RESEARCH PAPER

Formulation And Evaluation Of The Fast-Disintegrating Tablet Of Naproxen By Employing Natural Super Disintegrant And Calorie Free Natural Sweetener

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ABSTRACT

Objectives: To formulate and optimize fast disintegrating tablets (FDTs) of naproxen, a BCS Class II NSAID, employing Nelumbo nucifera rhizome starch as a novel natural superdisintegrant and Stevia rebaudiana leaf powder as a calorie-free sweetener, to improve dissolution performance and patient compliance in dysphagic, pediatric, and diabetic populations. **Methods:** Nine formulation batches (SF1–SF9) were prepared by direct compression using a 3^2 full factorial design, with Nelumbo nucifera rhizome starch (X_1: 10–30 mg) and Crospovidone (X_2: 10–30 mg) as independent variables. Disintegration time (Y_1, minimize) and cumulative drug release at 30 min (Y_2, maximize) were designated as dependent variables. Drug-excipient compatibility was assessed by FTIR and DSC. All batches were evaluated for pre- and post-compression parameters, wetting time, water absorption ratio, and in vitro drug release. The optimized batch was selected based on maximum desirability using Design-Expert® software and subjected to release kinetics modeling, comparative dissolution against Naprosyn® 500, and accelerated stability testing per ICH Q1A(R2). **Results:** FTIR and DSC confirmed physicochemical compatibility. All batches met pharmacopeial specifications. The optimized formulation SF6 (X_1 = 20 mg, X_2 = 30 mg), selected on the basis of overall desirability score of 0.9117, achieved disintegration time of 74 ± 1.9 s, cumulative drug release of 97.1 ± 2.3% at 30 min, and wetting time of 57.9 ± 1.6 s, significantly outperforming marketed Naprosyn® 500 (81.6 ± 2.1% at 30 min). Drug release followed first-order kinetics with Fickian diffusion (n = 0.29). Stability studies confirmed no significant change in drug content (98.38 ± 0.46%) or disintegration time (77 ± 2.2 s) after three months. **Conclusion:** The developed naproxen FDT formulation demonstrated superior disintegration and dissolution performance over the conventional marketed product, with excellent stability, offering significant clinical potential for rapid analgesic onset in patient populations with swallowing difficulties. Future in vivo pharmacokinetic evaluation is recommended to confirm bioavailability enhancement and support clinical translation.

Keywords: Fast disintegrating tablets; Naproxen; Nelumbo nucifera rhizome starch; Natural superdisintegrant; Stevia rebaudiana; 3^2 Factorial design; Direct compression; Dissolution enhancement.

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INTRODUCTION

Despite being one of the most common and incapacitating problems of human populations, pain continues to impose significant burden on health systems and quality of life of patients [1]. Musculoskeletal disorders, arthritis and other postoperative pain and dysmenorrhea together affect more than 1.71 billion people worldwide and consequently, there is a great need for effective pain relief [2]. Conventional oral solid dosage forms have important drawbacks for special patient groups such as pediatric, geriatric and dysphagic patients who have a difficulty in swallowing whole tablets. This challenge leads to patient non-compliance, subtherapeutic drug levels and treatment failures [3]. Dysphagia, or swallowing problems, are estimated to affect about 26-35% of the general population and significantly decrease adherence to oral tablet based therapy [4]. Also, the economic costs of poorly managed pain (such as lost productivity, multiple healthcare visits, and the consequences of non-compliance) cost hundreds of billions of dollars each year. The issues all highlight the importance of patient-centered oral dosage forms that are easy to use yet remain effective [5].

Naproxen belongs to the class of medications known as non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used for the treatment of mild to moderate pain, inflammation, fever and rheumatic conditions [6]. Naproxen, a weakly acidic compound, is the carboxylic acid analogue of ibuprofen and has a carboxylic acid functional group, with its molecular formula of (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid, and a molecular weight of 230.26 g/mol. It acts by nonselective inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, which inhibit the prostaglandin biosynthesis and lessen the inflammatory cascade [7]. The pharmacokinetics of Naproxen are also favorable, with a protein binding of ~99% and a relatively long half-life in plasma of 12-17 hours, thus providing a good chance for once or twice daily dosing [8]. It has a poor aqueous solubility in neutral and acidic environments (BCS Class II) thus affecting its dissolution rate and delaying therapeutic effect when formulated as a conventional tablet. Literature has been available to support that significant improvements can be made in the disintegration and dissolution of naproxen using advanced formulation methods, which can have a positive impact on the onset of action in clinical trials [9].

Fast disintegrating tablets (FDTs) are a novel oral drug delivery system that is designed to disintegrate quickly in the oral cavity or when in contact with saliva, without the need for water to be swallowed. Superdisintegrants play a key role in the formulation of FDTs to ensure rapid tablet disintegration through capillary action, swelling and water uptake [10]. In addition to being a new excipient that has not been reported in naproxen FDT formulations, natural superdisintegrants like Nelumbo nucifera rhizome starch have significant properties which are beneficial over synthetic counterparts such as biocompatibility, biodegradability, cost effectiveness and minimal regulatory concern [11]. Crospovidone (Kollidon® CL) was used as co-superdisintegrant, as it is well known for its strain recovery mechanism and wicking property [12]. *Stevia rebaudiana* leaf powder was added as a calorie-free natural sweetener to improve palatability without adding calories, particularly for patient populations with diabetes and/or a focus on calorie reduction [13]. The combination of both superdisintegrants were systematically assessed in 3^2 full factorial design for nine formulation batches to get a proper statistically designed Rangoonwan optimization strategy and response surface [14].

The aim of present work was to develop and optimize the fast disintegrating tablets of Naproxen (500 mg, direct compression) using a new natural super disintegrant (Nelumbo nucifera rhizome starch, X_1: 10 – 30 mg) and another super disintegrant (Crospovidone, X_2: 10 – 30 mg) using Stevia rebaudiana leaf powder as a calorie-free sweetener in 3^2 full factorial design. The main aim was to reduce disintegration (Y_1) and increase cumulative release of the drug at 30 min (Y_2) using Design-Expert® software while achieving the optimum formulation by experimental confirmation of predicted optimum. The secondary objectives were to evaluate the drug-excipient compatibility using FTIR, to characterize pre and post compression of all nine batches, to perform comparative dissolution study with marketed Naprosyn® 500 tablets, to model the drug release from the optimized batch and to conduct accelerated stability

study of the optimized batch for three months under ICH Q1A(R2) condition at 40°C/75%RH.

MATERIALS AND METHODS

MATERIALS

Naproxen (gift sample, purity ≥ 99%) was received from Dr. Reddy's Laboratories Ltd. (Hyderabad, India). Nelumbo nucifera rhizome starch was extracted in-house from commercially procured lotus rhizomes (local market, Pune, India). Crospovidone (Kollidon® CL, NF grade) was obtained from BASF SE (Ludwigshafen, Germany). Stevia rebaudiana leaf powder (food grade) was procured from Sciquaint Chemicals (Pune, India). Mannitol (Pearlitol® SD 200, directly compressible grade) and microcrystalline cellulose (Avicel® PH101, NF grade) were sourced from Roquette Frères (Lestrem, France) and FMC BioPolymer (Philadelphia, USA), respectively. Colloidal silicon dioxide (Aerosil® 200, Ph. Eur. grade) was obtained from Evonik Industries AG (Essen, Germany). Magnesium stearate, talc, potassium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid (0.1 N) were purchased from Research Lab Fine Chem Industries (Mumbai, India) and Neeta Chemicals (Mumbai, India). Methanol (HPLC grade) and potassium bromide (IR grade) were procured from Sciquaint Chemicals (Pune, India). Distilled water was prepared in-house throughout the study. All other chemicals and reagents used were of analytical grade unless otherwise specified.

METHODS

Calibration Curve of Naproxen

A stock solution (100 µg/mL) was prepared by dissolving 10.0 mg of naproxen in minimum amount of methanol and then diluting to 100 mL with 0.1 M pH 7.4 phosphate buffer solution. Standard solutions were prepared by a series of dilutions to a buffer of known concentration (2–12 µg/mL). Each solution was placed in a cuvette and absorbance was measured at 272 nm in UV-Visible spectrophotometer (Model LMSPUV1000B, Labman Scientific Instruments Pvt. Ltd., Chennai, India) and blank correction was used. A calibration curve was built by plotting the absorbance against the concentration and the linearity was established by using the regression equation $y = mx + c$ and the correlation coefficient (R^2). All measurements were done in triplicate (n = 3) and results are presented as mean ± SD [15].

FTIR Analysis

To ensure that there will be no chemical interactions between the drug and selected excipients, compatibility of naproxen with different excipients was tested using FTIR spectroscopy. KBr pellet method was used for the analysis of pure naproxen and its physical mixture with excipients (in optimized ratio). 2 mg of sample was triturated with 200 mg of dried KBr and then compressed using a hydraulic pellet press (Kimaya Engineers, Mumbai, India) at 10 tonnes. FTIR spectra were taken on a Bruker Corporation (Ettlingen, Germany) FTIR spectrophotometer (Alpha II), with a resolution of 4 cm^{-1} in the range of 4000 to 400 cm^{-1}. The characteristic peaks of the pure drug were identified and compared for any shift, disappearance or appearance of peaks in the physical mixture with the pure drug in order to detect any drug-excipient interaction (n = 3) [16].

DSC Analysis

Differential scanning calorimetry was used to determine the thermal compatibility of naproxen with excipients to check for any changes in melting behavior due to interaction between the two. The samples (5–8 mg) were analyzed on a differential scanning calorimeter (Model STA 8000, PerkinElmer Inc., Waltham, USA) using an empty crimped aluminum pan as reference, by heating from 30°C to 250°C at a rate of 10°C/min under nitrogen purge (50 mL/min). The onset temperature, peak temperature and enthalpy of fusion were measured for both samples and compared, looking for any suppression or shift in the characteristic naproxen endotherm (n = 3) [17].

Solubility Study

The pH-dependent dissolution behaviour of naproxen was characterized by determining its equilibrium solubility in distilled water as well as in 0.1 N HCl (pH 1.2) and 0.1 M phosphate buffer pH 7.4, and an appropriate dissolution medium was selected. Ten milliliters of each medium was filled into the sealed glass vials, and excess drug was added to each and shaken continuously at 37 ± 0.5°C at 50 rpm in an orbital shaking water bath (Sciquaint Innovations Pvt. Ltd., Pune, India) for 48 h. The samples were filtered through

the 0.45 micron membrane filter and suitably diluted with the respective mediums and absorbance was recorded at 272 nm using UV-Visible spectrophotometer (Model LMSPUV1000B, Labman Scientific Instruments Pvt. Ltd., Chennai, India). The concentrations of drugs were obtained from the standard calibration curve and the results are presented as mean ± SD (n = 3) [18].

Experimental Design

Two independent variables, namely the compression force and the compression speed were studied in this experiment using a 3^2 full factorial design to systematically examine the effect of individual and interaction of these two variables on the critical quality attributes of naproxen fast disintegrating tablets. Two independent variables, namely, the concentration of Nelumbo nucifera rhizome starch (X_1) and Crospovidone (X_2) were selected and tested at three levels, low (−1), medium (0), and high (+1), where low, medium, and high refers to 10, 20, and 30 mg per tablet, respectively. Nine formulation batches (SF1 to SF9) were prepared following the formulation design matrix. Dependent variables were: disintegration time (Y_1, minimize) and cumulative drug release at 30 min (Y_2, maximize). The answers obtained were plotted as quadratic polynomial:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where b_0 is the intercept, b_1 and b_2 are main effects coefficients, b_{12} is the interaction coefficient, and b_{11} and b_{22} are quadratic coefficients. Design-Expert® software (Version 13.0, Stat-Ease Inc., Minneapolis, USA) was used for statistical analysis such as ANOVA, model significance and lack-of-fit evaluation, where a p value > 0.05 was deemed acceptable for lack-of-fit [19,20].

Table 1: Independent and Dependent Variables for 3^2 Factorial Design

Variable	Factor	Level (-1)	Level (0)	Level (+1)
X_1	Nelumbo nucifera rhizome starch (mg/tablet)	10	20	30
X_2	Crospovidone (Kollidon® CL) (mg/tablet)	10	20	30
Response	**Dependant Variables**			Goal
Y_1	Disintegration time (s)			Minimize
Y_2	Cumulative drug release at 30 min (%)			Maximize

Preparation of Naproxen Fast Disintegrating Tablets

Naproxen (500 mg) tablets were prepared by direct compression that disintegrate rapidly. Each of the ingredients (naproxen, Nelumbo nucifera rhizome starch, Crospovidone, Stevia rebaudiana leaf powder, mannitol and microcrystalline cellulose PH101) were individually passed through BSS mesh no. 60 and loaded into a double-lined polybag. Colloidal silicon dioxide was added and tumbled for 15 min followed by addition of magnesium stearate and tumbled with it for 3 min as lubricant, and talc and tumbled with it for 3 min as glidant. The final blend was compressed into 500 mg tablet using 10 station rotary tablet compression machine (Lab Press, Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India) with force ranging from 3 to 4 kg/cm² using 12 mm round with flat faced punches [21].

Table 2: Formulation Composition of Naproxen Fast Disintegrating Tablets (Total Tablet Weight: 500 mg)SS

Ingredient	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
Naproxen (mg)	250	250	250	250	250	250	250	250	250
Nelumbo nucifera rhizome starch (X_1, mg)	10	10	10	20	20	20	30	30	30
Crospovidone - Kollidon® CL (X_2, mg)	10	20	30	10	20	30	10	20	30
Stevia rebaudiana leaf powder (mg)	20	20	20	20	20	20	20	20	20
Mannitol (mg)	167	157	147	157	147	137	147	137	127
Microcrystalline cellulose PH101 (mg)	25	25	25	25	25	25	25	25	25

Colloidal silicon dioxide (mg)	5	5	5	5	5	5	5	5	5
Magnesium stearate (mg)	8	8	8	8	8	8	8	8	8
Talc (mg)	5	5	5	5	5	5	5	5	5
Total (mg)	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Bulk Density and Tapped Density

The bulk and tapped densities of the powder blends were measured in order to evaluate the packing and compressibility properties before compression. A 100 mL graduated glass cylinder was used to carefully transfer 10 g of each blend into the cylinder without tapping and the unsettled volume was measured to calculate the bulk density. Then the cylinder was tapped with 500 number of taps at a drop height of 14 ± 2 mm, 300 taps per minute in tap density apparatus (Model ET-1020, Electrolab India Pvt. Ltd., Mumbai, India) and the final tapped volume was measured. The bulk and tapped densities were determined by dividing the mass by the bulk or tapped volume respectively:

Bulk Density (g/mL) = Mass / Bulk volume

Tapped Density (g/mL) = Mass / Tapped volume

All results are presented as mean ± SD (n = 3) [22].

Carr's Index and Hausner's Ratio

Carr's index and Hausner's ratio were calculated from bulk and tapped density values as indirect measures of powder flowability and compressibility. The following equations were applied:

Carr's Index (%) = [(Tapped Density − Bulk Density) / Tapped Density] × 100

Hausner's Ratio = Tapped Density / Bulk Density

Values of Carr's index below 15% and Hausner's ratio below 1.25 were considered indicative of good flowability as per standard pharmacopeial guidelines (n = 3) [23].

Angle of Repose

The fixed funnel method was also used to determine the angle of repose for powder flow. A funnel of 10 mm inner diameter of the stem was kept 10 cm above a flat horizontal surface. Each blend was allowed to flow freely through the funnel to form a stable cone, and the height (h) and base radius (r) were measured. The angle of repose (θ) was determined by: $\theta = \tan^{-1}(h / r)$

Flowability is excellent when values are below 30°, good to passable when values are between 30° and 40°, and poor flowability when values are greater than 40°. The mean ± SD (n = 3) for results were reported [24].

Tablet Thickness and Diameter

Tablets were compressed and thickness and diameter of the tablets were measured in order to ensure dimensional uniformity among all the batches. A digital Vernier (Mitutoyo Corporation, Kawasaki, Japan) calibrated digital vernier caliper was used to measure the 10 randomly selected tablets from each batch and the instrument was set to zero before each measurement. Thickness was measured along the length of the tablet's center and diameter was measured across the widest plane at right angles to that. Data are reported as means ± SD (n = 10) [25].

Hardness

Mechanical integrity of the tablets was measured to assess the hardness of the tablets by Monsanto hardness tester (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India). The individual tablets were crushed and fracture force was noted in kg/cm², using a diametral crushing machine. The target range of 3–5 kg/cm² was found to be acceptable for fast disintegrating tablets as acceptable handleability without compromising the disintegration. Mean ± SD (n = 10) values were reported [26].

Friability

The friability was tested to determine the mechanical resistance of tablets during handling and packing.

Twenty friability tablets were loaded in the friability tester (Model EF-2, Electrolab India Pvt. Ltd., Mumbai, India) and 100 rotations of 25 rpm were made in conformity with the IP/USP specifications. Tablets were then dedusted and reweighed, then the percentage friability was calculated as:

% Friability = [(W_0 − Wf) / W_0] × 100

where W_0 and Wf are initial and final weights respectively. A value not more than 1.0% was considered acceptable (n = 20) [27].

Weight Variation

Twenty tablets were individually weighed in a calibrated analytical balance (Sartorius AG, Goettingen, Germany) and the average weight was calculated, and the uniformity of weight was evaluated. Each tablet's deviation from the mean was determined as:

% Deviation = [(Individual weight − Mean weight) / Mean weight] × 100

The test was interpreted as per the IP specifications - for tablets weighing more than 250 mg, the difference in the mean weights of not more than 2 out of 20 tablets should not be more than 5% and difference in weight of not more than 10% (n = 20) [28].

Drug Content Uniformity

To verify uniformity of drug content, the amount of naproxen in tablet blanks was determined in each sample. Ten tablets per batch were powdered and 250 mg of naproxen was dissolved in minimum methanol, diluted to 100 mL with 0.1 M phosphate buffer pH 7.4, and filtered through 0.45 µm membrane syringe filter and further diluted. The absorbance was measured at 272 nm by using UV-Visible spectrophotometer (Model LMSPUV1000B, Labman Scientific Instruments Pvt. Ltd., Chennai, India) and drug content determination was made from the calibration equation. The acceptance criteria was 100 ± 5% of labeled amount as per IP guidelines (n = 3) [29].

Wetting Time and Water Absorption Ratio

The wetting time and water absorption ratio were determined to assess the hydrophilicity and moisture absorbing capacity of the tablets and both were directly related to disintegration. The double-folded tissue paper was transferred to a Petri dish (9cm diameter) with 10mL of distilled water and a few drops of 0.1% w/v amaranth dye solution. A tablet was carefully placed at the center of the moisture without pressure and the time (s) taken for complete surface wetting was recorded with the help of a digital stopwatch. The wetted tablet was then weighed and the water absorption ratio (R) calculated as:

R = [(Wa − Wb) / Wb] × 100

where Wa and Wb are weights after and before wetting respectively. Results were expressed as mean ± SD (n = 3) [30].

In Vitro Disintegration Time

Disintegration time was determined as a critical quality attribute by the use of a digital disintegration test apparatus (Model ED-2L, Electrolab India Pvt. Ltd., Mumbai, India) as per IP/USP guidelines. Six tablets per batch were placed in the basket assembly operated in 900 mL of 0.1 M phosphate buffer pH 7.4 at 37 ± 2°C and 28–32 cycles/min. The endpoint was total tablet disintegration with no solid residue remaining on the mesh of the basket. For fast disintegrating tablets (n = 3), the disintegration time was measured in seconds and not more than 180 s was set as limit [31].

In Vitro Drug Release

The in vitro drug release study was performed using USP Type II paddle dissolution apparatus (Model TDT-08L, Electrolab India Pvt. Ltd., Mumbai, India) in 900mL of 0.1M phosphate buffer pH 7.4 at 37±0.5°C and 50 rpm. Aliquots (5mL) were taken at 5, 10, 15, 20, 30 and 45 min through a 0.45 µm in-line filter and replaced with an equal volume of fresh pre-warmed medium to maintain sink conditions. Samples were subsequently filtered and diluted as per requirement and the absorbance was measured at 272 nm in the UV-Visible spectrophotometer (Model LMSPUV1000B, Labman Scientific Instruments Pvt. Ltd., Chennai, India). The calibration curve was used to determine the cumulative percentage drug released and plotted as a function of time. The accepted criterion of the release rate was set as a minimum of 85% at 30 min (n = 3) [32].

Accelerated Stability Studies

Accelerated stability testing of the optimized formulation was conducted as per ICH Q1A(R2) guidelines at 40°C ± 2°C and 75% ± 5% RH for three months in a stability chamber (Thermolab Scientific Equipments Pvt. Ltd., Mumbai, India). To avoid moisture and light, tablets were placed in amber glass vials that were covered with a rubber stopper and aluminum crimp cap. Samples were collected at 0, 1, 2, and 3 months and tested for physical appearance, hardness, friability, variation in weight, drug content, wetting time, water absorption ratio, disintegration time and for in-vitro drug release at 30 min as described in the respective sections. The change was considered a significant change if it was more than 5% from initial value or if it failed to meet any of the acceptance criteria (n = 3) as per ICH Q1A(R2) [33].

RESULTS AND DISCUSSION

RESULTS

Calibration Curve of Naproxen

The absorbance of Naproxen was found to be linearly related with the concentration (2–12 µg/mL) in 0.1 M phosphate buffer pH 7.4 at 272 nm and found to be regression equation y = 0.0388x + 0.0094, with a high correlation coefficient R^2 = 0.9989, thus fulfilling Beer Lambert's law (Figure 1).

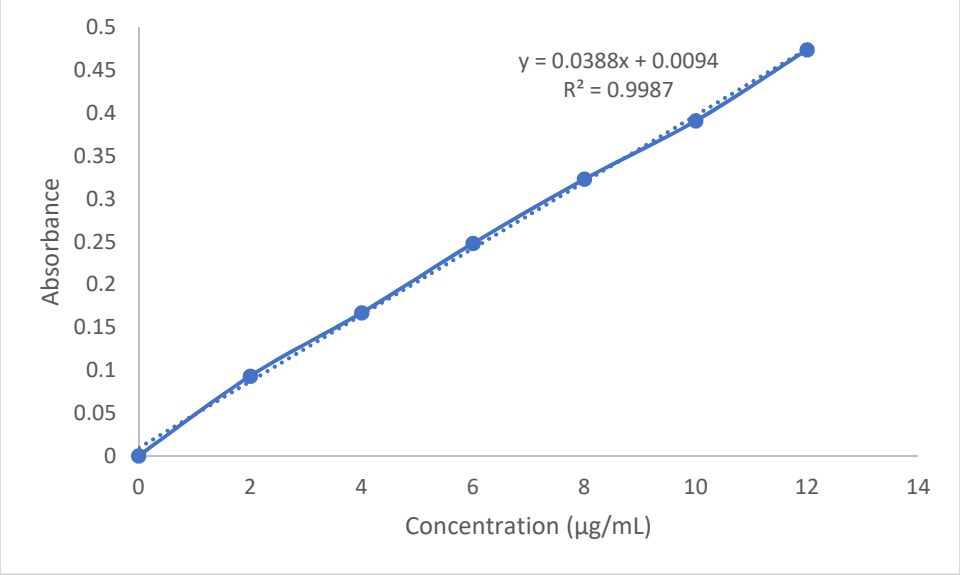

Figure 1: Calibration curve of naproxen in 0.1 M phosphate buffer pH 7.4 (λ_{max} 272 nm)

Solubility Studies

As shown in Table 3 naproxen exhibited strongly pH-dependent solubility in 0.1 N HCl (0.016 ± 0.002 mg/mL), which is practically insoluble, and slightly higher in distilled water (0.048 ± 0.003 mg/mL). The value of pH 7.4 in phosphate buffer was seen to increase markedly with each step to 0.98 ± 0.04 mg/mL, which is due to progressive ionization of carboxylic acid group, thus making it suitable as a dissolution medium.

Table 3: Equilibrium solubility of naproxen in different media at 37 ± 0.5°C

Dissolution Medium	Solubility (mg/mL)	BCS Classification
Distilled water	0.048 ± 0.003	Practically Insoluble
0.1 N HCl (pH 1.2)	0.016 ± 0.002	Practically Insoluble
Phosphate buffer (pH 7.4)	0.98 ± 0.04	Very Slightly Soluble

Values are expressed as mean ± SD, (n=3).

FTIR analysis

The FTIR spectra of pure naproxen and physical mixture of naproxen with excipients are shown in Figure 2. The

physical mixture of naproxen did not show any significant changes in all its principal absorption bands, such as the O–H stretch (3244 cm^{-1}), C=O stretch (1726 cm^{-1}) or the aromatic C=C vibrations (1607 cm^{-1}). No new bands and peak disappearances were observed indicating the physicochemical compatibility between naproxen and the selected excipients.

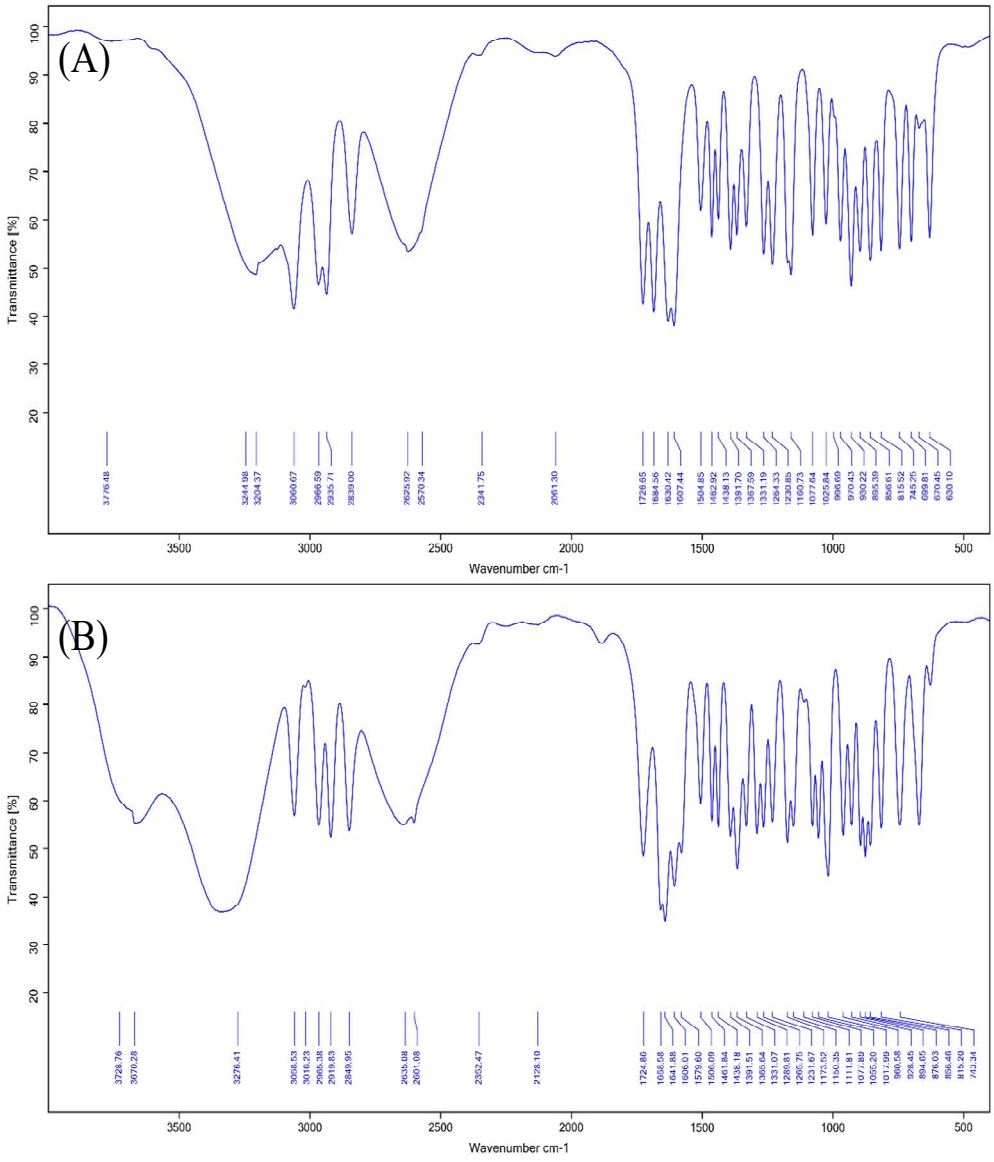

Figure 2: FTIR Spectra of (A) Pure Drug and (B) Physical mixture

DSC analysis

The DSC thermograms of pure naproxen (NP) and its physical mixture (PM) are presented in Figure 3. Purity of crystalline was confirmed from the sharp melting endothermic peak of pure naproxen at 152.35°C which matched its reported melting range of 152-154°C. The peak of the endotherm of naproxen in the physical mixture was at 152.37°C in addition to the peak of mannitol at 191.02°C. The unaltered peak position and peak enthalpy confirmed that there was no thermal drug/excipient interaction.

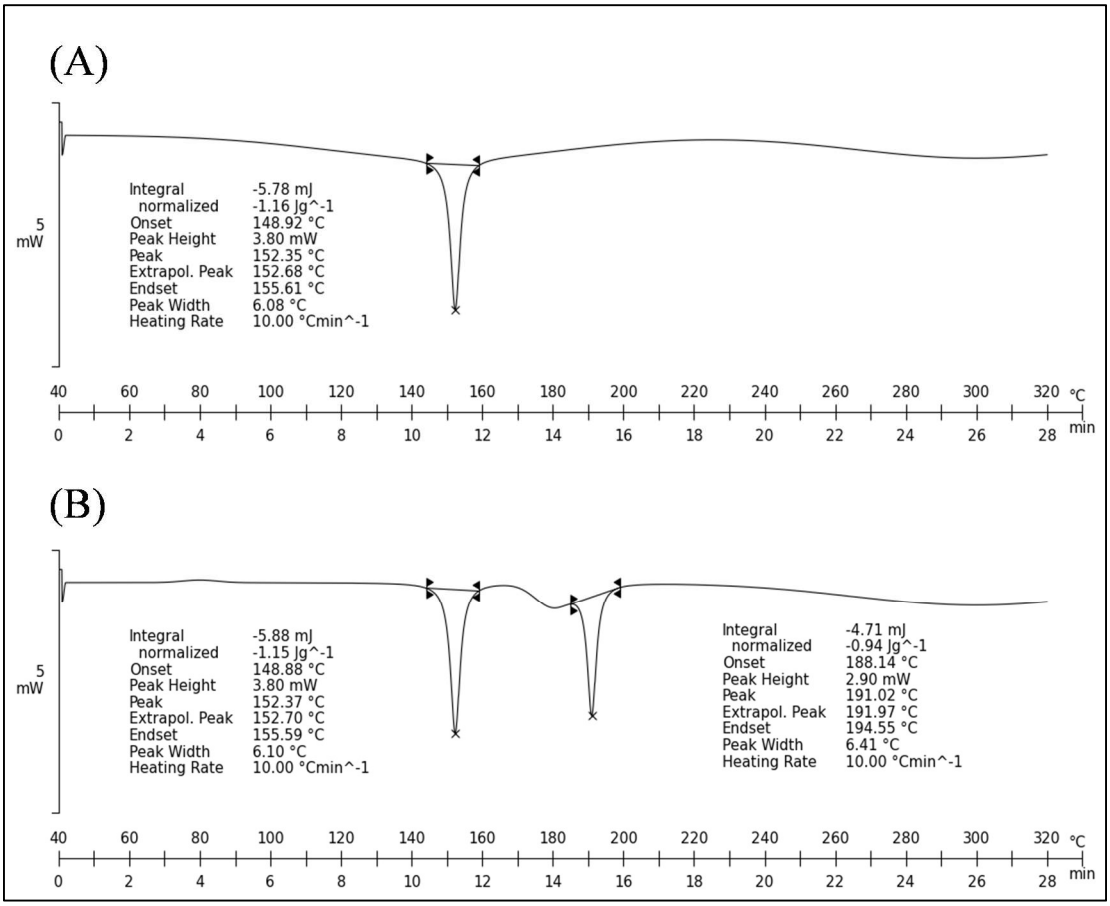

Figure 3: DSC Spectra of (A) Pure drug [152.35] and (B) physical mixture [152.37 and 191.02]

RESULTS OF CHARACTERIZATION OF NAPROXEN FAST DISINTEGRATING TABLET

Results of Precompression Study

The results of pre-compression evaluations are reported for all nine formulation batches in Table 4. Bulk density ranged from 0.412 ± 0.008 to 0.441 ± 0.008 g/mL and tapped density from 0.481 ± 0.009 to 0.512 ± 0.009 g/mL across SF1–SF9. The index values of Carr (13.87% to 14.52%) and Hausner (1.161 to 1.170) were within acceptable limits and the angle of repose values (26.62° to 28.14°) showed excellent flowability for all batches, which confirmed suitability for direct compression.

Table 4: Pre-compression evaluation of powder blends of naproxen fast disintegrating tablet formulations (SF1-SF9)

Batch	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
SF1	0.412 ± 0.008	0.481 ± 0.009	14.34 ± 0.41	1.167 ± 0.012	28.14 ± 0.38
SF2	0.418 ± 0.007	0.489 ± 0.008	14.52 ± 0.36	1.170 ± 0.010	27.92 ± 0.44
SF3	0.421 ± 0.009	0.492 ± 0.011	14.43 ± 0.48	1.169 ± 0.014	27.68 ± 0.51
SF4	0.425 ± 0.006	0.496 ± 0.007	14.31 ± 0.33	1.167 ± 0.009	27.45 ± 0.36
SF5	0.429 ± 0.008	0.499 ± 0.009	14.03 ± 0.42	1.163 ± 0.011	27.18 ± 0.42
SF6	0.431 ± 0.007	0.502 ± 0.008	14.14 ± 0.39	1.165 ± 0.010	27.31 ± 0.47
SF7	0.434 ± 0.009	0.506 ± 0.010	14.23 ± 0.44	1.166 ± 0.013	27.09 ± 0.53
SF8	0.437 ± 0.007	0.509 ± 0.008	14.14 ± 0.37	1.165 ± 0.011	26.87 ± 0.39

SF9	0.441 ± 0.008	0.512 ± 0.009	13.87 ± 0.40	1.161 ± 0.012	26.62 ± 0.46

Values are expressed as mean ± SD, (n=3).

Results of Post Compression study

Post-compression physical evaluation results are presented in Table 5. The thickness of tablets and their diameter were all the same in each batch: 3.82–3.87 mm and 12.01–12.03 mm respectively. Hardness was in the range of 3.4 ± 0.10 to 3.8 ± 0.12 kg/cm² and a very slight decrease was observed with the increase in the concentration of superdisintegrant. All batches were found to be below 1.0% friability, which is indicative of acceptable mechanical durability. In all nine batches, there was no evidence of variation in weight and drug content outside of the limits specified in the pharmacopeia, which are ±5% and 100 ± 5% respectively.

Table 5: Post-compression physical evaluation of naproxen fast disintegrating tablets (SF1–SF9)

Batch	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg)	Drug Content (%)
SF1	3.82 ± 0.04	12.01 ± 0.03	3.8 ± 0.12	0.72 ± 0.04	500.4 ± 2.1	98.24 ± 0.42
SF2	3.84 ± 0.05	12.02 ± 0.04	3.7 ± 0.14	0.68 ± 0.05	499.8 ± 1.8	98.46 ± 0.38
SF3	3.83 ± 0.04	12.01 ± 0.03	3.6 ± 0.11	0.65 ± 0.04	500.6 ± 2.4	98.61 ± 0.44
SF4	3.85 ± 0.06	12.03 ± 0.04	3.7 ± 0.13	0.69 ± 0.05	500.2 ± 2.0	98.38 ± 0.41
SF5	3.86 ± 0.05	12.02 ± 0.03	3.6 ± 0.12	0.64 ± 0.04	499.6 ± 1.9	98.72 ± 0.36
SF6	3.84 ± 0.04	12.01 ± 0.03	3.5 ± 0.10	0.61 ± 0.03	500.8 ± 2.2	98.85 ± 0.39
SF7	3.87 ± 0.06	12.03 ± 0.04	3.7 ± 0.14	0.67 ± 0.04	500.1 ± 2.1	98.41 ± 0.43
SF8	3.85 ± 0.05	12.02 ± 0.03	3.5 ± 0.11	0.63 ± 0.04	499.9 ± 1.7	98.79 ± 0.37
SF9	3.83 ± 0.04	12.01 ± 0.03	3.4 ± 0.10	0.58 ± 0.03	500.3 ± 2.0	98.93 ± 0.35

Values are expressed as mean ± SD, (n=3).

The functional evaluation results are shown in Table 6. As the superdisintegrant level increased, the wetting time decreased progressively from 87.4 ± 1.8 s (SF1) to 49.1 ± 1.4 s (SF9) and the water absorption ratio increased correspondingly from 68.2 ± 1.4% to 94.8 ± 2.4%, indicating higher hydrophilicity at higher superdisintegrant levels. There was a consistent reduction in disintegrating time from 148 ± 3.2 s (SF1) to 54 ± 1.6 s (SF9) with all the batches being within the regulatory limit of ≤ 180 s for fast disintegrating tablets.

Table 6: Post-compression functional evaluation of naproxen fast disintegrating tablets (SF1–SF9)

Batch	Wetting Time (s)	Water Absorption Ratio (%)	Disintegration Time (s)
SF1	87.4 ± 1.8	68.2 ± 1.4	148 ± 3.2
SF2	79.6 ± 2.1	73.4 ± 1.7	124 ± 2.8
SF3	71.2 ± 1.9	79.8 ± 2.0	103 ± 2.4
SF4	74.8 ± 2.3	76.1 ± 1.6	119 ± 2.6
SF5	64.3 ± 1.7	84.6 ± 1.9	89 ± 2.1
SF6	57.9 ± 1.6	89.3 ± 2.2	74 ± 1.9
SF7	68.7 ± 2.0	81.4 ± 1.8	96 ± 2.3
SF8	58.4 ± 1.8	88.7 ± 2.1	71 ± 1.8
SF9	49.1 ± 1.4	94.8 ± 2.4	54 ± 1.6

Values are expressed as mean ± SD, (n=3).

***In vitro* drug release study**

The cumulative drug release profiles for all nine batches, in 0.1M phosphate buffer pH 7.4 are shown in Figure 4.

The 30 min drug release ranged from 81.3 ± 2.0% (SF1) to 99.2 ± 2.4% (SF9) and increased with increasing concentration of superdisintegrant. The batch SF1 came up just short of the target criterion of ≥ 85 % at 30 min; the other batches SF3 and above were always within the acceptance criterion. Optimized batch SF6 released 97.1 ± 2.3% at 30 min which is well beyond the target.

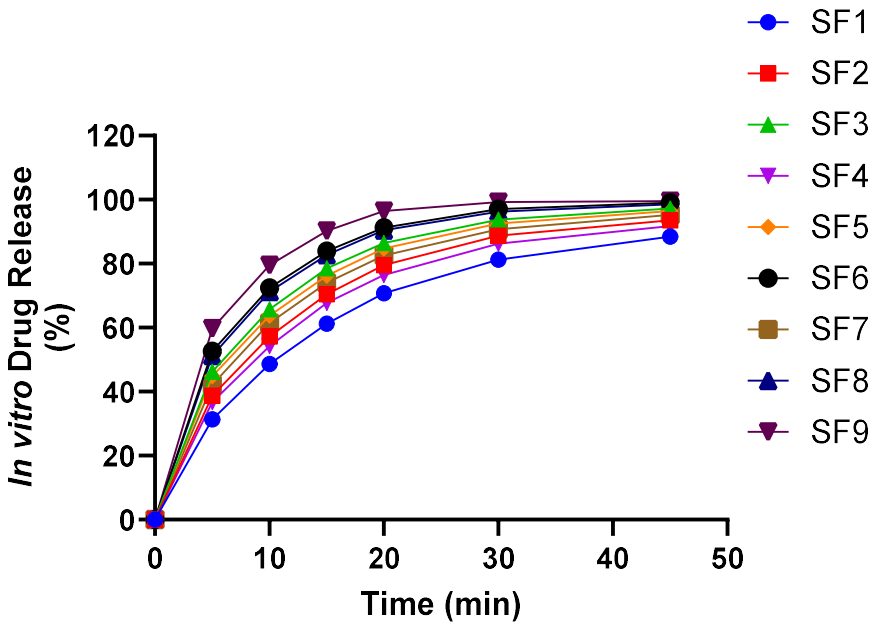

Figure 4: Cumulative percentage in vitro drug release from naproxen fast disintegrating tablets (SF1–SF9) in 0.1 M phosphate buffer pH 7.4 at 37 ± 0.5°C.

Optimization of naproxen fast disintegrating tablet

Disintegration Time (Y_1)

The quadratic model for disintegration time (Y_1) was statistically significant ($F = 324.39$, $p = 0.0003$) as presented in Table 7. Disintegration time (Y_1) showed highly significant negative main effect for both the independent variables, with Nelumbo nucifera rhizome starch (A) showing greater effect ($F = 922.00$, $p < 0.0001$) than Crospovidone (B) ($F = 677.39$, $p = 0.0001$). The interaction term AB was not significant ($p = 0.5212$), which indicates that the effect of both superdisintegrants is independent of each other. A^2 and B^2 were significant ($p = 0.0357$ and $p = 0.0596$, respectively) indicating that the response surface was non-linear. The model had an excellent fit, with R-square value of 0.9982, adjusted R-square value of 0.9951, and predicted R-square value of 0.9843, and there was a small difference of only 0.2 between the adjusted and predicted R-square values. The acceptable level of precision was obtained, 56.39, which means that there is an adequate signal-to-noise ratio (Table 8). The regression equation for disintegration time is given by:

$$Y_1 = 91.1111 - 25.6667A - 22B + 0.75AB + 5.3333A^2 + 4.3333B^2$$

The negative values of the coefficients of A (−25.6667) and B (−22) indicate that both variables have a dominant disintegrating effect on each other, with A having a comparatively more strong effect. The contour plot (Figure 5A) and 3D response surface (Figure 5B) showed that the disintegration time decreased as the concentrations of both A and B increased, having the lowest disintegration time at high concentrations of both A and B.

In Vitro Drug Release at 30 min (Y_2)

Table 7 showed that the model for cumulative drug release at 30 min (Y_2) was highly significant ($F = 1435.47$, $p < 0.0001$). Both the parameters (crospovidone (B) and Nelumbo nucifera rhizome starch (A)) were found to have significant positive main effects over drug release with increasing concentration (F =

4655.32, $p < 0.0001$ and $F = 2330.56$, $p < 0.0001$, respectively). The interaction term AB (AB) was statistically significant ($p = 0.0017$) and had a (–) coefficient signifying a mild antagonistic effect in higher combined concentration. The quadratic term B2 was significant ($p = 0.0035$), thus indicating the non-linear effect of Crospovidone concentration, whereas A2 was not significant ($p = 0.1259$), suggesting the linear predominant contribution of Nelumbo nucifera rhizome starch in the studied range. The model showed high statistical performance, $R^2 = 0.9996$, R^2 adjusted = 0.9989, R^2 predicted = 0.9955 and the model was adequately precise with an error of 116.51, which confirms very good model reliability (Table 8). The regression equation for the in vitro drug release at 30 min is given by:

$$Y_2 = 92.7222 + 3.75A + 5.3B - 1.025AB - 0.2833A^2 - 1.1333B^2$$

The positive values of A (+3.75) and B (+5.30) support the enhancing effects of both superdisintegrants on drug release with B having a relatively higher effect. The contour plot (Figure 5C) and 3D response surface plot (Figure 5D) indicated that the drug release was increasing uniformly with the increase in both the variables and maximum release was obtained at high concentration of A and B. The dissolution enhancement patterns shown along the B-axis of both the plots further substantiated the main contribution of Crospovidone to dissolution enhancement.

Table 7: Fit Summary of Quadratic Models for Optimization of Naproxen Fast Disintegrating Tablets

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Disintegration Time					
Quadratic	0.0415		0.9951	0.9843	Suggested
Drug Release at 30 min					
Quadratic	0.0075		0.9989	0.9955	Suggested

Table 8: ANOVA Summary of Quadratic Models for Disintegration Time (Y_1) and In Vitro Drug Release at 30 min (Y_2)

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Disintegration Time (Y_1)						
Model	6953.36	5	1390.67	324.39	0.0003	Significant
A – Nelumbo nucifera Rhizome Starch	3952.67	1	3952.67	922.00	< 0.0001	Significant
B – Crospovidone	2904.00	1	2904.00	677.39	0.0001	Significant
AB	2.25	1	2.25	0.5248	0.5212	Non-significant
A^2	56.89	1	56.89	13.27	0.0357	Significant
B^2	37.56	1	37.56	8.76	0.0596	Non-significant
Residual	12.86	3	4.29	—	—	
Cor Total	6966.22	8	—	—	—	
In Vitro Drug Release at 30 min (Y_2)						
Model	259.85	5	51.97	1435.47	< 0.0001	Significant

A – Nelumbo nucifera Rhizome Starch	84.38	1	84.38	2330.56	< 0.0001	Significant
B – Crospovidone	168.54	1	168.54	4655.32	< 0.0001	Significant
AB	4.20	1	4.20	116.08	0.0017	Significant
A^2	0.1606	1	0.1606	4.43	0.1259	Non-significant
B^2	2.57	1	2.57	70.96	0.0035	Significant
Residual	0.1086	3	0.0362	—	—	
Cor Total	259.96	8	—	—	—	

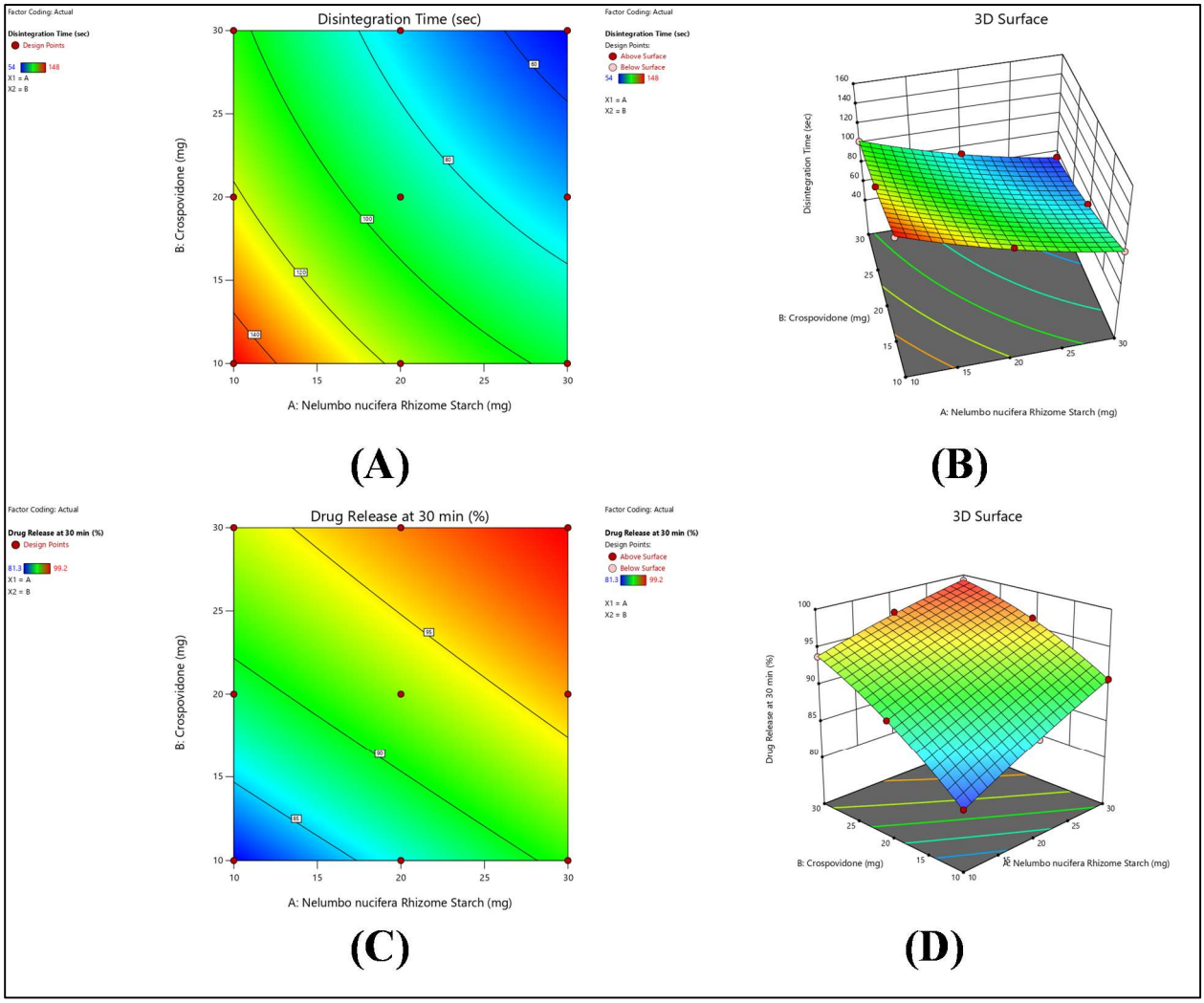

Figure 5. Effect of Nelumbo nucifera rhizome starch (X_1) and Crospovidone (X_2) concentrations on critical quality attributes of naproxen fast disintegrating tablets. (A) 2D contour plot and (B) 3D response surface plot illustrating the combined effect of X_1 and X_2 on disintegration time (Y_1); (C) 2D contour plot and (D) 3D response surface plot illustrating the combined effect of X_1 and X_2 on cumulative in vitro drug release at 30 min (Y_2).

Validation statistical model

The optimized formulation SF6 was validated experimentally against the models developed, and the accuracy of the models were verified, as summarized in Table 9. The percentage relative error between the experimentally observed and predicted values were 0.76% for disintegration time (predicted 73.44 s; observed 74 ± 1.9 s) and 0.22% for drug release at 30 min (predicted 96.89%; observed 97.1 ± 2.3%), which were both within the acceptable limit of ≤ 5%. The overall desirability score of 0.9117 has demonstrated the simultaneous optimisation of both optimisation goals.

Table 9: Validation of statistical models for optimized naproxen fast disintegrating tablet formulation

Response	X_1 *Nelumbo nucifera* Rhizome Starch (mg)	X_2 Crospovidone (mg)	Predicted Value	Experimental Value	% Relative Error	Desirability
Disintegration Time (s)	20	30	73.44	74 ± 1.9	0.76	0.9117
In vitro Drug Release at 30 min (%)	20	30	96.89	97.1 ± 2.3	0.22	

Drug Release Kinetics

Optimized formulation SF6 release kinetic plots of the optimized formulation SF6 fitted to mathematical models are presented in Figure 6. The first-order model gave the best correlation coefficient (R^2 = 0.9874) suggesting that the drug release is dependent on the concentration, which is indicative of the hydrophilic matrix system. The zero order model had the lowest R^2 value (0.6199). The release exponent n = 0.29, which is below the threshold of 0.45 for Fickian diffusion, validated Fickian diffusion as the main transport pathway for the drug from the fast disintegrating tablet matrix.

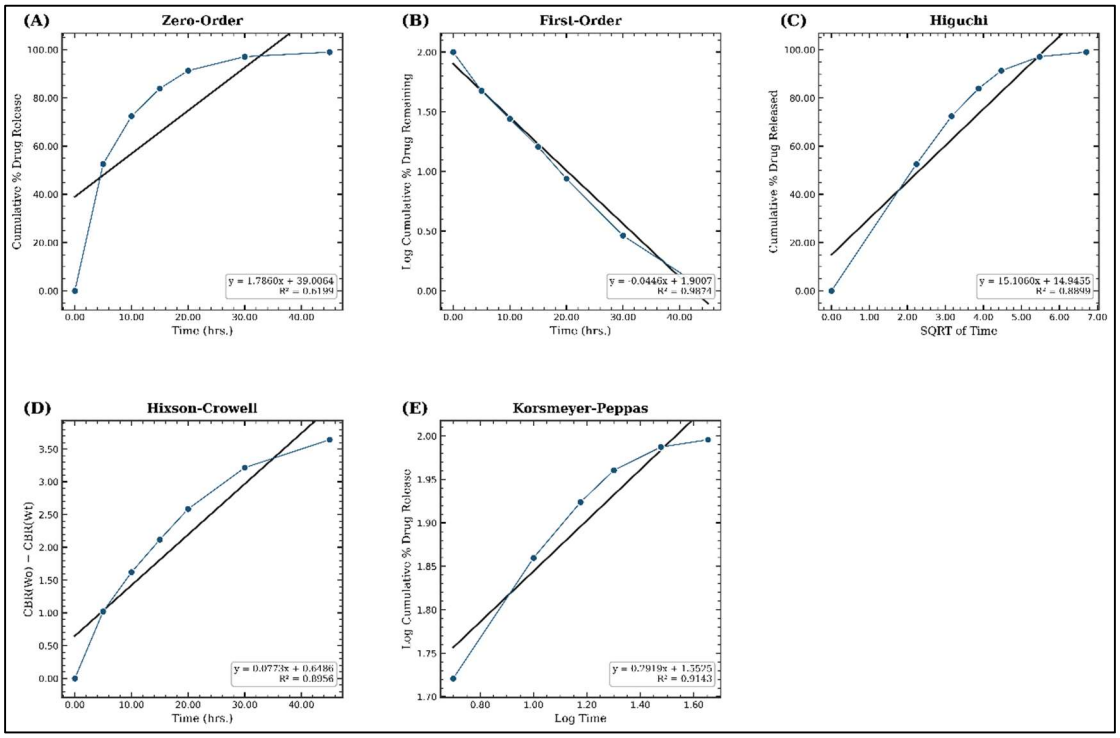

Figure 6: Release kinetic plots of optimized naproxen fast disintegrating tablet (SF6) fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models

Comparative in vitro drug release profile of optimized formulation SF6 versus marketed tablet

Comparing the optimized formulation SF6 to the marketed tablet (drug release profile) in vitro. The dissolution profiles of SF6 and marketed Naprosyn® 500 are compared in Figure 7. SF6 had significantly greater drug release at all time points (52.6 ± 1.7%, 22.4 ± 1.3% for Naprosyn® 500). The dissolution of SF6 was 97.1 ± 2.3% after 30 min whereas the marketed tablet was 81.6 ± 2.1% which was not in compliance with the requirement of ≥ 85% confirming the advantage of dissolution of developed fast disintegrating formulation.

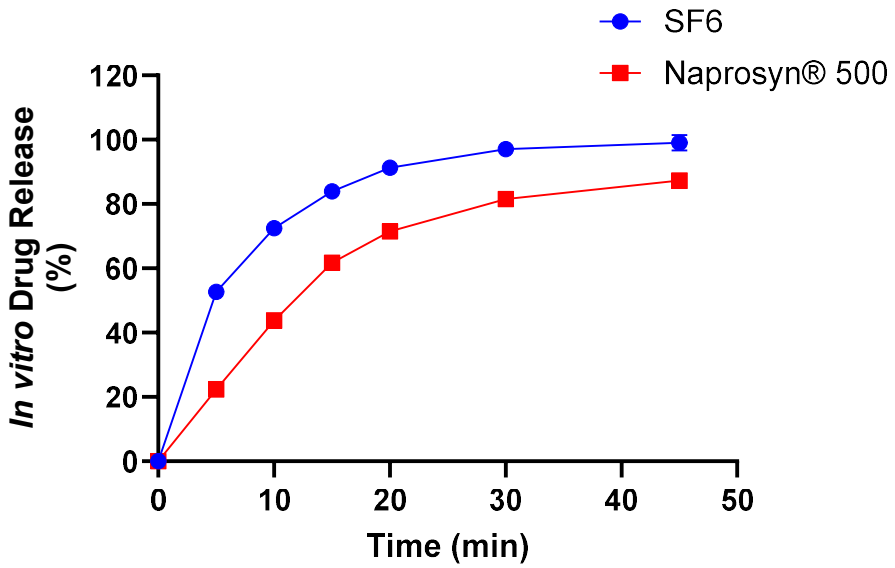

Figure 7: Comparative in vitro drug release profile of optimized formulation SF6 versus marketed tablet Naprosyn® 500 in 0.1 M phosphate buffer pH 7.4 at 37 ± 0.5°C.

Accelerated stability studies

The results of accelerated stability testing of the optimized formulation SF6 at 40°C and 75%RH for a period of three months is given in Table 10. No physical changes were seen throughout the study. There were no significant changes in hardness, friability and weight variation throughout the study. Drug content decreased marginally from 98.85 ± 0.39% to 98.38 ± 0.46%, well within the ICH limit of ±5%. The disintegration time was measured to be 74 ± 1.9 s, compared to 77 ± 2.2 s, which proved the excellent physicochemical stability of SF6 under stressed conditions.

Table 10: Physical and chemical stability parameters of optimized naproxen fast disintegrating tablet (SF6) under accelerated conditions (40°C ± 2°C / 75% ± 5% RH) as per ICH Q1A(R2) guidelines.

Parameter	Initial (0 Month)	1 Month	2 Months	3 Months
Appearance	White, flat-faced, round tablet	White, flat-faced, round tablet	White, flat-faced, round tablet	White, flat-faced, round tablet
Hardness (kg/cm²)	3.5 ± 0.10	3.5 ± 0.11	3.4 ± 0.12	3.4 ± 0.13
Friability (%)	0.61 ± 0.03	0.62 ± 0.03	0.63 ± 0.04	0.64 ± 0.04
Weight variation (mg)	500.8 ± 2.2	500.9 ± 2.3	501.1 ± 2.4	501.2 ± 2.5
Drug content (%)	98.85 ± 0.39	98.71 ± 0.41	98.54 ± 0.43	98.38 ± 0.46

Wetting time (s)	57.9 ± 1.6	58.3 ± 1.7	58.8 ± 1.8	59.4 ± 1.9
Water absorption ratio (%)	89.3 ± 2.2	88.9 ± 2.1	88.4 ± 2.3	87.8 ± 2.4
Disintegration time (s)	74 ± 1.9	75 ± 2.0	76 ± 2.1	77 ± 2.2

Values are expressed as mean ± SD, (n=3).

DISCUSSION

In the present study, fast disintegrating tablets of naproxen were obtained by direct compression of the drug using a novel starch of Nelumbo nucifera rhizome as a superdisintegrant with the addition of Crospovidone (Kollidon® CL) which is known for its superdisintegrating capacity and Stevia rebaudiana leaf powder as calorie-free sweetening agent [34]. The physicochemical identity of naproxen was confirmed by pre-formulation studies in which the melting point range obtained (153-155°C) matched that reported, similarly the characteristic FTIR bands, such as the C=O stretch at 1726.65cm-1 and aromatic C=C vibrations at 1607.44cm-1 matched the reported spectral data [35]. The complete drug-excipient compatibility was confirmed as there was no shift in all the main naproxen peaks in the spectrum of physical mixture (Figure 2) and the DSC confirmed the absence of new bands and shift in the naproxen endotherm (152.37°C) (Figure 3), as reported in literature for naproxen associated with starch based excipients. The pH dependent solubility of the sample (Table 3) indicated BCS Class II and justified the selection of pH 7.4 as the dissolution medium as per USP monograph conditions [36]. The pre-compression parameters (Table 4) such as Carr's index (13.87–14.52%), Hausner's ratio (1.161–1.170) and angle of repose (26.62°–28.14°) indicated good flowability in all batches and within the direct compression prerequisites reported in literature [37]. All batches passed post-compression evaluation (Table 5), and the slight drop in hardness from 3.8 to 3.4 kg/cm² with the increase in the superdisintegrant content is in accordance with the established behavior of FDTs, which indicate that the functional performance is not affected despite the increase in the disintegrant content and thus the creation of porosity. The functional evaluation (Table 6) showed that wetting time was reduced with increasing concentration (87.4 ± 1.8 s to 49.1 ± 1.4 s) while water absorption ratio increased (68.2 ± 1.4% to 94.8 ± 2.4%), which was due to the synergistic effect of swelling and wicking action of starch from Nelumbo nucifera rhizome and strain recovery action of Crospovidone [38]. There is ample literature available to support the disintegrating property of starches derived from plants, and Zea mays and Manihot esculenta starches are known to show comparable disintegrating property. ANOVA (Table 8) showed that disintegration time ($F = 922.00$, $p < 0.0001$) was influenced by the starch from the rhizome of Nelumbo nucifera and drug release enhancement was seen as influenced by Crospovidone ($F = 4655.32$, $p < 0.0001$), suggesting complementary mechanisms [39]. The large negative AB interaction ($p = 0.0017$) for Y_2 is similar to the one reported by others with the use of excessive combined superdisintegrant levels which cause premature surface wetting [40]. The optimized formulation SF6 ($X_1 = 20$ mg, $X_2 = 30$ mg; desirability 0.9117) was able to release 97.1 ± 2.3 % of the drug at 30 min with a disintegration time of 74 ± 1.9 s (Table 9) compared to the marketed Naprosyn® 500 (81.6 ± 2.1 % at 30 min; Figure 7), which was consistent with the improvements in dissolution reported for FDT platforms over conventional BCS Class II NSAID tablet products [41]. First order release ($R^2 = 0.9874$) and Korsmeyer-Peppas exponent $n = 0.29$ indicated that the Fickian diffusion was the dominant mechanism of release in the case of a rapidly disintegrating non-matrix system (Figure 6). A clinical dose of 20 mg Stevia rebaudiana per tablet is clinically rational and steviol glycosides are 200–300 times sweeter than sucrose, do not induce a glycemic response and are JECFA-approved safe; they are suitable for use by diabetic patients [42]. The accelerated stability testing at 40°C/75%RH for three months (Table 10) gave excellent stability, with drug content decreasing only 0.47% and disintegration time increasing slightly from 74 ± 1.9 s to 77 ± 2.2 s, which is similar to the published ICH-compliant stability profile for starch-based FDTs, thus demonstrating robustness and commercial scale-up potential [43].

CONCLUSION

The present study was successfully developed and optimized fast disintegrating tablets of naproxen with a new natural source of superdisintegrant Nelumbo nucifera rhizome starch and calorie free Stevia rebaudiana leaf powder by direct compression 3^2 full factorial design. The complete compatibility of drug and excipients was confirmed by FTIR and DSC studies. The optimized formulation SF6 (Nelumbo nucifera rhizome starch 20 mg; Crospovidone 30 mg) exhibited a disintegration time of 74 ± 1.9 s, cumulative drug release of 97.1 ± 2.3% at 30 min and a desirability score of 0.9117 compared to the marketed Naprosyn® 500 tablet which exhibited a disintegration time of 350 s, cumulative drug release of 94.0 ± 1.3% at 30 min and a desirability score of 0.7059. The drug release was found to be following first order kinetics with the model being Fickian diffusion. The accelerated stability study demonstrated physicochemical stability with ICH Q1A(R2) conditions for three months. The formulation has clinically relevant benefits for dysphagic patients, pediatric, geriatric and diabetic patients who require rapid onset of analgesic action without water. In vivo pharmacokinetic studies in the appropriate animal models are recommended to corroborate the observed in vitro dissolution benefits and to establish increased bioavailability.

Abbreviations

ANOVA: Analysis of Variance; API: Active Pharmaceutical Ingredient; BCS: Biopharmaceutics Classification System; BSS: British Standard Sieve; COX: Cyclooxygenase; CV: Coefficient of Variation; DSC: Differential Scanning Calorimetry; FDT: Fast Disintegrating Tablet; FTIR: Fourier-Transform Infrared Spectroscopy; ICH: International Council for Harmonisation; IP: Indian Pharmacopoeia; df: Degree of Freedom; λmax: Wavelength of Maximum Absorbance; MCC: Microcrystalline Cellulose; NSAID: Non-Steroidal Anti-Inflammatory Drug; ODT: Orally Disintegrating Tablet; pKa: Acid Dissociation Constant; R^2: Correlation Coefficient; RH: Relative Humidity; rpm: Revolutions Per Minute; SD: Standard Deviation; USP: United States Pharmacopeia; UV: Ultraviolet Spectroscopy; w/v: Weight per Volume.

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