Formulation, Optimization and Evaluation of Nanoparticulate Oral Fast Dissolving Film Dosage Form of Nitrendipine

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Abstract

The primary objective of the present research work was to develop nanoparticles incorporating (nanoparticulate) fast dissolving (orodispersible) film evincing enhanced solubility and bioavailability of nitrendipine (NIT). An antisolvent sonoprecipitation method was employed to produce the NIT nanosuspension (NS), which was optimized using the 3^2 optimal response surface design and then the optimized one was evaluated for various

parameters (Gandhi *et al.*, AAPS PharmSciTech 22 (1):1–15, 2021). The NIT nanoparticulate orodispersible film (N-ODF) was prepared utilizing the nanosuspension by the solvent casting method using the Vijay film-forming instrument. The N-ODF was optimized by the 2^3 full factorial design and was evaluated for several parameters. The optimized NS depicted a particle size of 505.74 ± 15.48 nm with a polydispersity index (PDI) of 0.083 ± 0.006 (Fig. 1b). The NIT nanoparticles showed a striking increment in saturation solubility (26.14 times), when compared with plain NIT (2). The developed NIT N-ODF exhibited thickness (0.148 ± 0.008 mm), folding endurance (280.33 ± 5.51 times), surface pH (6.86 ± 0.05), tensile strength (8.25 ± 0.13 kg/cm^2), % elongation (63.5 ± 1.97%), and disintegration time (24.60 ± 1.31 s) to be within the standard intended limit. The *in vitro* dissolution study unveiled 100.28 ± 2.64% and 100.68 ± 2.50% of NIT release from lyophilized nanocrystals (in 8 min) and N-ODF (in 3.5 min), respectively, whereas the conventional NIT tablet took 30 min to release 99.94 ± 1.57% of NIT (Gandhi *et al.*, AAPS PharmSciTech 22 (1):1–15, 2021). The *in vivo* pharmacokinetic study in rabbits inferred the achievement of significantly ($p < 0.05$) higher bioavailability of NIT on release from N-ODF in comparison to the conventional NIT tablet. Thus, the generation of N-ODF can be considered as a propitious move toward improving the efficacy of NIT to treat hypertension and angina pectoris.

INTRODUCTION

The low solubility of an active pharmaceutical ingredient (API) is one of the crucial aspects involved in the development of efficacious pharmaceuticals. Erratic absorption and thereby low oral bioavailability are the repercussions of poor solubility drug products. Around 40% of new chemical entities (NCEs) originating from drug discovery screens display low aqueous solubility (3). Such drugs fall into class II (low solubility and high permeability) or class IV (low solubility and low permeability) category of the biopharmaceutical classification system (BCS) (1, 4). Thus, one of the most exacting endeavors in drug development is to elevate drug solubility with the intention to enrich the bioavailability of these pharmaceutical entities. Various tactics to prevail over such constraints comprise the formation of polymorphs, hydrates, and solvates; solubilization employing surfactants; complexation with cyclodextrins; hydrotrophy; solid dispersions; and decreasing particle size by micronization or nanonization (5).

Particle size reduction pops up to be a powerful approach for enhancing effective surface area of drug particles, thereby increasing solubility, rate of dissolution, and absorption, and thus, bioavailability of the drug is enhanced consequently (6). However, micronization fails to elevate the saturation solubility of compounds (6, 7). Therefore, a further inventive step of nanonization came forth. Nanonization refers to the reduction in particle size of the drug to nanometer range (<1 μm), resulting in the generation of nanosized dispersions called nanosuspension or nanoemulsion (8). Nanosuspensions are defined as submicron colloidal dispersions of API particles (size below 1 μm) in a liquid phase, which are stabilized by surfactants and/or polymeric steric stabilizers. To improve the solubility of hydrophobic drugs, nanosuspensions have been considered a novel tool for over a decade. This can be attributed to the ease and effectiveness of the technique, which can swiftly launch the drug product commercially (9).

Nitrendipine (NIT) is a dihydropyridine calcium channel blocker (CCB) that acts chiefly by causing coronary and systemic arteries to dilate, and thereby, increased oxygen delivery to the

myocardial tissue is manifested (10). This makes NIT a potent drug to treat hypertension and angina pectoris. It is a practically water-insoluble drug belonging to BCS class II with a solubility of around 1.9–2.1 μg/ml in water at 37°C (11). Furthermore, NIT goes through substantial first-pass hepatic metabolism and exhibits a poor oral bioavailability (10–20%) in humans (12). Hence, there is an unfulfilled necessity to develop a novel formulation that can increase the solubility and dissolution rate of NIT along with minimization of its presystemic metabolism so as to curb the poor bioavailability associated with NIT swimmingly.

Therefore, the prime objective of the present research work was to develop and characterize nanoparticulate solid oral drug delivery system of NIT by integrating the optimized batch of formulated drug-loaded nanosuspensions with fast dissolving film dosage form, so as to proffer enhanced solubility, dissolution rate, bioavailability, and rapid onset of action of NIT.

Fast dissolving film (FDF) is the pharmaceutical dosage form intended to self-disperse rapidly within seconds, in contact with the hydrating environment of the oral cavity in the form of saliva (13,14,15). This fast dissolving drug delivery system (FDDDS) has been developed to render a rapid onset of action of a drug by gaining immediate plasma drug concentration mediated through the tongue's rich vascular network. The dosage form also intends to minimize first-pass hepatic metabolism through bypassing the liver, as a consequence of favored pregastric absorption of NIT. The use of FDF to deliver medicine into the buccal cavity has gained a huge heed in the recent era because of several advantages like ease of administration; improved patient acceptability; transportation friendliness; convenience of swallowing for dysphasic, pediatrics, and geriatrics patients; and improved bioavailability along with quick onset of action of the drug (16, 17).

In this study, an antisolvent sonoprecipitation method was used to develop a nanosuspension (NS) with a nanorange and uniform particle size. The impact of process parameters on the particle size of NS was studied employing the 3^2 optimal response surface design, and the obtained data was statistically analyzed by analysis of variance (ANOVA). The formulated NS was evaluated for several parameters like particle size and size distribution, saturation solubility, *in vitro* drug release, and stability study of nanocrystals (NCs) procured by lyophilization of the optimized NS. The NS was further transformed to orodispersible film through the solvent casting method using a film-forming instrument (Vijay Instruments,

India). The fabricated nanoparticulate orodispersible film (N-ODF) was optimized by the 2^3 full factorial design (FFD) using the Stat-Ease Design Expert software version 10, and ANOVA was implemented to analyze the obtained data statistically. Furthermore, the optimized N-ODF was evaluated by several methods including determination of organoleptic properties, thickness, weight variation, folding endurance, surface pH, moisture content, moisture uptake, tensile strength, % elongation, dispersion time, disintegration time, drug content uniformity, differential scanning calorimetry (DSC) analysis, powder X-ray diffraction (P-XRD) analysis, stability feature, *in vitro* dissolution, and *in vivo* pharmacokinetic profile in comparison to conventional NIT tablet.

MATERIALS AND METHODS

Materials

NIT was procured as a gift sample from Concept Pharmaceuticals Ltd., Aurangabad (M.S.), India. Hydroxypropyl methylcellulose-E6 (HPMC), polyvinyl alcohol (PVA), croscarmellose sodium (CCS), polyethylene glycol-400 (PEG-400), polyethylene glycol-200 (PEG-200), potassium dihydrogen phosphate, and sodium hydroxide were acquired from Vijay Scientific Supplies, Aurangabad. Octanol and acetone were bought from Dodal Enterprises, Aurangabad. All the materials and reagents utilized for the research project were of analytical grade.

Methods

Preparation of Nanosuspension

Nanosuspensions were prepared by an antisolvent sonoprecipitation method (18, 19). An antisolvent solution was prepared by dissolving HPMC-E6 in 20 ml of distilled water maintained at a temperature below 5°C utilizing an ice bath. Furthermore, a drug solution was prepared by dissolving 480 mg of NIT in 8 ml of solvent mixture of acetone:PEG-200 (1:1 v/v). Both the solutions were then passed through a 0.45-μm filter. Then, the drug solution in a volume of 4 ml was pushed rapidly through a needle (24 G) placed vertically over the antisolvent solution being stirred at 900 rpm to develop a suspension. The obtained suspension was instantly transferred to a Nessler's tube (2.5 cm diameter) and subjected to probe ultrasonication for a period of ultrasound burst set at 3 s with a pause of 3 s between two

consecutive ultrasound bursts, to finally obtain the NS. The whole process was conducted at a temperature below 5°C to accelerate the nucleation rate and minimize the crystal growth rate (2).

Optimization of NS

The 3^2 optimal response surface design was employed to optimize the NS formulations (20). The concentration of HPMC-E6 and the time length of probe ultrasonication were selected as the independent variables or factors. The influence of these factors was studied on the particle size of NIT, chosen as the dependent variable or response (2).

The obtained optimized NS was rapidly frozen in liquid nitrogen and lyophilized under vacuum (pressure < 10 Pa) for 15 h to obtain a fluffy dry powder (nanocrystals) soluble in water and was evaluated further.

Evaluation of NS

The optimized nanosuspension was evaluated for particle size, drug content, saturation solubility, *in vitro* drug release, and stability characteristics as per the previously reported established procedures (2).

Preparation of Nanosuspension-Loaded ODFs

NIT N-ODF was prepared by the solvent casting method using the film-forming instrument (Vijay Instruments, India) (21,22,23). An accurately weighed amount of HPMC-E6 was dissolved in an appropriate volume of distilled water by stirring at 1100 rpm uniformly for 15 min. Then PVA was added into the solution to generate a polymeric film casting solution with continued stirring for 2 h. A certain volume of the obtained optimized NIT nanosuspension without lyophilization (2) was added into the casting solution and stirring was further continued for 1 h. Next, the superdisintegrant (CCS) was accurately weighed and mixed into the drug–polymer film casting solution with continued stirring again for the next 1 and 1/2 h. Finally, the plasticizer (PEG-400) was dropped into the solution with stirring for one more hour. Then the solution was kept aside overnight for clearance of all the bubbles. The next day, it was dragged onto the film-forming instrument set at 63°C and the solution was left over the instrument for 45 min to obtain a uniformly dried film.

Optimization of N-ODFs

The 2^3 FFD was employed to optimize N-ODFs (24) using the concentration of film-forming polymers, concentration of plasticizer, and concentration of superdisintegrant as independent variables. The effect of variation of these three factors at two different levels was studied on dispersion time and film characteristics, chosen as dependent variables or responses. Initially, placebo films were prepared to figure out a balanced concentration of all the ingredients, with an intention to achieve the desired film characteristics and dispersion feature (Table I). Then a total of 8 runs were prepared as presented in Table II. The data procured was treated with a software and design matrix and analyzed statistically using ANOVA. Formulation F5 cropped up as the optimized one.

Table I Formulation of Preliminary Placebo ODFs

Table II Formulation and Optimization of NIT N-ODFs

Evaluation of N-ODF

Differential Scanning Calorimetry Analysis

Plain NIT, NIT in physical combination with different polymers individually (1:1% w/w), and NIT N-ODF were analyzed by the DSC analytical technique. A differential scanning calorimeter (TA-60WS Thermal Analyzer, Shimadzu, Japan) was used to record the thermograms of the samples by heating those at temperatures ranging from 30 to 300°C in a dry nitrogen atmosphere at a scan rate of 10°C/min. Al_2O_3 pan served as the reference material (11, 25).

Fourier Transform Infrared Spectroscopic Analysis

A Fourier transform infrared (FTIR) spectrophotometer (Shimadzu Corporation) was used to analyze the samples like plain NIT and NIT in physical combination with different polymers

separately (1:1% w/w) over the wave number 4000 to 500 cm^{-1} using KBr pellets, with the aim to determine the compatibility between drug and excipients. Small quantities of samples were placed in KBr pellets and then positioned into the sample holder. The infrared spectrum was acquired by uniform scattering of the sample (26).

Powder X-Ray Diffraction Analysis

An X-ray diffractometer (VirTis Advantage Plus at Wockhardt Ltd., Aurangabad, M.S., India) was used to determine the crystallinity of plain NIT and NIT N-ODF employing Cu-Kα radiation at a λ of 1.54 Å and voltage (V) of 40 kV, 50 mA. The samples were scanned through 5° to 60° diffraction angle (2θ) in increments of 0.02° at 1 s/step, putting to use a zero background sample holder (27, 28).

Organoleptic Properties

The optimized N-ODF was evaluated for color, odor, uniformity of appearance, texture, smoothness, and softness by physical touch and visual observation, as these are some important criteria for assessing the intake acceptance of such delivery systems (29).

Thickness

The thickness of the film (required for 10 mg of drug dose delivery, with a dimension of 2 × 3 cm^2) at five different locations (center and four corners) was determined using a digital thickness gauge (Vijay Instruments, India). The test was conducted thrice and the average value was recorded. Uniformity in the thickness of the film is a salient feature as it is directly related to the drug content uniformity of the film (30).

Weight Variation

Uniformity in weight (wt.) was determined by weighing ten films individually on a digital weighing balance (AUX220, Shimadzu Corporation, Tokyo, Japan) and the average weight was computed. The individual weight of each film was collated with the computed average weight and % deviation was documented. The test was performed thrice and the result was recorded as mean ± SD in g (31).

Folding Endurance

A film was folded and unfolded repeatedly at an identical location till it broke. The number of times the film was bent over on itself at a particular position without breaking was documented as folding endurance. The experiment suggests the extent of flexibility or brittleness of the film (32, 33).

Surface pH

The prepared N-ODF was moistened with 0.5 ml of distilled water in a Petri dish for 30 s. The pH meter electrode was brought in touch with the surface of the film for 1 min, allowing equilibration. Then the pH value was recorded employing a digital pH meter (Testronix, India). Three determinations were undertaken and the average value along with the standard deviation (SD) was documented. Determination of the surface pH of the film is of vital importance as oral mucosal irritation can be a consequence of the acidic or basic pH of the film (34).

Moisture Content

Accurately weighed N-ODF was placed in a desiccator accommodating fused anhydrous calcium chloride for 3 days. Subsequently, the film was taken off the desiccator and weighed again. The % moisture content of the film formulation was calculated by the following formula. The study was conducted three times (35).

$$ \%\mathrm{Moisture}\ \mathrm{content}=\mathrm{Initial}\ \mathrm{Wt}.-\mathrm{Final}\ \mathrm{Wt}./\mathrm{Initial}\ \mathrm{Wt}.\times 100 $$

Moisture Uptake

To determine % moisture uptake, three films were accurately weighed and then exposed to an environment of 75% relative humidity (RH) at room temperature (25 ± 2°C) for 7 days. After this, films were reweighed. The following formula was applied to estimate the uptake of moisture by the films (16):

$$ \%\mathrm{Moisture}\ \mathrm{uptake}=\mathrm{Final}\ \mathrm{Wt}.-\mathrm{Initial}\ \mathrm{Wt}./\mathrm{Initial}\ \mathrm{Wt}.\times 100 $$

Tensile Strength and % Elongation

The tensile strength and percent elongation of the films were evaluated by the Universal testing machine (International Equipments, Mumbai: INSTRON 3366-10 kN) equipped with a 10-kN load cell. Two clamps positioned at a distance of 3 cm from each other held the NIT N-ODF. At a rate of 5 mm/min, the film was pulled by the upper clamp until it rips apart, so as to facilitate the determination of the mentioned parameters (36).

Dispersion Time

To deduce dispersion time, 10 ml of PBS pH 6.8 kept at 37 ± 0.5°C was added to a beaker and the film was dropped over it. The point of time at which the film started rupturing was documented as the *in vitro* dispersion time. The test was conducted thrice (37).

Disintegration Time

The time required for full disintegration of each of the six films was measured as the disintegration time employing USP disintegration test apparatus (V-Scientific, India) with PBS pH 6.8 as simulated salivary fluid maintained at 37 ± 2°C. The basket-rack assembly bearing films in each of the cylindrical tubes was raised and lowered smoothly at a constant frequency of 28 to 32 cycles per minute through a distance of 50 to 60 mm. The experiment was executed in triplicate (38).

Drug Content Uniformity

In this study, five N-ODFs were used, where each film was shifted into a volumetric flask of 100 ml individually and was completely dispersed in a little amount of PBS pH 6.8. Then the volume of the flasks was made up by the buffer itself and was positioned on a sonicator (Toshcon, India) to get the drug nanoparticles completely dissolved. Through a membrane filter (0.45 μm), 1 ml of the solution was filtered and diluted up to 25 ml with the PBS again. The absorbance of this diluted solution was ascertained against PBS 6.8 as a blank employing a UV–visible spectrophotometer (Pharmaspec-1700, Shimadzu Corporation, Tokyo, Japan) at λ_{max} = 239 nm (39, 40).

In Vitro Dissolution Study

The *in vitro* drug release test of NIT from N-ODF was conducted in a cylindrical glass tube accommodating 30 ml of PBS pH 6.8 (simulated salivary fluid) as the dissolution medium

retaining a temperature of 37 ± 0.5°C and 100 rpm stirring speed and was compared with the conventional NIT tablet. This setup was chosen to avoid the floating of ODF over the dissolution medium surface. An N-ODF (equivalent to 10 mg of NIT) was dispersed into the dissolution medium, and at predecided time intervals of 0.5 min for 5 min, 3 ml of samples were withdrawn and the same volume of fresh medium was added immediately after the withdrawal. The withdrawn test samples were centrifuged and, after suitable dilutions of the collected supernatants with the dissolution medium, were analyzed at 239 nm using a UV–Visible spectrophotometer against the blank. The study was carried out thrice to create the drug release profile (36, 41).

In Vivo Pharmacokinetic Study

The *in vivo* pharmacokinetic study was performed after clearance from the Animal Ethical Committee (Savitribai Phule, Pune University). For the study, a total of 6 white rabbits (N = 6, n = 3 for each group and each formulation) weighing 2.3 ± 0.2 kg were utilized. The animals were fasted for around 12 h prior to the administration of the formulations, having unobstructed accessibility to water. "A" and "B" were the designations of two groups in which animals were randomly distributed, with three animals held by each group. An intravenous injection of phenobarbital at a dose of 25 mg/kg was given to animals of group A as anesthesia, so as to assure the retention of N-ODF in the oral cavity itself avoiding its slipping to the gastrointestinal tract. The rabbits were then oriented on a table using a rabbit holder in such a way that the lower jaw was shored in a horizontal position. This was followed by the careful placement of the N-ODF formulation on the tongues of rabbits of group "A." The conventional tablet of NIT was administered orally to rabbits of group "B" as a control via oral gavage after dispersing in 2 ml of distilled water. The respective group of animals was subjected to intake of a single formulation of ODF or control conventional tablet accommodating 10 mg of NIT.

The pharmacokinetic (PK) analysis was facilitated by the collection of blood samples (0.5 ml each) by marginal ear vein puncture at predetermined time intervals (0-predose, 15, 30, 45, 60, 120, 180, 360, 720, and 1440 min) after dosing. Centrifuge tubes carrying sodium citrate (3.4% w/v) as an anticoagulant were used to hold the blood samples (42). The samples were centrifuged at 10,000 rpm for 5 min at room temperature to separate out the plasma; 100 μl of plasma samples were vortexed and extracted with 0.5 ml of organic solvent mixture of cyclohexane:isopropyl alcohol = 50:2 v/v on a vortex mixer (Biolinx, India) for a time period of

5 min. To separate the organic layer, centrifugation for 5 min at 10,000 rpm was undertaken. The separated organic layer was then transferred to a clean tube and evaporated under a stream of nitrogen gas. At a temperature of −20°C, all the samples were preserved till analysis (11).

The HPLC (JASCO LC-NET II/ADC, Jasco Corporation, Japan) built with a UV-2070 UV–Visible detector and HiQ sil C^{18}Hs (5 μm, 250 × 4.6 mm) column was employed to determine the NIT content. A mixture of methanol, acetonitrile, and water (50:25:25, v/v/v) constituted the mobile phase. With each sample redissolved in 30 μl mobile phase and the UV detector set at 239 nm, 20 μl samples were subjected to HPLC analysis at a flow rate of 1.2 ml/min (11).

Through the time *versus* plasma drug concentration profile, employing a noncompartmental model with Kinetica® 5.0 PK/PD Analysis, Demo Version (Thermo Scientific, USA), the standard PK parameters (mean ± SD) of NIT were obtained. The experiment was executed thrice (43).

Stability Study

For stability testing, film formulation was wrapped in an aluminum pouch and was sealed. The sealed pouch was stored at 40 ± 2°C/75 ± 5% RH for a period of 6 months as per the ICH guidelines. At predetermined time intervals, NIT N-ODFs were evaluated for physical appearance, folding endurance, surface pH, *in vitro* dissolution trait, and *in vitro* disintegration time (36).

RESULTS AND DISCUSSION

Optimization of NS

Effect of Formulation Variables on Particle Size

The outcome of variation of factors like concentration of stabilizer (*A*) and probe ultrasonication time length (*B*) on the NS particle size was depicted through a 3D surface response plot and contour plot. NS 5 was selected as the optimized batch among all the nine batches formed for NS formulation as it exhibited the lowest particle size (505.74 ± 15.48 nm).

Statistical analysis employing ANOVA gave an *F*-value of 49.49 and a *p* value of 0.0001, which implies that the linear model obtained is significant ($p < 0.05$). The best-fitted model for particle size ($R^2 = 0.9612$) was found to be a linear model (2).

The polynomial equation generated in terms of coded factors for particle size was found to be:

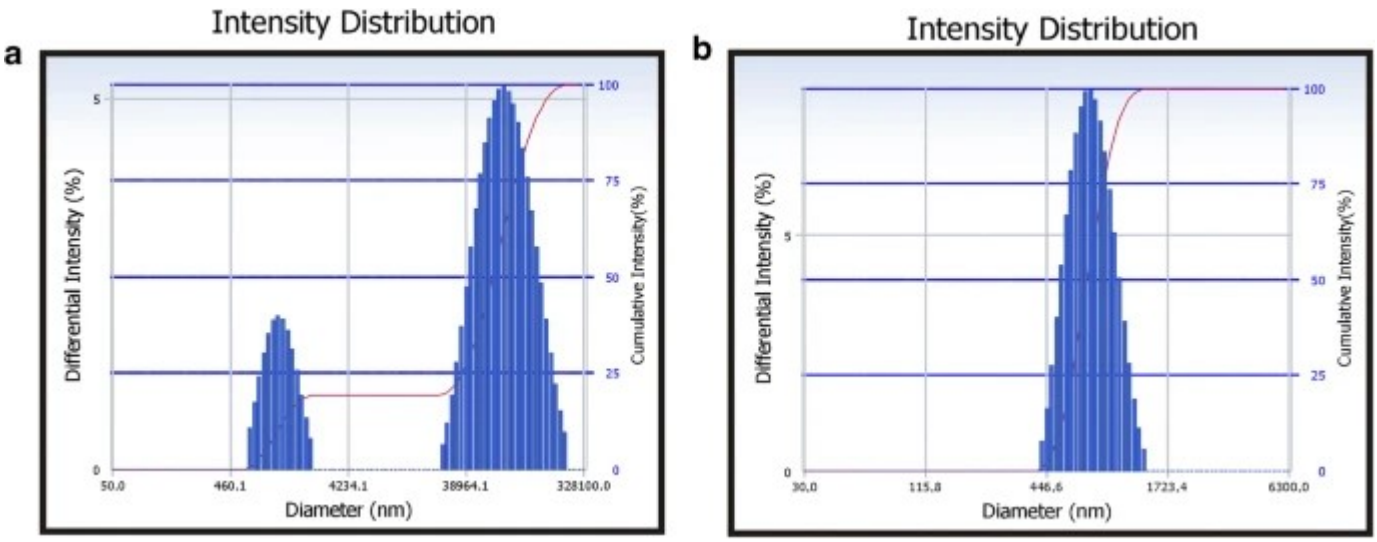
$$ \mathrm{Particle}\ \mathrm{size}=+533.44--31.55\ast A+84.5\ast B+40.41\ast AB+251.69\ast {A}^2 $$

Evaluation of NS

Particle Size Determination

Particle size of 505.74 ± 15.48 nm and polydispersity index (PDI) of 0.083 ± 0.006 were shown by the optimized batch of NS (Fig. 1b). The obtained PDI value indicates a narrow distribution of particle size and, thus, implies a stable formulation, too. The decrease in particle size of the plain NIT from 6599.47 ± 23.45 nm (Fig. 1a) to 505.74 nm as nanoparticles has been revealed in Fig. 1 (2).

Fig. 1



Particle size of a plain NIT and b optimized NIT NS

Drug Content

The optimized batch of NSs exhibited percent NIT content (% entrapment efficiency) of 78.4 ± 2.3% and drug loading percentage of 33.33 ± 1.1%. Both parameters primarily depend on the polymeric stabilizer content incorporated in the formulation. As the % stabilizer content increases to a certain level, the particle size of the drug decreases with increment in the drug loading capacity. But on increasing the concentration of the stabilizer further, the capacity of drug loading continues to increase with an increment in mean particle diameter, too. This can be attributed to the enhancement in the viscosity of the solution at a high concentration of the stabilizer, which in turn causes hindrance of the transmission of ultrasonic vibrations and thus the diffusion between the solvent and antisolvent during precipitation. Therefore, to avoid this undesired increment in drug particle size, an optimum concentration of stabilizer with optimum drug loading capacity and lowest drug particle size was chosen (2, 12, 44).

Saturation Solubility

The water solubility of NIT from NCs was recorded to be 50.46 ± 0.47 μg/ml, and the obtained value was found to be significantly ($p < 0.01$) raised (26.14 times) in comparison to that of plain NIT (1.93 ± 0.25 μg/ml). The reduction in NIT crystal size to nanoscale and, thus, the increment in effective surface area of drug crystals encountering the dissolution medium can be accredited for this prominent enhancement in water solubility of NIT from NCs (2).

Stability Study

The physical appearance (yellow fluffy dry powder), particle size, and PDI of NCs after 3 months (631.8 ± 22.34 nm with PDI of 0.145 ± 0.051) and 6 months (673.2 ± 18.56 nm with PDI of 0.237 ± 0.072) of storage at 40 ± 2°C/75 ± 5% RH revealed no significant differences. Thus, the stability of NCs was concluded by the acquired results (2).

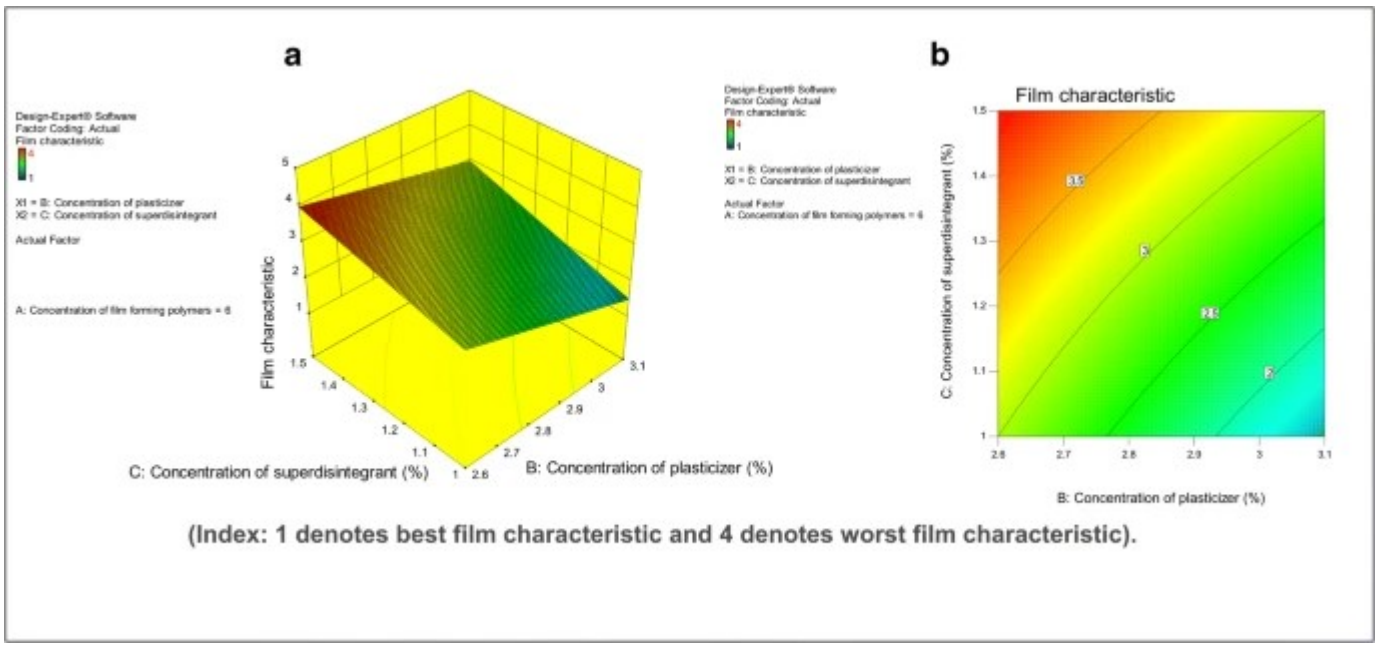
Optimization of N-ODF

Effect of Formulation Variables on Film Characteristics (Response 1)

A 3D surface response plot (Fig. 2a) and a contour plot (Fig. 2b) were used to display the effect of varying the factors like the concentration of plasticizer (B) and the concentration of superdisintegrant (*C*) on film characteristics (dependent variable-1). Independent variable "*B*" showed a positive effect (improved film characteristics with increased plasticizer

concentration) and "*C*" displayed a negative effect (declined film characteristics with increased superdisintegrant concentration). A total of 8 batches were prepared for ODF according to 2^3 FFD, and among the prepared ones, batch F5 was chosen as the optimized batch as it exhibited "very good—smooth and flexible" (denoted by digital value "1" in Fig. 2) film characteristics. According to the ANOVA result, the *F*-value was found to be 17 and the *p* value to be 0.0097, which denotes the significance of the linear model. The best-fitted model for film characteristics (R^2 = 0.9227) was found to be a linear model. The following linear model equation can describe the effect of formulation variables on film characteristics.

Fig. 2



a Response surface plot and b contour plot for independent variables of NIT N-ODF with film characteristics as response

The final equation for film characteristics in terms of coded factors is

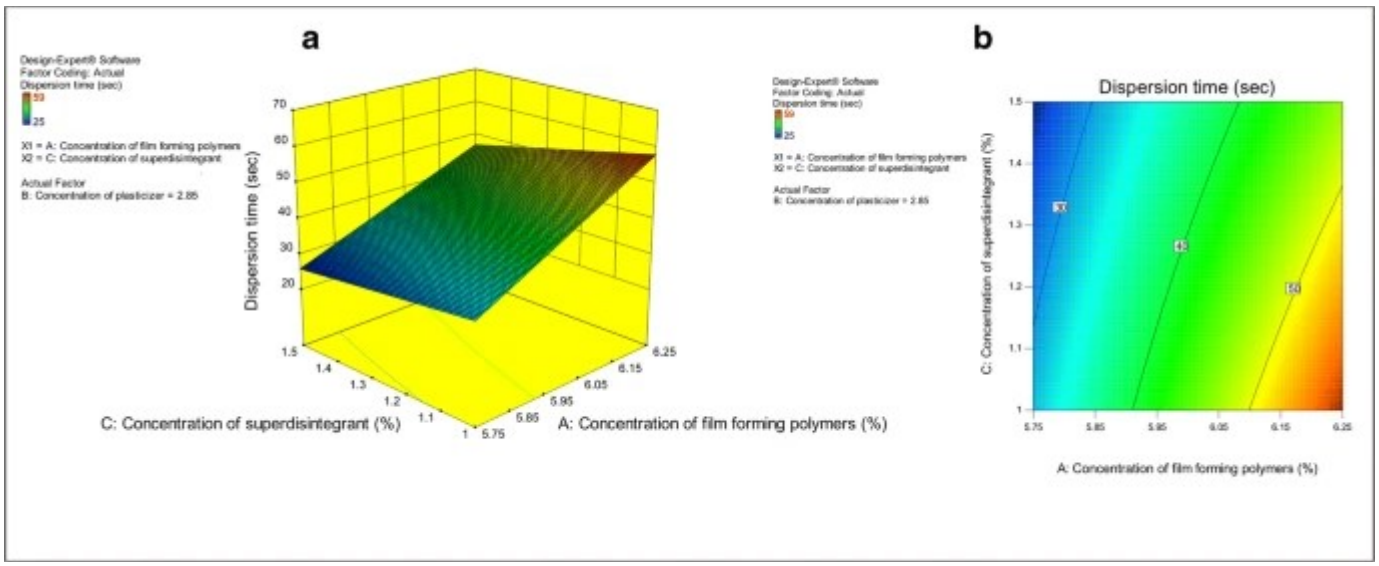
$$ \mathrm{Film}\ \mathrm{characteristic}=+2.88--0.63\ast B+0.63\ast C+0.13\ast BC $$

Effect of Formulation Variables on Dispersion Time (Response 2)

A 3D surface response plot (Fig. 3a) and a contour plot (Fig. 3b) indicate that the formulation

variable—concentration of film-forming polymers (*A*)—exerted a positive effect (increased dispersion time with increased polymer concentration), while another independent variable "*C*" unveiled a negative effect (decreased dispersion time with increased superdisintegrant concentration). According to 2^3 FFD, eight batches of ODF were manufactured and batch F5 was sorted out as the optimized one on account of revealing the lowest dispersion time (28 s). As per the ANOVA, the obtained *F*-value was 117.09 and the *p* value was 0.0013, which signals that the linear model was significant. The linear model was perceived as the best-fitted model for dispersion time of ODF (R^2 = 0.9936). On the basis of the best-fitted model, the following polynomial equation was fostered to make predictions about the response for the specified levels of each factor.

Fig. 3



a Response surface plot and b contour plot for independent variables of NIT N-ODF with dispersion time as response

The final equation for dispersion time in terms of coded factors is

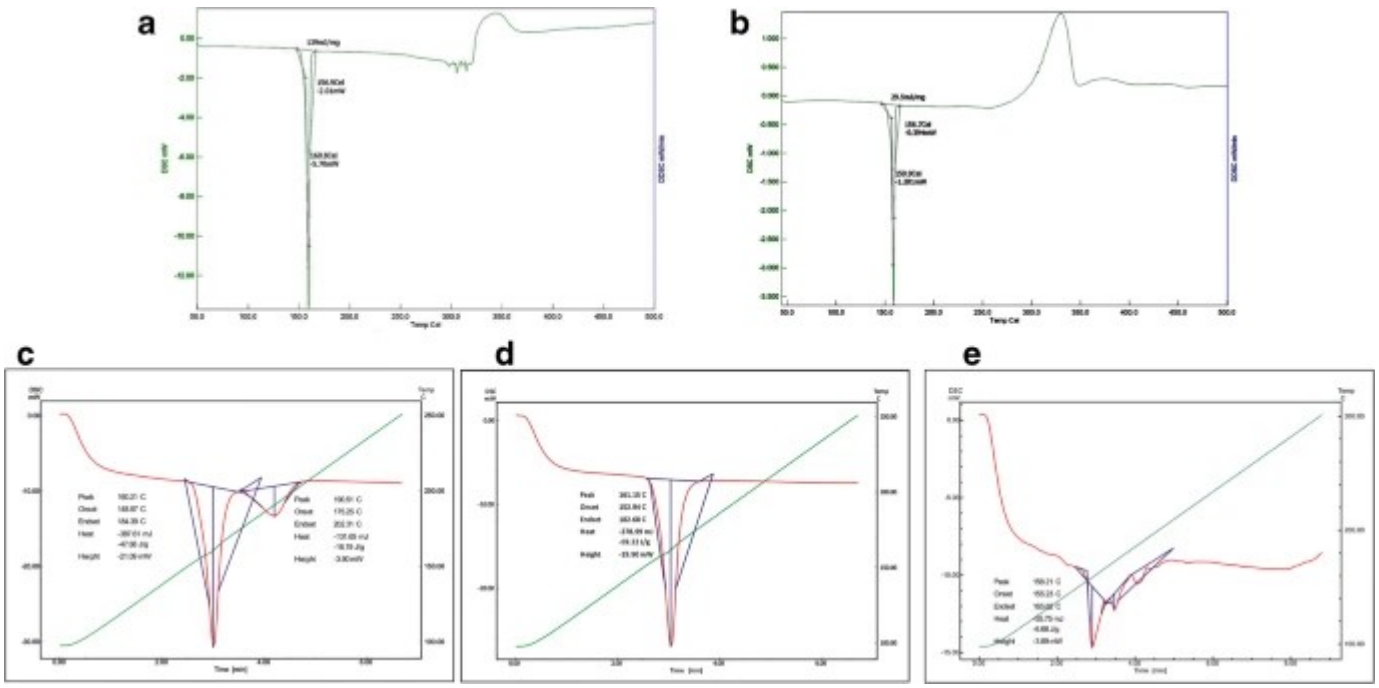
$$ \mathrm{Dispersion}\ \mathrm{time}=+40.63+11.88\ast A--1.88\ast B--4.13\ast C--1.37\ast AC $$

Evaluation of N-ODF

DSC Analysis

Drug–excipient compatibility and preserved drug integrity in the prepared NIT N-ODF was ensured by DSC analysis. The DSC thermograms of plain NIT, NIT in physical combination with different formulation excipients individually, and optimized N-ODF are depicted in Fig. 4. Plain NIT DSC thermogram (Fig. 4a) displayed a sharp endothermic peak at 160.8°C, which corresponds to the reported melting point of NIT. The DSC thermograms of NIT and HPMC-E6 physical mixture (Fig. 4b), NIT and PVA physical mixture (Fig. 4c), and NIT and CCS physical mixture (Fig. 4d) individually exhibited sharp endothermic peaks at 159.9°C, 160.21°C, and 161.15°C, respectively, which are in close proximity to the characteristic peak of plain NIT (Fig. 4a). This acquired result suggests maintenance of drug integrity in combination with different excipients, and thus, drug–excipient compatibility is inferred.

Fig. 4



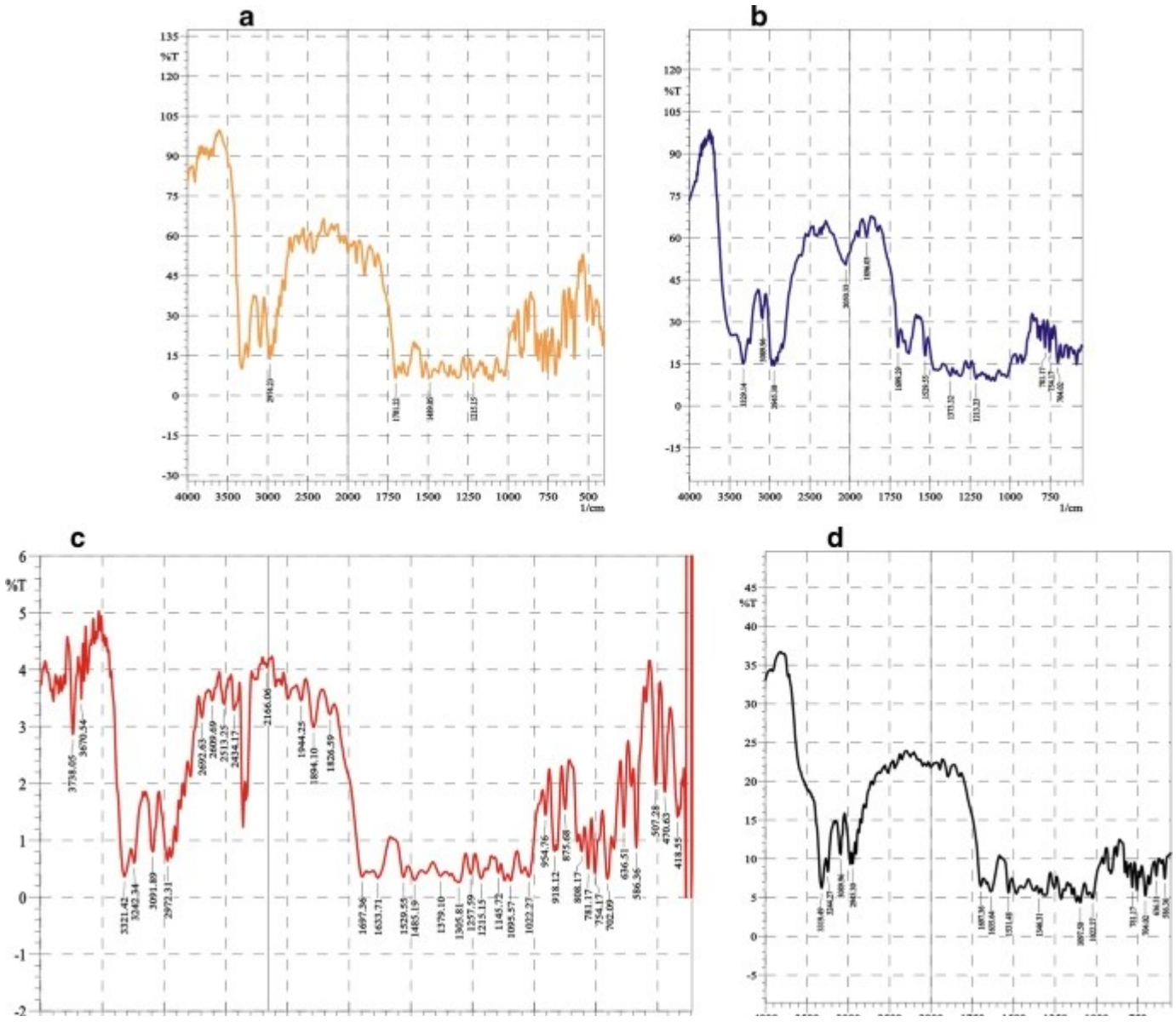
DSC thermograms of a plain NIT, b physical mixture of NIT and HPMC-E6, c physical mixture of NIT and PVA, d physical mixture of NIT and CCS, and e optimized NIT N-ODF

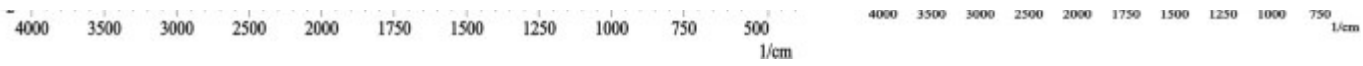
The DSC thermogram of optimized NIT N-ODF (Fig. 4e) reflects a sharp endothermic peak at 158.21°C which is a peak that drifted to 2.59°C left from the peak value of 160.8°C (Fig. 4a). The two peak values are very close to each other and this suggests that the drug integrity has been preserved on transforming its nanosuspension to N-ODF. Another short and broad endothermic peak around 190°C signals the melting point of PVA (36).

FTIR Analysis

The compatibility between drug and formulation excipients was reaffirmed by FTIR analysis (24). The FTIR spectra of plain NIT and NIT in combination with different formulation excipients individually are presented in Fig. 5.

Fig. 5





FTIR spectra of a plain NIT, b physical mixture of NIT and HPMC-E6, c physical mixture of NIT and PVA, and d physical mixture of NIT and CCS

The FTIR spectrum of plain NIT (Fig. 5a) showed distinctive peaks at around 1545 cm^{-1} and at 1701.22 and 1215.15 cm^{-1} which can be ascribed to N–H bending vibration for secondary amines and esterified carbonyl group, respectively. Besides, peaks at a wave number around 750 and 700 cm^{-1} are due to the monosubstituted benzene, and the peak around 3085 cm^{-1} is attributed to C–H stretching vibration of an aromatic ring (45).

The FTIR spectrum of the physical mixture of NIT with HPMC-E6 (Fig. 5b) disclosed peaks at wave numbers 1529.55, 1699.29, 1213.23, 3089.96, 754.17, and 704.02 cm^{-1}. All these peaks exist in close vicinity of the distinguishing peaks shown in the FTIR spectrum of plain NIT (Fig. 5a). This suggests NIT and HPMC-E6 to be compatible with each other.

The FTIR spectrum revealing findings of NIT in physical mixture with PVA is shown in Fig. 5c. The peaks at wave numbers 1529.55, 1697.36, 1215.15, 3091.89, 754.17, and 702.09 cm^{-1} are in correspondence to the distinguishing peaks of plain NIT (Fig. 5a).

The FTIR findings of NIT in physical mixture with CCS have been presented in the respective spectrum (Fig. 5d). The peaks present in the spectrum at wave numbers 1531.48, 1697.36, around 1215, 3089.96, around 750, and 704.02 cm^{-1} are in accordance with the distinguishing peaks of plain NIT (Fig. 5a).

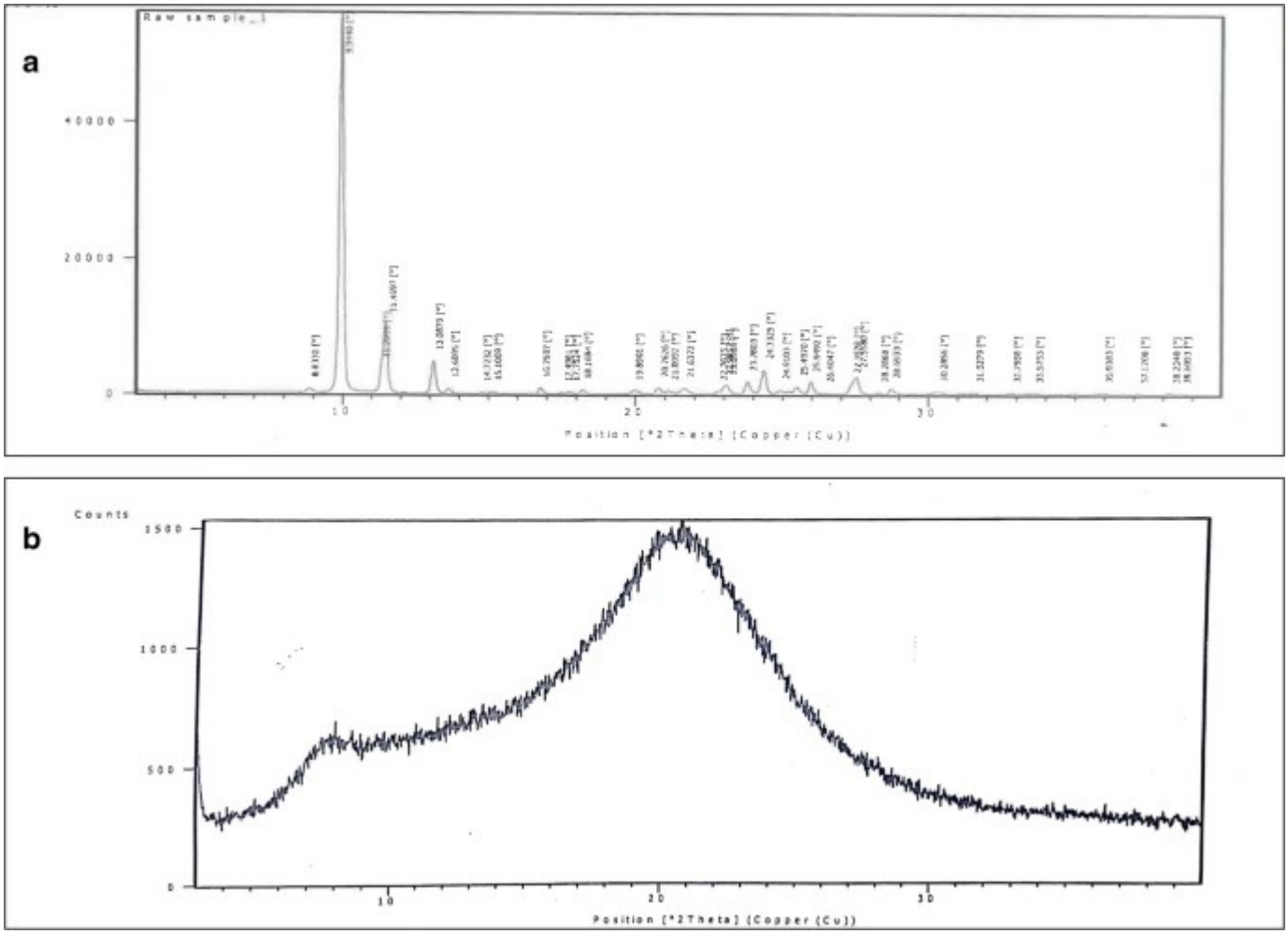
Thus, no objectionable interaction between the drug and any of the formulation excipients was observed, and thus, the compatibility between NIT and excipients was assured by FTIR analysis, too.

P-XRD Analysis

P-XRD analysis was executed to evaluate the physicochemical properties of plain NIT and

optimized NIT N-ODF, so as to assist in the ascertainment of the influence of process parameters in the preparation of ODF. Figure 6 presents the P-XRD pattern of both plain NIT and formulated film. The plain NIT P-XRD pattern (Fig. 6a) depicted distinctive high-energy diffraction peaks at 2θ values between 8° and 30°, with three most prominent peaks at 9.944°, 11.469°, and 13.087° propounding the crystalline structure of the NIT (11). The P-XRD pattern as shown in Fig. 6b reflects the semicrystalline nature of NIT film formulation (46). It suggests that the crystallinity of NIT has declined and its conversion to amorphous form in the N-ODF is marked. Ingredients of film formulation like HPMC-E6 and PVA get adsorbed on the surface of drug nanoparticles and prevent recrystallization of NIT, thus stabilizing the amorphous form of the drug. The amorphous state of nanoparticles embracing N-ODF implies a high dissolution rate of the formulation (35).

Fig. 6



X-ray diffraction patterns of a plain NIT and b optimized NIT N-ODF

Organoleptic Properties and Thickness

Further tests were conducted on a film accommodating 10 mg of NIT nanoparticles having a dimension of 2 × 3 cm^2.

The color, odor, appearance, and texture of the film were found to be yellow, odorless, and uniformly thin and soft, smooth, and flexible, respectively. The average thickness was found to be 0.148 ± 0.008 mm, which corresponds to the prescribed acceptable range (0.005−0.2 mm) for it (47).

Weight Variation and Content Uniformity

The average weight was found to be 0.223 ± 0.005 g, which is in accordance with the previously reported data (39), and uniformity in film weight was also achieved. This indicates uniformity of drug dose distribution, too, within the grafted film. The average drug content was found to be 103.06 ± 5.85%, which exists within the acceptable limit of 85–115% (33, 48).

Folding Endurance and Surface pH

Folding endurance is a measure of film flexibility or brittleness, and its obtained value for the formulated film is 280.33 ± 5.51 times, which indicates a flexible film (22). The surface pH of the film was found to be 6.86 ± 0.05, which is close to neutral and also to the oral cavity pH (6.7–7.3). This suggests null chances of irritation on the oral mucosal surface on the administration of the film (30).

Moisture Content and Uptake

Moisture content was recorded as 2.11 ± 0.201% and this value seemed not to affect the physical steadiness and integrity of the film. The concentration of hygroscopic ingredients existing in the film formulation governs the scope of moisture uptake. HPMC-E6 (the film-forming polymer), CCS (the superdisintegrant), and PEG-400 (the plasticizer) are all hygroscopic in nature, but are stable ingredients. So, the film is liable to gain moisture content to some extent (2.59 ± 0.326%). However, it did not affect the physical stability and integrity of ODF, and also the value is in accordance with the previously reported data (41).

Dispersion Time and Disintegration Time

The optimized N-ODF (formulation F5) revealed the shortest dispersion time of 28 ± 1.5 s and disintegration time value of 24.60 ± 1.31 s. This can be attributed to the presence of some key ingredients in specific amounts in the film formulation like film-forming polymers (HPMC-E6 and PVA), superdisintegrant (CCS), and plasticizer (PEG-400). These excipients provided porosity, flexibility, and softness to the film, which altogether resulted in quick dispersion of ODF and thus rapid drug release, which in turn rendered improved absorption and bioavailability of NIT. Values for both dispersion and disintegration time ranged within the prescribed acceptable limit of 5–30 s (48, 49).

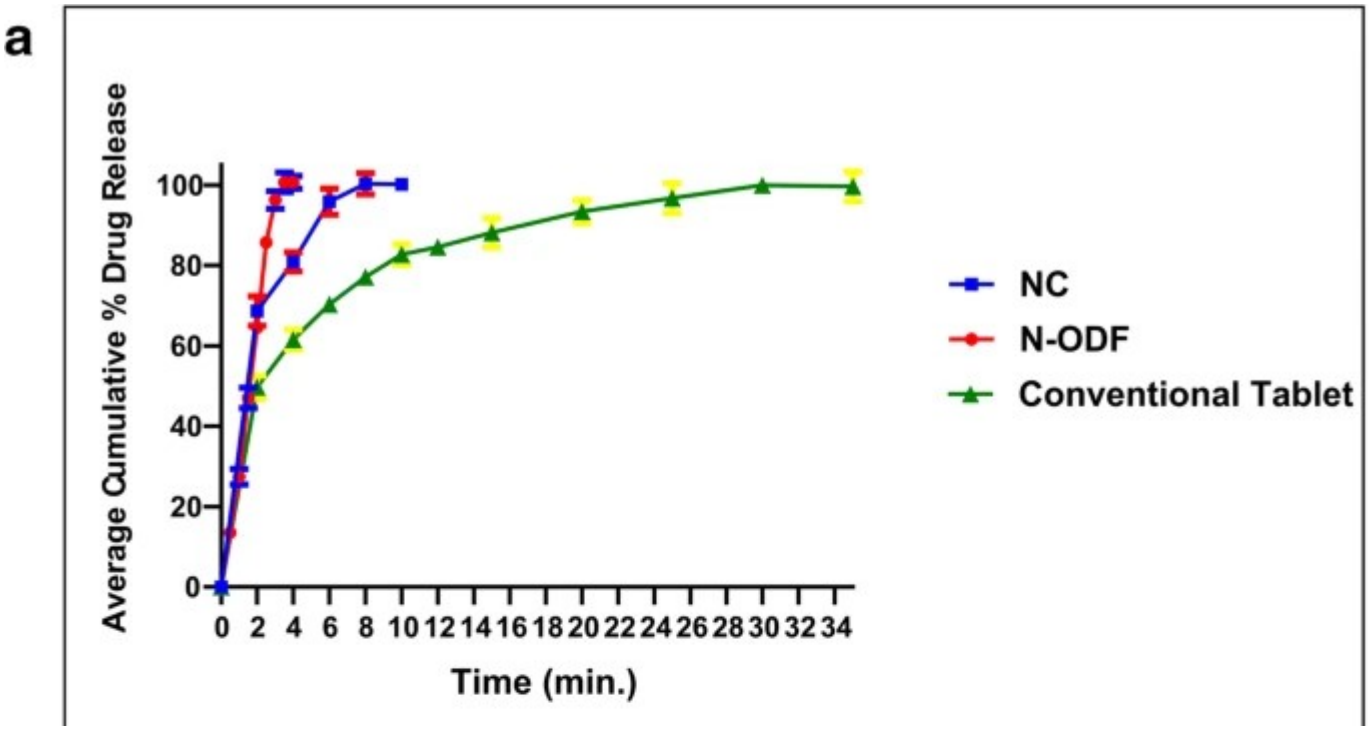
Physical Characteristics Determination

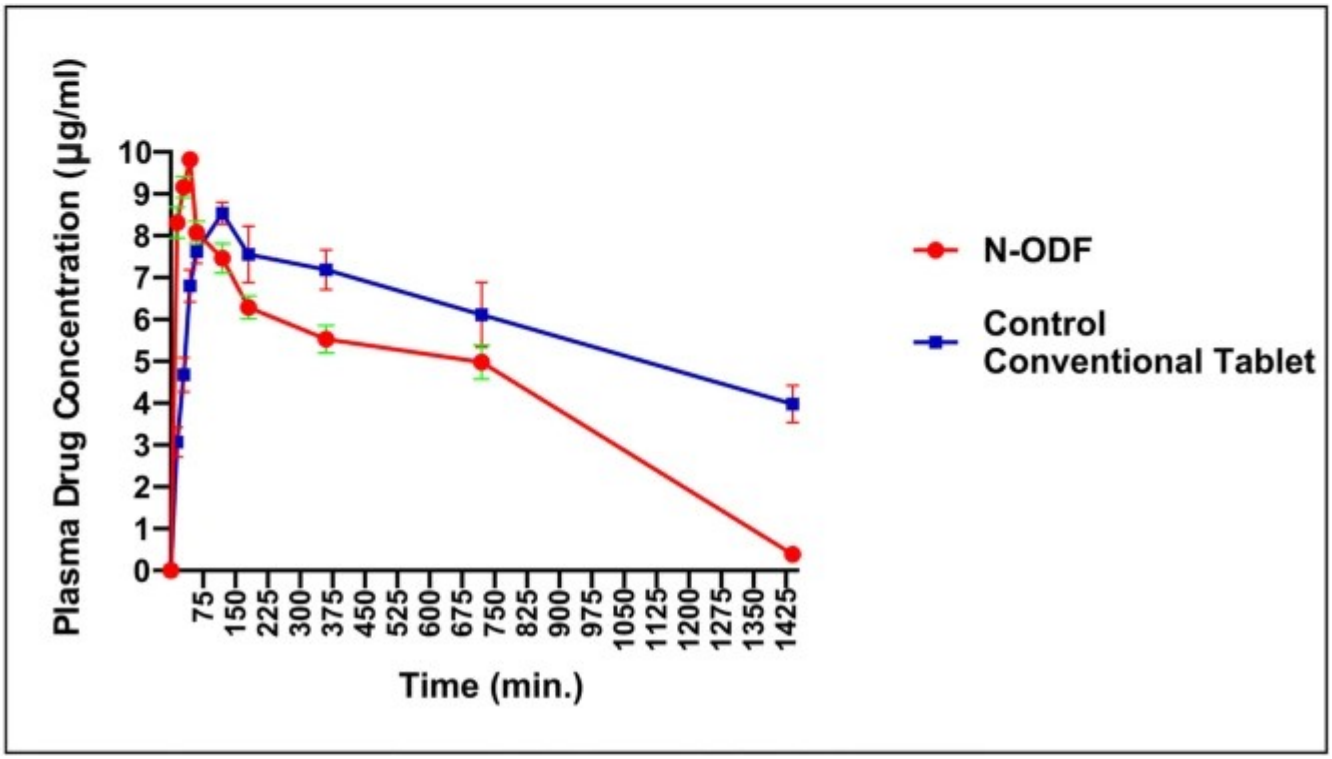
Soft and flexible films exhibit low tensile strength with high elongation values. Both the physical characteristics, tensile strength (8.25 ± 0.13 kg/cm^2) and % elongation (63.5 ± 1.97%) indicate a soft and flexible film (36, 47).

In Vitro Drug Release Study of NIT Formulations

The deduced *in vitro* release profile of NIT from N-ODF was collated with the drug release from lyophilized NCs and conventional tablet of NIT (Fig. 7a). N-ODF and NCs released 100.68 ± 2.50% NIT in 3.5 min and 100.28 ± 2.64% NIT in 8 min, respectively, while the time taken by the conventional NIT tablet to release nearly the same amount of NIT (99.94 ± 1.57%) was significantly ($p < 0.05$) higher (30 min) than both the developed nanoparticulate formulations. So, it is quite evident that the release of NIT from both N-ODF and NCs was found to be significantly swift in collation to conventional tablets of NIT. The remarkably quick *in vitro* NIT release from NCs can be ascribed to the enhancement in the effective surface area of drug nanoparticles encountering the dissolution medium. Furthermore, the rapid and pronounced NIT release from N-ODF can be accredited to the incorporated technological facet of nanosizing of drug crystals together with the quicker water uptake by the film due to the porosity imparted by the inclusion of superdisintegrant and other salient ingredients in the formulation, facilitating faster disintegration and also improved dissolution.

Fig. 7





a *In vitro* drug release profiles of NIT formulations and b plasma drug concentration *versus* time data of NIT formulations

In Vivo Pharmacokinetic Study

To assess the efficacy of the formulated N-ODF within the living organism, a PK study was conducted in male white rabbits and was compared to conventional NIT tablets. Figure 7b depicts the plasma drug concentration *versus* time data procured from the investigation. It reflects that in comparison to conventional NIT tablet there was a significant ($p < 0.05$) difference in T_{max} and C_{max} values of N-ODF. Rapid systemic delivery and engendering a quicker onset of action for NIT by N-ODF formulation is concluded, as the C_{max} of 8.54 ± 0.26 µg/ml attained by the control conventional tablet with T_{max} of 120 min has been shrunk to 15 min by the developed N-ODF formulation with almost similar plasma NIT concentration (8.31 ± 0.37 µg/ml) attainment. Moreover, NIT N-ODF exhibited a significantly higher C_{max} (9.82 ± 0.19 µg/ml) with reduced T_{max} (45 min) in comparison to conventional NIT tablet (8.54 ± 0.26 µg/ml in 120 min), implying enhanced bioavailability. The fast clearance, as seen through lower concentrations at later time points displayed by the developed film formulation in

comparison to the conventional tablet, is an added advantage. The increment in solubility and thus enhanced dissolution rate of the drug formed the basis for the improved oral bioavailability of NIT from N-ODF. Minimization of the first-pass effect as a consequence of favored pregastric drug absorption also contributed to the elevated bioavailability. Table III summarizes the results obtained after the analysis of the principal PK parameters like C_{max}, T_{max}, $t_{½}$, MRT, and [AUC_{0-24}].

Table III Pharmacokinetic Parameters of NIT Formulations

In Vitro Stability Study of N-ODF

A significant difference ($p < 0.05$) was not observed in the physical appearance, surface pH, disintegration time, folding endurance, drug content uniformity, and dissolution study of the optimized NIT N-ODF formulation on storage at 40 ± 2°C/75 ± 5% RH for 1, 3, and 6 months (Table IV). Thus, the *in vitro* stability of N-ODF formulation was inferred.

Table IV Stability Study of Optimized NIT N-ODF

CONCLUSION

The research work summarizes the successful development of NIT NS by the antisolvent sonoprecipitation method employing HPMC-E6 as the stabilizer. The optimized NS revealed an impressive nanorange of NIT crystals with enhanced solubility and dissolution rate of the drug. The NIT N-ODF formulated utilizing NS exhibited uniformity in thickness, weight, and drug content with rapid disintegration within 30 s. The DSC study of the optimized film formulation suggests that NIT integrity has been preserved on the transformation of its NS to N-ODF. The prepared N-ODF presented a rapid and complete release of NIT within 4 min on conduction of its *in vitro* dissolution study, which is far superior in comparison to conventional NIT tablets. The *in vivo* pharmacokinetic study of NIT N-ODF conferred remarkably elevated

oral bioavailability of NIT when compared to control conventional dosage form. Moreover, the N-ODF formulation of NIT displayed stability on storage at 40 ± 2°C/75 ± 5% RH. Thus, fabrication of N-ODF emerges as a potent platform for the effective delivery of poorly soluble drugs like NIT with enhanced solubility, dissolution rate, bioavailability, and improved patient compliance as an added advantage.

Data Availability

Applicable

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Neha Vishal Gandhi: conceptualization, methodology, investigation, software, formal analysis, data curation, writing—original draft, writing—review and editing, final approval of the version of the manuscript to be published, and agreement to be accountable for all aspects of the work. Uday Arvind Deokate: resources, writing—review and editing, final approval of the version of the manuscript to be published, and agreement to be accountable for all aspects of the work. Sachidanand Shankar Angadi: resources, writing—review and editing, final approval of the version of the manuscript to be published, and agreement to be accountable for all aspects of the work.

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Ethics declarations

Ethics Approval and Consent to Participate

Applicable (IAEC Approval No. MES/COP/IAEC/04/2017-18)

Consent for Publication

Not applicable

Competing Interests

The authors declare no competing interests.

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