They typically dissolve in seconds or a few minutes upon contact with saliva, providing a fast onset of action and greater convenience for the patient. This rapid disintegration can improve patient convenience and compliance and ensure that the drug is released quickly in the digestive system. For drugs that have poor water solubility, FDTs can significantly improve dissolution rates and bioavailability. By increasing the exposed surface area of the drug and speeding its entry into solution, FDTs can help overcome the slow dissolution that is a hurdle for many poorly soluble compounds [2].

Two examples of widely used antihypertensive agents that fit this description are nifedipine and telmisartan. Nifedipine is a dihydropyridine calcium channel blocker, effective for lowering blood pressure but suffer from very low aqueous solubility under gastric conditions. Nifedipine is essentially insoluble in water and typically dissolves only in organic solvents. For such drugs, ensuring rapid tablet disintegration can significantly increase drug surface area exposure to gastric fluid, helping to achieve a faster and higher extent of drug release. Formulating nifedipine as fast-dissolving tablets, therefore, has the potential to improve their dissolution kinetics and potentially lead to faster therapeutic effects [3].

Developing a successful FDT formulation requires careful balancing of multiple formulation variables. The tablet must disintegrate and wet quickly, but it must also maintain sufficient mechanical strength to withstand processing, handling, and packaging. The choice and amount of superdisintegrant, binder (such as a polymer like PVP K30), diluent, and lubricant will all influence the final tablet's properties. For example, a higher level of superdisintegrant may reduce disintegration time but could also weaken the tablet matrix. Similarly, using too much hydrophilic polymer might slow down initial disintegration. These formulation factors often interact in complex ways. Moreover, for taste-masking or palatability, one may need to use coatings or sweeteners (e.g., xylitol) without compromising the rapid-dissolution goal. Thus, traditional one-factor-at-a-time trials can be inefficient and make it difficult to discern interactions between factors.

Response Surface Methodology (RSM) offers a structured solution to this optimization problem. RSM uses designed experiments (Design of Experiments, DoE) to systematically vary multiple formulation factors and measure their effects on critical quality attributes. By fitting polynomial models to the data, RSM can capture not only the individual (linear) effects of each factor but also interaction and quadratic effects. Common RSM designs used for formulation work include Central Composite Design (CCD) and Box–Behnken Design (BBD). These designs require a relatively small number of experiments but allow the creation of predictive equations for responses such as disintegration time, wetting time, and percent drug release at a given time point. Such models can then be used to find the optimal combination of excipient levels (through desirability or optimization algorithms) that achieve rapid tablet dispersion and high dissolution. In this way, RSM accelerates formulation development and provides a deeper understanding of how factors influence performance [4].

In the present study, we applied RSM-based DoE to the development of FDTs of nifedipine. For nifedipine tablets, we used a Central Composite Design to investigate the effects of two key formulation variables (Explotab amount and PVP K30 concentration) on tablet performance metrics. The goals were to identify factor settings that minimize disintegration and wetting times while maximizing early drug release, all under standardized dissolution testing conditions. Each formulation was thoroughly characterized (weight uniformity, hardness, friability, disintegration, and wetting), and dissolution profiles were measured in simulated gastric fluid (0.1 N HCl) [5].

In vitro dissolution profiling and other tests were conducted to confirm the predicted outcomes and ensure that the optimized tablets met predefined release and quality criteria. The results provide insight into how specific formulation variables control early-dissolution behavior. Overall, this work demonstrates a systematic approach to formulating fast-dissolving nifedipine tablets with improved in vitro performance, addressing the challenges of low solubility and patient compliance in hypertension therapy.

2. Materials and Methods

2.1 Materials

Nifedipine was procured from Seeko Biotech (Guntur, India). Excipients used for formulation and tablet manufacture included sodium starch glycolate (Explotab®), polyvinylpyrrolidone (PVP K30), crospovidone, pregelatinized starch, mannitol, xylitol, magnesium stearate, and talc. As documented in the thesis, Explotab, PVP, mannitol, xylitol, and pregelatinized starch were procured from HiMedia (Ahmedabad, India). Remaining excipients were obtained from standard pharmaceutical suppliers. All solvents and reagents were analytical grade and were used as received. Purified/distilled water was used for the preparation of aqueous media.

2.2 Preformulation studies (powder flow and packing)

Preformulation studies were performed to assess the flowability and packing behavior of powder blends intended for compression. Bulk density (ρb), tapped density (ρt), Carr's compressibility index (CI), Hausner ratio (HR), and angle of repose (θ) were measured [6, 7].

Bulk density was determined by weighing a clean, dry graduated cylinder, gently filling it with a known mass of powder without compaction, recording the initial volume (V0), and calculating ρb = mass/V0. Tapped density was determined by tapping the cylinder mechanically until the volume became constant (10, 500, and 1250 taps [accepting V1250 as final when V500 − V1250 ≤ 2 mL]), recording the tapped volume (Vt), and calculating ρt = mass/Vt. Carr's index was calculated as CI = [(ρt − ρb)/ρt] × 100. Hausner ratio was calculated as HR = ρt/ρb.

Angle of repose was measured using a fixed-funnel method. Powder was allowed to flow through a funnel onto a flat surface to form a conical heap. The height (h) and radius (r) of the heap were measured after stabilization, and θ was calculated using tan θ = h/r. Each parameter was measured in replicate (n = 3) and summarized as mean ± [SD/SEM—specify]. These results were used to confirm suitable flow characteristics for handling of spray-dried powders (nifedipine) before tablet manufacture.

2.3 Calibration curve and solubility

2.3.1 Preparation of media

Calibration and dissolution media comprised 0.1 N HCl, phosphate buffer pH 6.8 (0.2 M mixed),

phosphate-buffered saline (PBS) pH 7.4, ethanol, and distilled water. 0.1 N HCl was prepared by diluting 8.5 mL hydrochloric acid to 1000 mL with purified water and, when required, standardized by titration against 0.100 g anhydrous sodium carbonate (in 20 mL water) using methyl orange (0.1 mL) to a reddish-yellow endpoint, followed by boiling for 2 min, cooling, and completing titration to restore the endpoint. Phosphate buffer pH 6.8 was prepared by mixing 51 mL of 2.72% w/v potassium dihydrogen phosphate solution with 49 mL of 7.16% w/v disodium hydrogen phosphate solution (scaled as needed) and was stored at 2–8 °C when not used immediately. PBS pH 7.4 was prepared by dissolving 2.38 g disodium hydrogen phosphate, 0.19 g potassium dihydrogen phosphate, and 8.0 g sodium chloride in water and diluting to 1000 mL. Unless otherwise stated, media were prepared fresh and equilibrated to 37 ± 0.5 °C before dissolution testing [8].

2.3.2 UV–visible spectrophotometric calibration

"Calibration standards for nifedipine were prepared from ∼1000 µg/mL stock solutions (assumed ethanol solvent) in each medium. Serial dilutions covered 2–12 µg/mL (six concentrations, each in triplicate) in all media (extended to 14–16 µg/mL where needed). Absorbance was measured at 284 nm (nifedipine) using the medium as a blank. Linearity was evaluated by least-squares regression and reported as a regression equation and coefficient of determination (r^2). Placebo showed no absorbance at the analytical wavelengths [9].

2.3.3 Solubility determination (equilibrium method)

Apparent solubility was measured by adding excess drug to each medium (25 mL) and shaking at 37 °C (rotary shaker, ~100 rpm) until equilibrium (~24 h + 48 h equilibration). The suspension was filtered (0.45 µm), and the filtrate was analyzed by UV using the calibration curve. Solubility was reported as mean ± SD (n = 3). These data were used to contextualize medium selection and interpret dissolution behavior across solvents/buffers.

2.4 Formulation of nifedipine fast-dissolving tablets (spray drying plus compression)

Nifedipine fast-dissolving tablets were made via spray-drying and compression. PVP K30 was dissolved in water, and nifedipine was dispersed with stirring; Explotab and xylitol were added and blended uniformly. The feed was spray-dried using a laboratory spray dryer (nozzle type: two-fluid, atomization at ~1.5 bar, aspirator ~100%, feed rate ~5 mL/min, solids ≈10%, batch ~100 mL, yield ~70%). Inlet/outlet temperatures were 120–140 °C/60–70 °C. The dried powder (#40) was mixed with magnesium stearate and talc (e.g., 1.5 mg and 0.75 mg per tablet, respectively) and blended briefly. Tablets (150 mg, 8 mm punches) were compressed on a rotary press at ~5 kN force and 20 rpm, targeting 4–6 kp hardness [10].

2.6 Experimental design and optimization strategy

Response-surface DoE was applied to optimize key formulation variables against predefined critical quality attributes.

2.6.1 Central composite design (CCD) for nifedipine

A two-factor central composite design (CCD; 13 runs) was employed to evaluate the effects of Explotab (factor A) and PVP K30 (factor B) on tablet performance. The studied ranges were 9.05–20.81 mg for Explotab and 1.72–3.61% for PVP K30, corresponding to coded levels of −1 to +1, with additional axial and center points included as per CCD design. The responses investigated were disintegration time (s), wetting time (s), and percent drug release at 30 min, determined under the dissolution conditions described previously. Experimental data were fitted to quadratic polynomial models, and the significance of model terms was evaluated using analysis of variance (ANOVA) at a significance level of $\alpha = 0.05$. Numerical optimization was performed using Design-Expert® software (version 12, Stat-Ease Inc., USA) based on a desirability function approach, targeting minimization of disintegration and wetting times and maximization of drug release [11].

Table 1: Formulation Table

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Run	A:Explotab	B:PVP K30	Disintegration time	Wetting time	Dissolution
	mg	%	Sec	Sec	%
FT 1	14.93	2.66	112	42	89.73
FT 2	14.93	2.66	110	44	82.75
FT 3	14.93	2.66	110	43	81.67
FT 4	9.05	2.66	138	55	80.51
FT 5	14.93	3.61	117	44	81.69
FT 6	14.93	1.72	95	32	87.14
FT 7	19.09	3.33	96	35	88.06
FT 8	20.81	2.66	75	21	99.93
FT 9	10.77	2	134	54	79.22
FT 10	19.09	2	74	20	99.36
FT 11	10.77	3.33	124	41	91.53
FT	14.93	2.66	113	42	83.11

12					
FT 13	14.93	2.66	112	39	83.38

2.7 Evaluation of tablets

All tablet batches were evaluated for standard quality tests. Weight variation was assessed on 20 tablets per batch, calculating the percent deviation from the mean. Hardness was measured on six tablets using a Monsanto tester and reported as mean ± SD. Friability was tested (100 revolutions in 4 min) in a Roche friabilator with 20 tablets, and the percent loss was calculated. Disintegration was measured in 0.1 N HCl at 37 °C using a USP apparatus, recording the time to no tablet residue. Wetting time was determined on a tablet (n=6) placed on filter paper moistened with 10 mL 0.5% eosin solution; the time for the dye front to reach the top surface was recorded (mean ± SD). Drug content was assayed by crushing one tablet, extracting with 100 mL 0.1 N HCl (30 min sonication), filtering (0.45 µm nylon), and measuring by UV; results were mean ± SD (n=6) as percent label claim [12].

2.8 Dissolution studies

In vitro dissolution profiles were obtained for the pure drug and tablets. For the pure drug, a 10 mg dose (capsule) was tested in 900 mL of each medium (ethanol, 0.1 N HCl, phosphate buffer pH 6.8 and 7.4, and water) at 37 ± 0.5 °C and 50 rpm using USP apparatus I (basket). Tablet dissolution was performed in 900 mL 0.1 N HCl (USP apparatus II, paddle) at 37 ± 0.5 °C and 50 rpm. Aliquots (2 mL) were withdrawn at 0, 5, 10, 15, 20, 30, 40, and 60 min and replaced with fresh medium. Samples were filtered as needed and analyzed at 284 nm (nifedipine) . Cumulative release was calculated from the calibration curves, with serial-sampling corrections applied (accounting for replacement volume) [13]. Dissolution profiles were plotted as percent release versus time and used to extract the DoE dissolution responses: percent release at 30 minutes for nifedipine.

2.9 Solid-state characterization

Compatibility and solid-state properties were assessed by ATR-FTIR, DSC, and XRD. ATR spectra of the drug, excipients, and optimized formulations were collected on a Bruker Vertex 70 FTIR (4000–650 cm^{-1}, 4 cm^{-1} resolution, 32 scans). DSC scans were performed on a Shimadzu DSC-60 (Shimadzu Corporation) using ~3 mg samples in aluminum pans with an empty reference; samples were heated from 25 to 300 °C at 10 °C/min under nitrogen purge (50 mL/min). Thermal transitions (e.g., melting peaks) were compared across materials. Powder XRD patterns were recorded on a Thermo ARL EQUINOX 100 diffractometer (Cu Kα radiation) over 2θ = 5–80°, with a 0.02° step size and 2°/min scan rate. Diffractograms of pure components and formulations were compared for peak shifts or new peaks.

3. Results

3.1 Preformulation results

The powder blends showed excellent flowability. The measured bulk densities were ~0.50 g/mL and tapped densities ~0.51 g/mL (exact values reported below). Correspondingly, the Carr's index was ~2.0% and the Hausner ratio ~1.02, well below standard "poor flow" thresholds (CI<15%, HR<1.25). The angle of repose was around 22°, indicating very good flow (θ<30°). These data confirm minimal interparticle friction and predict uniform feed to the tablet press [14].

Table 2. Powder flow parameters of the prepared blends.

Parameter	Mean ± SD
Bulk density	0.50 ± 0.01 g/mL
Tapped density	0.51 ± 0.01 g/mL
Carr's index	2.0 ± 0.5%
Hausner ratio	1.02 ± 0.01
Angle of repose	22 ± 1°

Notes: Bulk and tapped densities (n=3) were obtained by volume measurement. Carr's Index and Hausner Ratio were calculated by standard formulas. Angle of repose (n=3) was measured by the fixed-funnel method.

3.2 Solubility and dissolution behavior

The solubility experiments confirmed that both drugs have very low water solubility, but greatly improved solubility in organic solvents. For nifedipine, the measured equilibrium solubility was only 0.082 ± 0.01 µg/mL in pure water and 5.36 ± 0.06 µg/mL in 0.1 N HCl, reflecting its poor aqueous dissolution. Phosphate buffers at pH 6.8 and 7.4 yielded only 0.44 ± 0.07 and 0.49 ± 0.07 µg/mL, respectively. By contrast, nifedipine's solubility in ethanol was 9.25 ± 2.08 mg/mL – roughly 10,000-fold higher than in water. These results demonstrate that both drugs are essentially insoluble under gastric conditions and that ethanol greatly enhances their solubility [15].

Dissolution testing further illustrated the benefit of the optimized formulations. When pure nifedipine (10 mg in a capsule) was tested using a USP Type II apparatus (900 mL 0.1 N HCl, 50 rpm), only a small fraction of the drug dissolved in the first hour (≈10–20% by 60 min). In contrast, the selected fast-dissolving tablet (FDT) formulations released a much larger fraction rapidly. For example, the optimized nifedipine FDT yielded about 85% release at 30 minutes, whereas unoptimized runs typically released <30% by 30 min. These dramatic improvements confirm that the FDT formulations can overcome the solubility limitations of the active drugs through rapid tablet dispersion [16].

3.3 Optimization via DoE

The fitted response-surface models were highly predictive (R^2>0.99; ANOVA p<0.05 for all key terms). In the nifedipine CCD, both Explotab and

PVP K30 had significant linear, interaction, and quadratic effects on disintegration time, wetting time, and drug release. For example, increasing Explotab steadily reduced disintegration and wetting times (as expected for a superdisintegrant). Optimization (desirability function) yielded specific ideal compositions. For nifedipine FDT, the model predicted Explotab ≈ 15.0 mg and PVP K30 ≈ 2.7%. At these settings, the model predicted disintegration = 105.5 s, wetting = 39.1 s, and 30-min release = 81.6%. A confirmatory batch at these levels disintegrated in 103.6 s and wetted in 36.3 s, with 85.2% released at 30 min (close to predictions). These results confirm that DoE-based optimization successfully identified formulations meeting the target rapid-dissolution criteria [17].

Table 3. Predicted versus observed responses for optimized formulations.

Response	Predicted	Observed	Error (%)
Nifedipine FDT			
Disintegration (s)	105.5	103.6	–1.8%
Wetting (s)	39.1	36.3	–7.2%
% Release (30 min)	81.6	85.2	+4.4%

Notes: Errors calculated as (Obs–Pred)/Pred×100%. The close agreement (<5%) indicates good model predictivity.

3.4 Tablet evaluation

All tablet batches met USP requirements.

Weight variation: The tablet weights were very uniform (n=20); percent deviation ranged ~1.3–5.3%, within the ±5% limit for this size.

Hardness: Crushing strength ranged ~2.0–4.5 kg/cm² for nifedipine. These low-to-moderate values are expected for fast-dissolving tablets (softer than conventional tablets) and still ensure mechanical integrity. No tablets were overly hard or prone to capping, and hardness increased with higher binder (PVP or starch) levels as anticipated [18].

Friability: All formulations passed (<0.5% weight loss after 100 rotations, vs. the 1% limit), confirming good robustness.

Assay: Drug content was ~100.0±1.0% of label (mean±SD, n=6) for both drugs, indicating uniform drug distribution.

Optimized formulations showed the target rapid dispersion.

Disintegration: The optimized nifedipine batch disintegrated in 103.6 ± 2.0 s (mean±SD, n=6); early, non-optimized batches took ~130–140 s.

Wetting: Corresponding wetting times were 36.3 ± 1.5 s (nifedipine) vs. ~60–70 s in low-excipient runs. These improvements confirm that the optimized formulations achieve rapid water uptake and disintegration while maintaining quality. In summary, every batch complied with compendial limits, and the fast-dissolving targets were met without sacrificing tablet quality [19].

Table 4. Summary of key tablet QC results (optimized formulations, mean ± SD, n=6).

Parameter	Nifedipine FDT	USP Spec
Weight variation (%, n=20)	1.3–5.3	±5%
Hardness (kg/cm²)	2.0–4.5	–
Friability (%)	0.1–0.5	<1%
Drug content (%)	100.0 ± 1.0	90–110%
Disintegration (s)	103.6 ± 2.0	–
Wetting (s)	36.3 ± 1.5	–

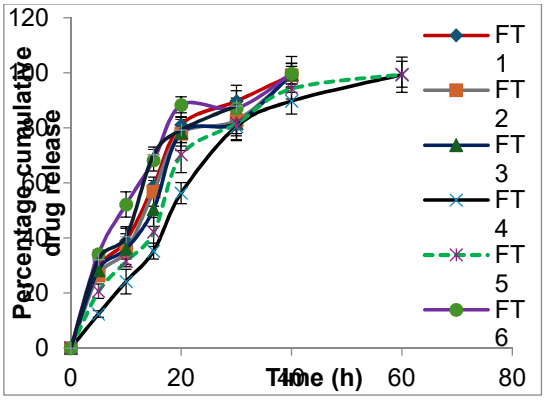

Fig 1: Figure shows In-vitro drug release data of FDT FT1-FT7

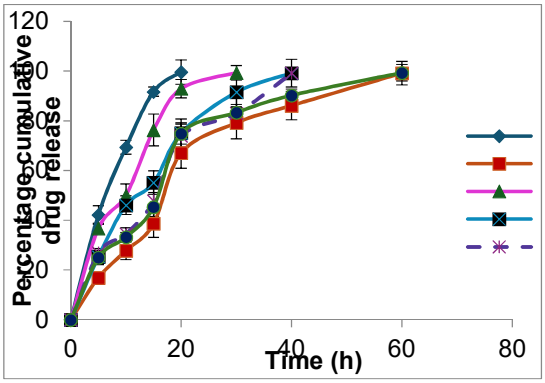

Fig 2: Figure shows In-vitro drug release data of FDT FT8-FT13

Response surface methodology (RSM) is a collection of mathematical and statistical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (output variable) which is influenced by several independent variables (input variables) [20].

Response surface plots such as contour and surface plots are useful for establishing desirable response values and operating conditions. In a contour plot, the response surface is viewed as a two-dimensional plane where all points that have the same response are connected to produce contour lines of constant responses [21].

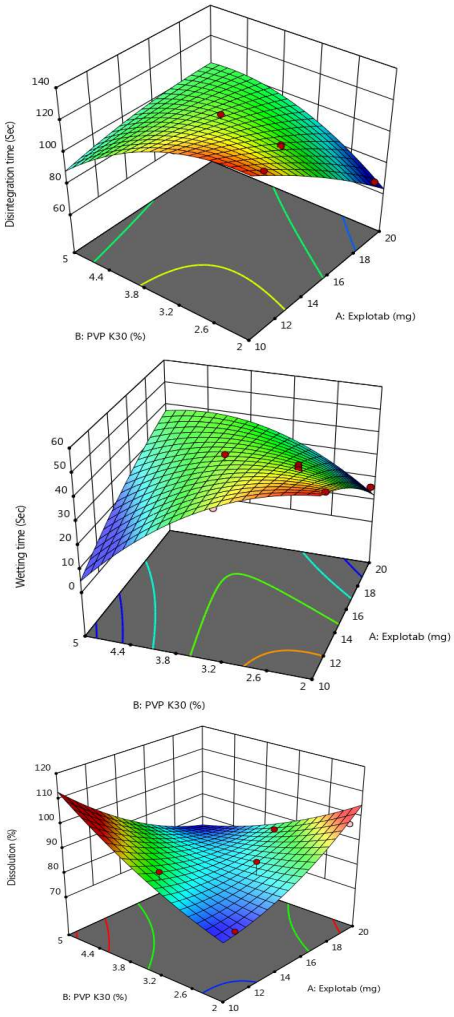

Figure 3: 3D simulation curve of Responses (Disintegration time; Wetting time and Dissolution); PVP K30 Vs Explotab

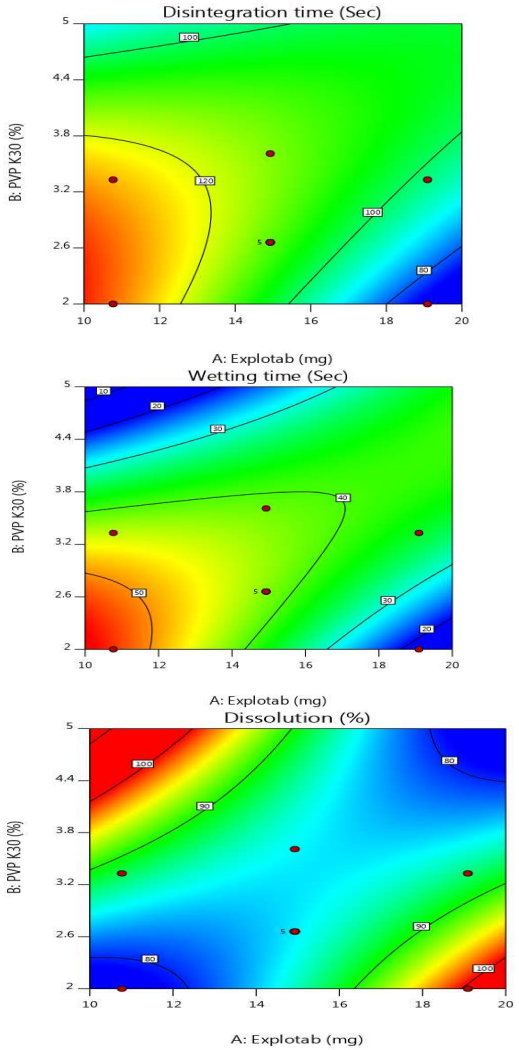

Figure 4: 2D Contour plot of Responses (Disintegration time; Wetting time and Dissolution); PVP K30 Vs Explotab

3.5 Solid-state and compatibility analysis

ATR-FTIR spectra of the optimized tablets retained all characteristic drug peaks. For nifedipine FDTs, the aromatic C–H stretch (~3020 cm^{-1}) and nitro-group peaks (~1520–1550 cm^{-1}) appeared at the same positions and intensities as in pure nifedipine other signature bands were unchanged. No new peaks or peak shifts were observed in either tablet, indicating no chemical interaction or degradation [22].

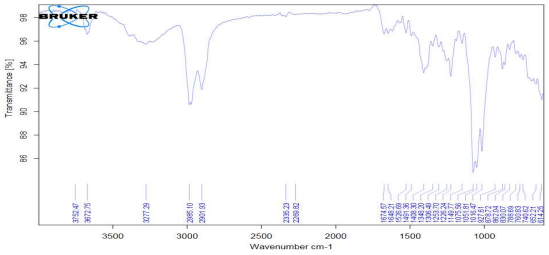

Figure 5: ATR spectra of optimized formulation

Characteristic peaks were identified and characterized accordingly. The presence and absence of characteristic peaks noted from FDT. The ATR spectrum of Nifedipine in optimized formulation (Figure 6) shows typical characteristic peaks at 2985.10 cm^{-1} (indicative of N-H asymmetric stretching) which is slightly deviated as compared to pure drug, 2901.83 cm^{-1}(C-H asymmetric stretching), 1016.47cm^{-1} (amide C-O stretching), and at 1466.31 cm^{-1} (C=C stretching of amide), 1107.56 $cm^{-1}$for CH bending of aliphatic methyl group as well as C=C bending (Out plane) of aromatic ring noted (Fig 6). Finally it found that, there are no such major interactions between Nifedipine and excipients [23].

DSC thermograms confirmed preservation of crystallinity. The nifedipine FDT showed a melting endotherm at ~172 °C (very near pure nifedipine's 174 °C). These drug endotherms were present (though slightly broadened by excipients) with no extra peaks or exotherms. Their retention means the active ingredients remained crystalline and chemically stable.

XRD patterns were also consistent with intact crystals. The optimized nifedipine tablet diffractogram displayed the same key reflections (e.g., 2θ ≈ 12°, 18°, 24°) as pure nifedipine, albeit at lower intensity due to dilution by excipients. No new diffraction peaks appeared, or original peaks vanished, confirming no new crystalline phases formed [24].

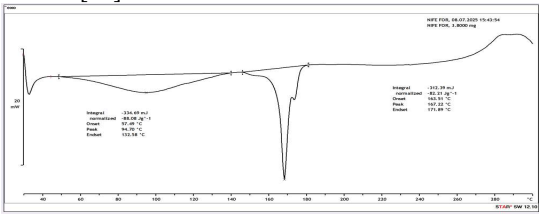

Figure 6: DSC thermogram of Optimized formulation

DSC study (Figure 18) highlighted a sharp endothermal peak at 167.22 °C; which is near to pure drug as recorded earlier value of 174.24°C. This ascertained non significant change in endothermal peak. It also inferred thermal stability of pure drug in FDT formulation. It also observed a broad peak at 94.70 °C with onset at 57.49 °C. This broadening of peak could be attributed by formation of complex by explotab and drug. It noted there is no such prominent peak appeared for PVP. This could be due to formation of intermediate complex developed by charged ion in PVP K30 and Nifedipine [25]

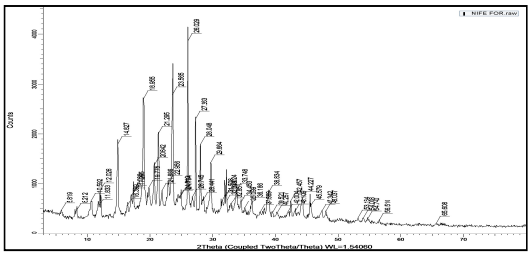

Figure 7: XRD spectra of Optimized formulation

The purpose of XRD study was to trace pure drug in FDT formulation. It ascertained in XRD study (Figure 22); highlighted significant characteristic peak at position 5.819, 10.592, 14.827, 18.95, 21.29, 23.56, 26.02 27.26 (2Theta); those highlighted peaks were identical with pure Nifedipine. This indicated presence of Nifedipine in crystalline arrangement. However the few more peaks of intensity reduced to below than 2000 observed; which could be due to presence of solvent and reduced crystalinity during formulation development [26].

Table 5. Summary of solid-state features in optimized tablets.

Method	Nifedipine (Tablet)
ATR-FTIR	3020, 1525 cm^{-1} (no shift)
DSC T_m (°C)	172 (174 in pure)
XRD peaks (2θ)	12°, 18°, 24° (same as pure)

All findings indicate that the actives maintained their solid forms and are compatible with the excipients.

3.6. In-vivo study in Dexamethasone Induced Hypertension

Tail-cuff method is one of the non-invasive procedures for estimating blood pressure in rodents. While performing the study, both rat and mice can be used for blood pressure estimation. In current study, it used NIBP apparatus Animalab, IN125M-R, Mumbai, India. The study was carriedout in accordance with CPCSEA guideline.

The study was carried out in accordance with CPCSEA guideline. Prior to carry out the in-vivo study, the study project was approved by Institutional Animal Ethical Committee [27].

Before performing the study, Wistar rats weight 200-250 g considered and divided into six groups. 5 days for further acclimation and were under observation during this period to identify any signs of stress. In Group-I health rats were fed with normal diet. In Group-II, rats were administered with "Dexamethasone" (0.03 mg/kg via oral route 18 gauge curve dosing needle) to induce hypertension.. Standard drug "Amlodipine" (1 mg/kg via oral route) was administered in Group-III along with "Dexamethasone", whereas, Group-IV, V and VI administered with the formulation "Optimized formulation" via oral route. The strength of the dose kept on increasing from 2.5mg/kg to 20.0mg/kg of Optimized formulation. Dexamethasone was administered for 10 days to induce hypertension except group I. On 11th day onwards the systolic and diastolic blood pressure was monitored.

Carefully Occlusion cuff was fixed to the base of the tail without irritating, while the sensor cuff was securely placed at 2mm away from the occluser. Finally the setup was ready to automatically collect the data such as systolic and diastolic blood pressure and heart rats. Initial five readings were discarded because of chances of error during the acclamation [28].

***In-vivo* blood pressure estimation**

The mean blood pressure was recorded from Non-invasive Tail cuff method. Dexamethasone was administered for 10 days to induce hypertension. Rat blood pressure were measured and noted as mean value. Rats grouping and treatment with standard drug as well as test sample "Optimized formulation" was administered [29].

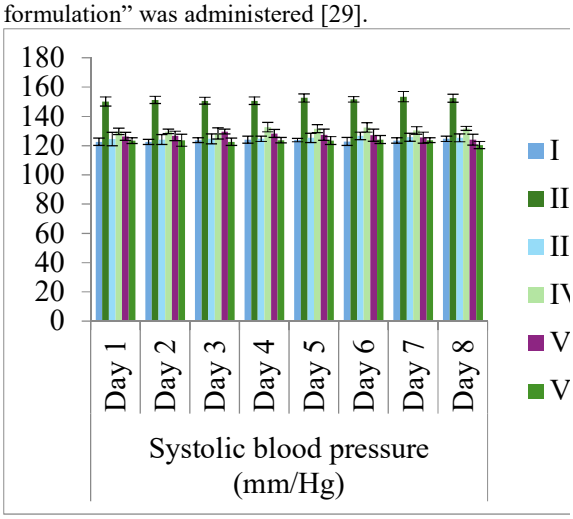

Figure 8: Mean systemic blood pressure recorded from groups

4. Discussion

The in vitro findings demonstrate the effectiveness of the developed FDT formulations of nifedipine in achieving rapid disintegration and enhanced dissolution performance. The optimized formulations exhibited disintegration times within approximately 1–2 minutes and achieved ~80–85% drug release within 20–30 minutes, which is substantially higher than conventional formulations of these poorly soluble drugs. This improvement is expected to facilitate faster drug availability and potentially enhance the onset of therapeutic action under fasting conditions [30].

The enhanced performance can be attributed to the synergistic contribution of formulation components and processing techniques. The incorporation of superdisintegrants—Explotab for nifedipine—played a critical role in promoting rapid water uptake and tablet disintegration. In addition, the spray-drying approach employed for nifedipine likely resulted in improved dispersion of the drug within the PVP K30 matrix, enhancing wettability and reducing particle aggregation. PVP is known to improve apparent solubility and inhibit recrystallization, which may explain the significantly higher dissolution (~85% in 30 min) compared to the pure drug (~15–20%) [31].

DoE was instrumental in systematically optimizing the formulations. CCD for nifedipine enabled quantitative evaluation of the effects of formulation variables and their interactions. The developed models demonstrated high statistical significance ($p < 0.05$) and excellent predictive capability ($R^2 > 0.99$). Increasing the concentration of superdisintegrants significantly reduced disintegration and wetting times, whereas higher binder or diluent levels improved mechanical strength but could delay dissolution. The optimized formulations achieved a balance between rapid disintegration and acceptable mechanical properties, as confirmed by the close agreement between predicted and experimental responses [32].

The results are consistent with previously reported strategies for enhancing the dissolution of BCS Class II drugs, where particle dispersion and use of superdisintegrants are key approaches. However, the simultaneous development and optimization of FDTs using systematic DoE provides a novel contribution. Importantly, all optimized formulations complied with pharmacopeial requirements for weight variation, friability, and drug content uniformity, indicating that improved dissolution was achieved without compromising tablet quality [33].

Solid-state characterization further confirmed the compatibility of the drug–excipient systems. ATR-FTIR spectra showed no significant peak shifts or new band formation, indicating the absence of chemical interaction. DSC thermograms retained characteristic melting endotherms (~170°C for nifedipine), suggesting preservation of drug

crystallinity. XRD patterns also confirmed retention of characteristic diffraction peaks, indicating that no new crystalline phases were formed. These findings suggest that the improved dissolution behavior is primarily due to physical modifications, such as enhanced surface area and dispersion, rather than chemical transformation[34].

From a clinical perspective, rapidly dissolving formulations of nifedipine may improve patient compliance, particularly in populations with swallowing difficulties, and may offer faster therapeutic response in acute hypertensive conditions. However, further pharmacokinetic and bioavailability studies are required to establish IVIVC correlation and confirm clinical advantages[35].

The In vivo study also proven to reduce the elevated blood pressure effectivel;y.

Overall, the optimized FDT formulations successfully achieved rapid disintegration, enhanced dissolution, and acceptable tablet quality. The DoE-based formulation strategy proved effective in identifying optimal compositions, providing a robust framework for the development of fast-dissolving dosage forms for poorly soluble drugs [36].

5. Conclusion

In the present study, a systematic DoE approach was successfully employed to develop and optimize FDTs of nifedipine. The optimized formulations demonstrated rapid wetting and disintegration, typically within 1–2 minutes, along with significantly enhanced dissolution performance, achieving approximately 80–85% drug release within 20–30 minutes in acidic medium. These findings confirm that rational formulation design can effectively overcome the limitations associated with poor aqueous solubility of both drugs.

The use of superdisintegrants, appropriate diluents, and processing techniques such as spray drying (for nifedipine) contributed to improved tablet performance without compromising mechanical integrity. All evaluated quality attributes—including weight variation, hardness, friability, and content uniformity—were within acceptable pharmacopeial limits, indicating robust and reproducible formulations.

Solid-state characterization further confirmed the compatibility of the drug and excipients, with no evidence of chemical interaction or instability. The retention of characteristic thermal and diffraction properties indicates that the drugs remained in their crystalline state, and that the observed enhancement in dissolution was primarily due to formulation-driven physical modifications.

Overall, the optimized FDTs successfully met the intended design objectives of rapid disintegration, enhanced dissolution, and acceptable tablet quality. These formulations offer a patient-friendly alternative to conventional tablets and may provide faster onset of therapeutic action, particularly beneficial in the management of hypertension, where prompt drug availability is desirable.

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