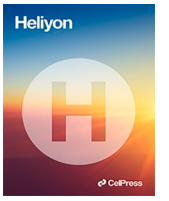
Heliyon 9 (2023) e15432

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Preparation and characterization of naproxen solid dispersion using different hydrophilic carriers and in-vivo evaluation of its analgesic activity in mice

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ARTICLE INFO

Keywords:
Naproxen
Solid dispersion
PEG 8000
Sodium starch glycolate
Analgesic activity
solvent evaporation method

ABSTRACT

Background: Solid dispersion (SD) has been used conventionally as a successful technique for improving the dissolution profile and bioavailability of poorly water-soluble drugs. The aim of this study was to progress the dissolution rate and bioavailability of naproxen (BCS class II) by SD technique.

Materials & methods: In this study, hydrophilic carriers are used for preparing solid dispersion of naproxen by evaporation method. The prepared optimized SDNs were evaluated by *in-vitro* drug dissolution test, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). The in-vivo analgesic effects tests of the optimized SDNs (SDN-2 and SDN-5) were performed by tail immersion method and writhing method.

Results: All the prepared SDNs exhibited a significant increase in the dissolution of naproxen compared to that of the pure drug. Among them, SDN-2 (the dispersion with sodium starch glycolate at 1:2 ratio of naproxen and sodium starch glycolate) and SDN-5 (using the combination of PEG-8000 and sodium starch glycolate with naproxen at 1:1:1 ratio) showed faster dissolution rate as compared to other solid dispersions (SDNs) and pure naproxen. SDN-2 showed 5.4 times better dissolution rate and SDN-5 depicted 6.5-fold increment of dissolution rate compared to pure naproxen drug. DSC, PXRD and SEM microscopy showed that the drugs crystallinity was decreased during the preparation process. FTIR study revealed that naproxen was stable in polymeric dispersions and there was no interaction among the drug and polymers. In writhing method, the percentage inhibition of the number of writhes showed significantly greater ($p < 0.01$), ($p < 0.0001$) analgesic activity for the higher dose treatment groups SDN-2(H), and SDN-5 (H), respectively, when contrasted to the pure drug naproxen. For tail immersion test, there is increase in latency time at 90 min which is significantly greater ($P < 0.01$), ($P < 0.05$), ($P < 0.01$) for treatment groups SDN-2(H), SDN-5(L), and SDN-5(H), respectively that ultimately authenticates that the optimized SDNs (SDN-2, SDN-5) showed better analgesic activity in mice in comparison with the pure drug.

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https://doi.org/10.1016/j.heliyon.2023.e15432
Received 4 January 2023; Received in revised form 24 March 2023; Accepted 7 April 2023
Available online 26 April 2023
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Conclusion: It can be concluded that dissolution of the naproxen could be improved by the making solid dispersion using sodium starch glycolate and/or combination of sodium starch glycolate and PEG 8000 due to the complete transformation of drug into amorphous form with the entire loss of crystallinity, as evidenced by DSC, PXRD, and SEM and also consequences the enhanced analgesic activity in mice.

1. Introduction

Oral medication is the foremost widespread approach for administering drugs because it is easy to administer and it offers many advantages over other dosage forms including ease of manufacture, dose accuracy, and stability. Around 60% of developed medication objects that are commercially accessible are managed through the oral route [1]. Orally given medications can also be indispensable for specific critical ailments like stomach and colorectal malignancies, bowel diseases, various infections, inflammations, gastro-duodenal lesions, and gastroesophageal reflux syndromes. In addition to these advantages, oral preparation has a number of drawbacks, most of which are caused by the drug's physical and chemical properties, such as its poor water solubility and membrane permeability. Additionally, drug absorption from oral drug delivery might be hampered by poor chemical and biological integrity, along with physiologic obstacles such as efflux carriers, pH and metabolic enzymes. Moreover, a number of medicines may induce discomfort and nausea in the local region when administered orally [2].

In the present era, most of the newly discovered pharmaceuticals which are poorly water-soluble, are facing absorption-related problems resulting in showing toxicity and owing to their limited water solubility, may not make it to reach the market [3]. Among formulation experts, the issue of poor solubility is a serious problem [4]. Fortunately, formulation scientists are trying to use different technological approaches to resolve this challenge [5]. The scientists are trying several attempts to get the better dissolution rate of inadequately water-soluble compounds have been documented in the research by chemical changes like salt precipitation, co-crystallization, co-solvency, hydrotropy, innovative solubilizer employment, nanotechnology, etc and physical changes like microencapsulation, micronization, nano-suspension, polymorphs, complex formation, lyophilization/freeze-drying process, micro-emulsions, self micro-emulsifying controlled drug release, and drug dispersion in crystalline solids and solid dispersions [6,7]. Solid dispersion (SD) has been reported as efficient and easiest among many of these different ways accustomed to optimize the solubility of poorly water-soluble substances [8].

Naproxen (6-methyl-2-naphthyl acetic acid) is a non-steroidal anti-inflammatory substance that seems to be a weak acid (pk_a = 4.15) and belongs to BCS class II drug that is poorly soluble in water [9]. Naproxen exhibits very poor solubility causing patient discomfort and variations in plasma drug concentration that could have harmful effects. Naproxen at normal doses/low doses can produce hepatic reactions, hepatotoxicity, and liver damage [10]. Poor solubility and dissolution of naproxen can cause serious side effects in the gastrointestinal system, such as upper GI tract bleeding [11]. Formulations experts are using solid dispersion as a safe, effective, economic, and convenient method to accelerate the dissolution rate of naproxen [12]. In this investigation, we attempted to boost the solubility of naproxen employing the solid dispersion procedure due to its easier and cost-effective method than others and to investigate the impact of various carriers on the dissolution rate of the poorly water-soluble drug naproxen.

Despite the fact, several SD methods have been glanced at the previous investigation for the purpose of dissolution enhancement using various carriers including [13–21] polyvinylpyrrolidone, gelucire 44/14, pearlitol SD 200, PEG-4000, PEG-6000, urea, eudragit RS, eudragit RL, lactose, crospovidone, $\alpha-$ cyclodextrin, hydroxypropylmethylcellulose, *Elaeagnus Angustifolia* fruit powder. However, there is no earlier study concerning the use of a blend of sodium starch glycolate and PEG-8000 on dissolution property of naproxen. PEG-8000 and sodium starch glycolate was used as hydrophilic carriers to prepare solid dispersion of naproxen due to their lesser toxicity, minimum cost, chemical compatibility, greater aqueous solubility, ability to generate solid dispersion in an amorphous form, enhancement of significant drug absorption [22–24]. Furthermore, there is no previous report on *in-vivo* evaluation of SDN in mice. Hence, this study's goal was to increase naproxen's ability to dissolve utilizing a combination of sodium starch glycolate and PEG-8000 using solvent evaporation method and also in-vivo evaluation of its analgesic activity in mice.

2. Materials and methods

2.1. Materials

For this study, Naproxen was bought as a drug sample from Merck & Co., Inc. (Germany). Excipients Na starch glycolate, and PEG-8000 were also purchased from Merck & Co., Inc. (Germany). The membrane filter (0.2 μm) was used for filtering analyte samples. Solvents like ethanol and methanol were purchased from Sigma (USA). All the chemicals, and solvents (ethanol, methanol, and distilled water) used for the laboratory work were of analytical grade.

2.2. Methods

2.2.1. Preparation of naproxen solid dispersion (SDN)

Using various weight ratio of drug and carriers (w/w) (Table 1), the solid dispersions of naproxen were formulated with the help of a solvent evaporation method. More tersely, the desired proportion of naproxen pure powder and the various proportion of polymers

such as Na starch glycolate, PEG-8000 or their combinations were dissolved in the desired amount of ethanol solution. In the meantime, to permit a reasonable loading of drugs into the carrier and a magnetic stirrer was used to stir the solution continuously at a speed of 200 rpm at 50 °C in order to evaporate the solvent from the dispersion system. The remaining solid dispersion was dried at room temperature following the complete solvent evaporation before being ground into a fine powder. Finally, the dried SDNs were passed through 120 mesh screens to get dried granules of uniform size. Thus, six SDNs i.e. SDN-1, SDN-2, SDN-3, SDN-4, SDN-5, and SDN-6 fabricated. The prepared formulations were kept separately and at room temperature in a screw-cap vial for further research and lab tests.

2.2.2. *Percentage of yield*

The yield percentage was measured to determine the method's efficiency; as a result, the method's selection could easily be scrutinized. Therefore, the percentage yield for the desired solid dispersion was computed from the following equation [25].

$$\%\ Yield = \frac{Practical\ Mass\ (Solid\ Dispersion)}{Theoretical\ Mass\ (Drug + Carrier)} \times 100 \tag{1}$$

Theoretical yield: The quantity of product is acquired when the entire controlling chemical has reacted.
Actual yield: Quantity of product is obtained by testing from a chemical reaction.
Percentage yield: The ratio of the real yield to the theoretical yield is multiplied by 100.

2.2.3. *Estimation of encapsulation efficiency (%)*

The encapsulation efficiency of SDNs was measured by utilizing the customized protocol of Kenneth C et al. as discussed earlier [26]. Approximately, The SDNs were carefully weighed out at 10 mg and dissolved in 10 ml of methanol. The solution was vigorously shaken, filtered, and the filtrate's naproxen content was measured spectrophotometrically at 264 nm. Using the following calculation, the amount of medication encapsulated in the SDNs was determined to determine the percentage of encapsulation efficiency:

$$\%\ EE = \frac{\text{Actual drug content}}{\text{Theoritical drug content}} \times 100 \tag{2}$$

To acquire the encapsulation efficiency as the average of three replicate measurements, the aforementioned technique was repeated.

2.2.4. *In-vitro dissolution study*

Using an in vitro dissolution test, the performance of the pure Naproxen powder and SDN were observed and they were done following the paddle method (USP Apparatus 2) by a dissolution tester (Electrolab, India), where distilled water was used as the medium. A quantity of SDN equivalent to 25 mg naproxen powder was added to the distilled water of 500 ml and it was maintained thermostatically at 37 ± 0.5°C at 50 rpm (paddle speed). 10 ml specimens were withdrawn from the dissolution vessel at specific time intervals from 5 min to 120 min (5, 10, 15, 30, 45, 60, 90, 120 min) and the vessel was refilled with 10 ml distilled water to maintain the volume of dissolution medium and then filtered. After that, 10 ml of filtered solution was conveyed to a volumetric flask and simultaneously diluted up to 25 ml of distilled water. Drug content of NPX at each point was assayed by measuring absorbance at 264 nm with the help of a UV-spectrophotometer (Shimadzu UV-1800, Japan). Three replicates of each measurement were carried out and mean value was calculated to obtain dissolution profile. The standard solution was generated by adding 25 mg naproxen powder to dissolve it into 25 ml methanol. Then, 0.5 ml solution was taken to a volumetric flask followed by the addition of methanol up to 25 ml to get the final desired concentration of 20 μg/ml.

2.2.5. *Characterization of prepared SDN*

2.2.5.1. Differential scanning calorimetry (DSC). Thermograms comprising Naproxen, PEG-8000, Na starch glycolate, physical mixture, SDN-2, and SDN-5 had been acquired with the help of the TGA-DSC Simultaneous Thermal Analyzer (NETZSCH STA 449F5 STA449F5B-0167-M). The laboratory test was performed at the Institute of Glass and Ceramic Research & Testing (IGCRT), Bangladesh Council of Scientific and Industrial Research (BCSIR). For the execution of the desired tests, every sample of 3–5 mg was taken in a

Table 1
Formulations of naproxen solid dispersion (SDN) using different drug-carrier ratios.

Group	Formulation	Drug (Naproxen)	Na starch glycolate	PEG-8000	Ratio
I	SDN-1	100 mg	100 mg	–	1: 1
	SDN-2	100 mg	200 mg	–	1: 2
II	SDN-3	100 mg	–	100 mg	1: 1
	SDN-4	100 mg	–	200 mg	1: 2
III	SDN-5	100 mg	100 mg	100 mg	1: 1: 1
	SDN-6	100 mg	200 mg	200 mg	1: 2: 2

Group I: SDN containing Na starch glycolate; Group II: SDN containing PEG-8000; Group III: SDN containing a mixture of PEG-8000 with Na starch glycolate.

sealed aluminum pan (Al_2O_3 85 μl, with a lid) and the naproxen, PEG-8000, Na starch glycolate, physical mixture, SDN-2, and SDN-5 were heated from 28 °C to 200 °C, from 28 °C to 300 °C, from 28 °C to 300 °C, from 30 °C to 200 °C, from 28 °C to 200 °C and from 28 °C to 300 °C respectively, where the scanning rate was 5 °C/min and the whole process was done under the nitrogen purge. Besides that, another reference was a vacant aluminum pan.

2.2.5.2. Powder x-ray diffraction (PXRD). Diffraction was studied using a smart lab SE (Rigaku) x-ray diffractometer. All of the specimens were taken to the Institute of Glass and Ceramic Research & Testing (IGCRT), Bangladesh Council of Scientific and Industrial Research (BCSIR), where the requisite tests were carefully performed. The specimens (Naproxen, PEG-8000, Na starch glycolate, physical mixture, SDN-2, and SDN-5) were tested under *Cu-kβ* radiation at *Cu* Tube and 1.5408 Å (40 kV, 50 mA) and they were scanned from 5 ° - 45 ° at the rate of 10 °/min.

2.2.5.3. Fourier transform infrared spectroscopy (FTIR). An FTIR spectrometer IR Prestige-21 (Shimadzu Corporation, Japan) with Miracle- 10 ATR Accessory was used to observe the drug-carrier interactions where the attenuated total reflection method in transmittance mode was employed for IR spectra. The Institute of Glass and Ceramic Research & Testing (IGCRT), Bangladesh Council of Scientific and Industrial Research (BCSIR) conducted the tests for all supplied specimens inside their laboratory. The disk of every grounded specimen (Naproxen, PEG-8000, Na starch glycolate, physical mixture, SDN-2, and SDN-5) was organized and combined with potassium bromide. During the laboratory test of the specimens, 400-4000 cm^{-1}, 4 cm, and 30 were the scanning range, resolution, and number of scans respectively.

2.2.5.4. Scanning electron microscopy (SEM). The morphology of shape, cross-section, and surface of pure Naproxen, PEG-8000, Na starch glycolate, physical mixture, SDN-2, and SDN-5 were monitored by the SEM system called Phenom Pro Desktop (Phenom 1481), Thermo Fisher Scientific, USA. The experiments were also performed at the Institute of Glass and Ceramic Research & Testing (IGCRT), Bangladesh Council of Scientific and Industrial Research (BCSIR). During the laboratory tests, 15 kV was set as an accelerating voltage and CeB6 was used as the electron beam-generating source.

2.2.6. In-vivo evaluation of SDN

2.2.6.1. Experimental animal. For the experiment, 60 male Swiss albino mice weighing 25–30 g were obtained from the International Center for Diarrheal Disease and Research, Bangladesh (ICDDRB), an animal testing division, at an age of 3–4 weeks. All of the mice were kept in conventional settings (temperature: 23.0 ± 2.0 °C, RH: 55–65%, and a 12-h light/12-h dark cycle) and also had *ad libitum* and water exposure to feed as well as drink. Before the actual trial, the mice were allowed a week to adjust to the research setting. Under reference number, ERC/FBST/JUST/2021–122, the Ethical Review Committee of the Faculty of Biological Science and Technology at Jashore University of Science and Technology authorized all guidelines for such an experimental animal model as well as all ethical standards regarding the use of live animals in the practice of research. This authorization was issued on September 5, 2022.

2.2.6.2. Analgesic activity. By using the mouse acetic acid-induced writhing test [27], it was determined if NPX and SDN had any peripheral analgesic activity. The tail immersion method was used to assess the central analgesic activity [28].

i) Acetic acid-induced writhing in mice [27].

The method of acetic acid-induced writhing was chosen to assess the analgesic efficacy. Stretching is characterized as tension to one side, extension of the back legs, contraction of the abdomen till the mouse's belly meets the ground, and trunk rotation (twist). Any writhing is regarded as a favorable reaction. For the purpose of evaluating the analgesic effectiveness, a total of 30 Swiss albino mice weighing 20–30 g was separated into six groups (A-F), each with five mice. Each mouse was given a unique marking. 12 h before the medication delivery and during the experiment, food was withheld. The animals were appropriately weighed and numbered. Standard medications and the test/treatment were administered orally.

Group A mice served as the normal control (NC, 1% (w/v) Na CMC, n = 5); groups B and C served as lower and higher dose treatment groups (SDN-2, 50 mg/kg body and 500 mg/kg body weight, n = 5); groups D and E served as lower and higher dose treatment groups (SDN-5, 50 mg/kg body and 500 mg/kg body weight, n = 5); and group F served as a standard-dose group (pure Naproxen, 500 mg/kg BW, n = 5)).

An intraperitoneal injection of 1% acetic acid dissolved in distilled water at a volume of 0.1 ml/10 g body weight was used to cause writhing after 60 min. Naproxen was dissolved in a standard solution of normal saline water at a dose of 500 mg/kg/10 ml. The stretching motions, which included back arches, torso lengthening, and hind limb extensions, were counted during the 30-min recording of the writhing episodes.

Inhibition percentage was calculated using the following formula:

$$\left(\%\right) \text{ inhibition} = \frac{100 \times (\text{mean constrictions in control group} - \text{number of constrictions in treated group})}{\text{mean constrictions in control group}} \quad (3)$$

ii) Tail immersion test

The tail immersion test was performed to assess the response to thermal stimuli using Hasan's approach [28]. A total of 30 Swiss albino mice were arbitrarily separated into six groups (A-F), each including five animals, and all of them starved for 12 h having free access to a safe water supply as well as *ad libitum*. Before their tails got immersed the mice were allowed a 1-h pre-treatment with normal control for group A mice (NC, 1% w/v Tween-80, n = 5), group B treated as a standard-dose group (pure Naproxen, 500 mg/kg BW, n = 5), whereas groups C, and D as lower and higher dose treatment groups (SDN-2, 50 mg/kg and 500 mg/kg body weight, n = 5), and E, and F as lower and higher dose treatment group (SDN-5, 50 mg/kg and 500 mg/kg BW, n = 5), respectively. The test/treatment and standard drugs were treated in animals with oral intubation. Animals were then confined with the tail stretching out in an appropriate restrainer. The pain reaction time (PRT) or tail-flick latency of each mouse was measured by dipping approximately 1–2 cm of its tail into a water bath that included hot water up to a temperature of 55 ± 10 °C and documenting the time required for the mouse to flick its tail or pull back it off the hot water throughout sec. To minimize risks to the tail tissues, the optimum cutoff interval during immersion remained 180 s. Reaction time was measured as a mean for the following two readings after the first reading was erased. Following the administration of medicines, the latent time of the tail-flick response was calculated at 0, 30, and 90 min.

2.2.7. Statistical analysis

MS Office Excel and IBM SPSS applications were used to organize and interpret data. The significance level between means was determined using one-way repeated measures analysis of variance (ANOVA), and the obtained values were presented as mean ± standard error of the mean (SEM). For multiple comparison tests, Dunnett's test was used. The level of significance was determined as a *P*-value of less than 0.05.

3. RESULTS and DISCUSSION

3.1. Results

3.1.1. Percentage of yield

The percentage of yield is an important parameter for determining the proficiency of a formulation. In Table 2, the percentage yield of SDN formulations was computed and represented. The yield as a percentage was determined to be between 87.5% (SDN-1) and 98.33% (SDN-5).

3.1.2. Encapsulation efficiency

The encapsulation efficiency is an important measurement that gives a clear idea about the entrapment efficiency of a drug and scale up capabilities of the technique. Encapsulation efficiency was accomplished to determine exactly how much naproxen was entrapped in the formulation which in turn is necessary to calculate the equivalent weight of SDN formulations to that of the marketed product [26]. The highest encapsulation efficiency was obtained by SDN-5 (95.44%). This might be due to the maximum adsorption efficiency of naproxen to the surface of naproxen.

3.1.3. Physicochemical evaluation of SDN

3.1.3.1. In-vitro dissolution study. The dissolution profiles of pure naproxen (NPX), SDN1, SDN2, SDN3-SDN4, and SDN5- and SDN6 has been shown in Fig. 1. Dissolution study was performed to evaluate the dissolution profile of formulated SDNs in comparison with pure NPX. Fig. 1 below displays the total % of medicine released throughout the course of 120 min. According to in vitro dissolution experiments, all solid dispersions of NPX dissolve at a noticeably faster pace than pure NPX does within the range of 5–120 min.

In comparison to pure drug (9.68%), the immediate drug release of SDN-1, SDN-2, SDN-3, SDN-4 was 3.22 (31.18%), 4.29 (41.49%), 1.47 (14.23%), 2.58 (25.05%) times greater than that of pure NPX (9.68%) at 5 min. Considering pure drug and developed SDN-1, SDN-2, SDN-3, SDN-4 formulations, the in vitro release studies revealed that percentage of drug release following 30 min reached at 11.64%, 41.05%, 52.88%, 30.23%, 41.68%, accordingly. The dissolution level of SDN-1, SDN-2, SDN-3, SDN-4 showed 3.53, 4.54, 2.60, 3.58-fold enhancement than that of the pure NPX at 30 min. Following 120 min, the values exhibited 4.76 (68.19%), 5.40 (77.29%), 3.54 (50.73%), 4.16 (59.52%) fold higher when contrasted to pure drug naproxen (14.30%). Among these four formulations, it is seen that SDN-2 comprising NPX and sodium starch glycolate at the ratio of 1:2 showed higher dissolution rate that

Table 2
Yield obtained in naproxen solid dispersion (SDN).

Formulation code	Percentage of yield	%EE (Mean ± SEM)
SDN-1	87.50	83.27 ± 1.01
SDN-2	98.05	93.65 ± 0.72
SDN-3	89.12	85.27 ± 0.99
SDN-4	96.67	90.58 ± 0.88
SDN-5	98.33	95.44 ± 0.49
SDN-6	97.80	91.50 ± 0.12

NPX: Naproxen. SDN-1 (NPX: Na starch glycolate ratio 1:1), SDN-2 (NPX: Na starch glycolate ratio 1:2), SDN-3 (NPX: PEG ratio 1:1), SDN-4 (NPX: PEG ratio 1:2), SDN-5 (NPX: PEG: Na starch glycolate ratio 1:1:1), SDN-6 (NPX: PEG: Na starch glycolate ratio 1:2:2). n = 3; SEM = standard error of the mean.

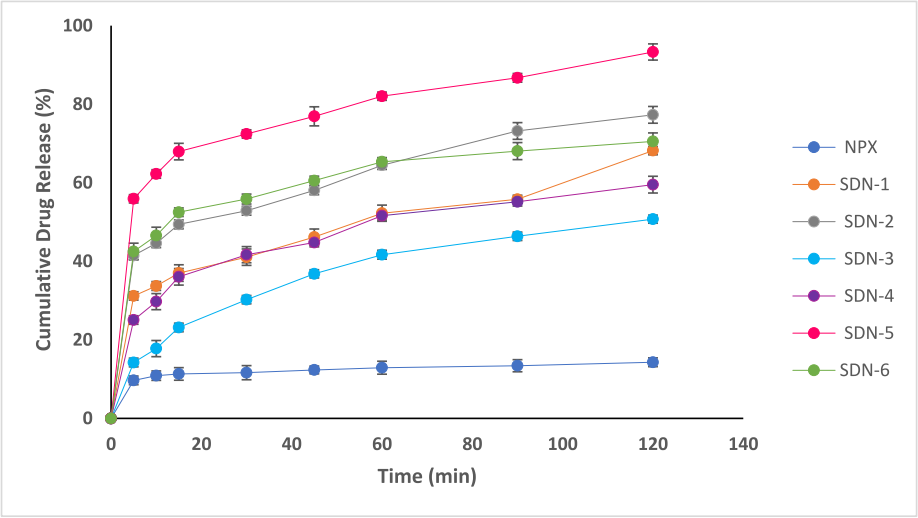

Fig. 1. In-vitro Dissolution Profile of Pure NPX 1, SDN-1, SDN-2, SDN-3, SDN-4, SDN-5, and SDN-6. Values are expressed as mean ± SD (n = 3). SD= Standard deviation.

SDN-1 having NPX and sodium starch glycolate at the ratio of 1:1. Similarly, SDN-4 having NPX and PEG-8000 at the ratio of 1:2 exhibited greater dissolution that SDN-1 containing NPX and PEG-8000 at the ratio of 1:1. By comparing these four formulations, it is observed that the highest value was recorded for the dispersion of naproxen with sodium starch glycolate at a ratio of 1:2 (SDN-2).

Depending on these observations, two new formulations (SDN-5 and SDN-6) were prepared using two carriers together. When compared to pure NPX, the percentage of drug release of naproxen from SDN-5 prepared with NPX, PEG-8000 and sodium starch glycolate at a ratio of 1:1:1 indicated 5.78 (55.91%), 6.22 (72.42%), and 6.52 (93.30%) times enhancement of solubility at 5, 30, and 120 min. SDN-5 where an additional hydrophilic polymer PEG-8000 was used along with sodium starch glycolate indicating that these

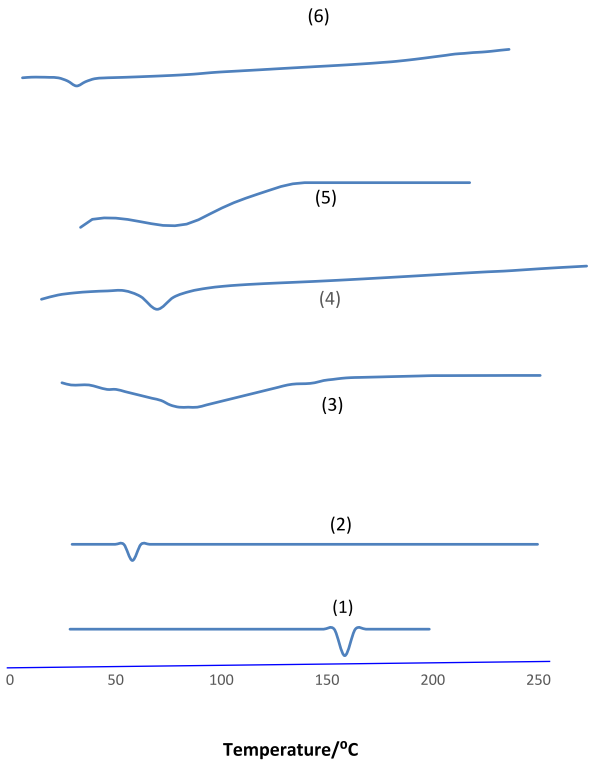

Fig. 2. DSC curve of (1) NPX, (2) PEG-8000, (3) sodium starch glycolate, (4) physical mixture of NPX with PEG-8000 and Na starch glycolate at a ratio of 1:1:1, (5) SDN-2 and (6) SDN-5.

two hydrophilic polymers might have synergistic effects on drug dissolution, and that would be further characterized by DSC, PXRD, FTIR and SEM analysis. As relative to the pure drug, SDN-6 containing NPX, PEG-8000 and sodium starch glycolate at a ratio of 1:2:2 showed drug release which was 4.39 (42.51%), 4.80 (55.85%), 4.93 (70.53%) fold higher than that of pure NPX. Therefore, the among these two formulations comprising of NPX, PEG-8000 and sodium starch glycolate, SDN-5 having the carrier ratio of 1:1:1 disclosed higher dissolution rate.

From the in vitro drug release profile, it can be seen that formulation SDN5 containing NPX, PEG, and Na starch glycolate (1:1:1 ratio of NPX: PEG: Na starch glycolate) showed the highest dissolution rate at each sampling point throughout 120 min compared with other formulations. The improvement of the drug's wettability, transformation into an amorphous state, and solubilization of the drug by hydrophilic carriers may all be responsible for this outcome.

The two formulations (SDN-2 and SDN-5) which showed higher percent of yield and encapsulation efficiency and exhibited higher drug release from the formulations after 120 min was taken for further physicochemical characterization and in-vivo evaluation in mice.

The preceding was the descending order of the increment in dissolution rate after 120 min: pure naproxen > SDN-3 > SDN-4 > SDN-1 > SDN-6 > SDN-2 > SDN-5.

3.1.4. Solid state characterization of SDN

3.1.4.1. DSC analysis. Fig. 2 shows DSC thermal thermograms of pure Naproxen, PEG, Na starch glycolate, physical mixture, and optimized solid dispersion formulation of naproxen (SDN-2 as well as SDN-5). In the thermograms, sharp endothermic peaks were observed for pure naproxen, and PEG-8000, at 153.34 °C and 57.62 °C, respectively confirming the crystalline nature of those compounds. A broad peak for sodium starch glycolate was found at 95.5 °C which directs poor crystalline characteristic of this material. There was no endothermic peak corresponding to naproxen on the DSC thermogram of SDN-2, however, there was a broadened peak at 69.62 °C corresponding to PEG-8000 due to most likely the deformation of PEG-8000. The thermogram of SDN-5 also did not show any endothermic peak for pure naproxen, rather exhibited a broadened peak corresponding to PEG-8000 at 58.30 °C. Furthermore, the thermogram of physical mixture also did not show any endothermic peak for pure naproxen rather showed a peak (65.1 °C) corresponding to PEG-8000. As no endothermic peak corresponding to the melting point of pure crystalline naproxen, it has been suggested that when SDN-2 and SDN-5 is generated, naproxen undergoes a transition from crystalline to amorphous nature.

3.1.4.2. Powder X-ray diffraction studies. When a drug is formed into a solid dispersion, any changes in crystallinity of the drug that precipitates in an amorphous form can be examined using powder X-ray diffraction analysis. Any changes in the drug's crystallinity

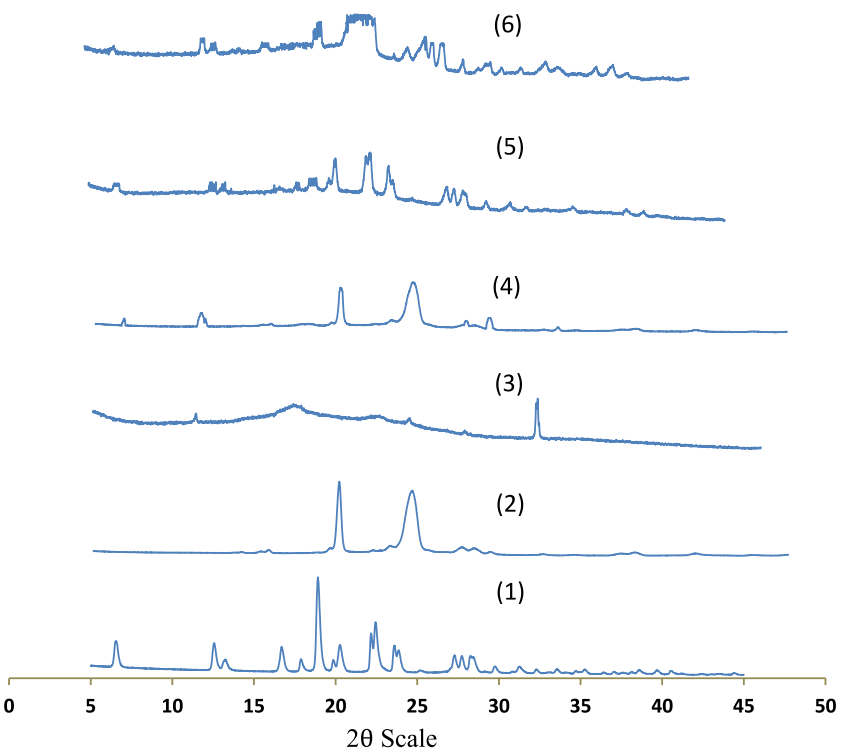

Fig. 3. Powder X-ray diffraction patterns of (1) NPX, (2) PEG-8000, (3) sodium starch glycolate, (4) physical mixture of NPX with PEG-8000 and Na starch glycolate at a ratio of 1:1:1, (5) SDN-2 and (6) SDN-5.

that might be one of the mechanisms causing better dissolution could be studied using PXRD. To validate the outcomes of the DSC experiments, an XRD analysis was conducted. Fig. 3 displays the X-ray diffractograms of optimal solid naproxen dispersions (SDN-2 and SDN-5), physical mixture, physical mixture, PEG-8000, Na starch glycolate, and pure naproxen. Pure naproxen's XRD pattern displayed multiple sharp, narrow, and strong peaks with extremely high intensities at 2θ angles 6.58, 12.64, 13.34, 16.77, 18.71, 18.91, 20.1, 20.31, 22.21, 22.47, 23.58, 23.85, 27.37, 27.81, 28.39° which reflects its high crystallinity [29]. It was observed that the diffraction pattern of the carrier PEG-8000 revealed two distinct peaks for crystallinity at 19.17, and 23.39°, whereas another carrier Na starch glycolate only showed one sharp peak for crystallinity at 31.63°. The XRD pattern depicted by the carrier PEG-8000 and Na starch glycolate revealed a reduction in the number of peaks, which most likely indicates a drop in crystallinity. The spectrum of SDN-2 and SDN-5 are similar to that of a normal amorphous material and lacks any distinctive sharp peak that would correlate to NPX with a sizable intensity. As, most of the naproxen crystallinity peak was destroyed after the SDN-2 and SDN-5 formulations were created, indicating that naproxen has changed from a crystalline to a completely amorphous state (Fig. 3). On the other hand, diffraction pattern of physical mixture (Naproxen: sodium starch glycolate: PEG-8000) showed partial amorphization of the naproxen, as some of the naproxen crystalline peak was disappeared. Along with these consequences, the amorphous property of naproxen in its formulation with sodium starch glycolate and PEG-8000 was considered to be mainly responsible for the dissolution enhancement [30,31].

3.1.4.3. FTIR analysis. Fourier transform infrared (FT-IR) spectra of naproxen, PEG-8000, sodium starch glycolate, physical mixture and solid dispersions of naproxen (SDN-2 and SDN-5) are shown in Fig. 4. The FT-IR spectra were collected in the 400–4000cm-1 range in order to assess compatibility.

Because pure naproxen exhibited distinctive peaks at 3361 cm^{-1}, 3030 cm^{-1}, 2963 cm^{-1}, and 1727 cm^{-1}, for –OH, -CH3, -CH3, and –C═O stretchings respectively. It was also revealed *C*–O stretching at 1090 cm^{-1}, symmetric (aryl-O) stretchings at 1264 cm^{-1} and 1028 cm^{-1}, (C═C) aromatic stretchings at 1604 cm^{-1}, 1481 cm^{-1}. PEG-8000 shows peaks at 2877 cm^{-1} (alkyl CH stretching),1465, 1342, 1284,1278, and 1244 cm^{-1} (alkyl CH deforming), 1110 cm-^{1}(*C*–*O*–C stretching),1080cm-1 (*C*–OH stretching). The spectra of sodium starch glycolate showed –OH, –C═O, -CH2, –CH, and -*C*-C stretching at 3388.1 cm^{-1}, 1579.7 cm^{-1}, 1384.88- cm^{-1}, 1330.68 cm^{-1}, -*C*-C at 989.2 cm^{-1} respectively.

The spectra of the optimized formulation (SDN2 and SDN5) did not differ from that of the area of the main naproxen absorption bands indicating the absence of any hydrogen bonding interaction between drug and polymers (PEG-8000 and sodium starch glycolate). The spectra of physical mixture clearly exhibited the absorption bands, demonstrating the existence of naproxen, sodium starch glycoate and PEG-8000.

As the formulations (SDN2 and SDN5) prepared by sodium starch glycolate and PEG-8000 showed characteristic peaks (C═O stretching and *C*–O ester stretching) at almost similar positions with that specify the compatibility of the carriers with naproxen or there was no chemical interaction or decomposition of naproxen during the preparation of the solid dispersions. Furthermore, the spectra can be simply regarded as the superposition of drug and carrier.

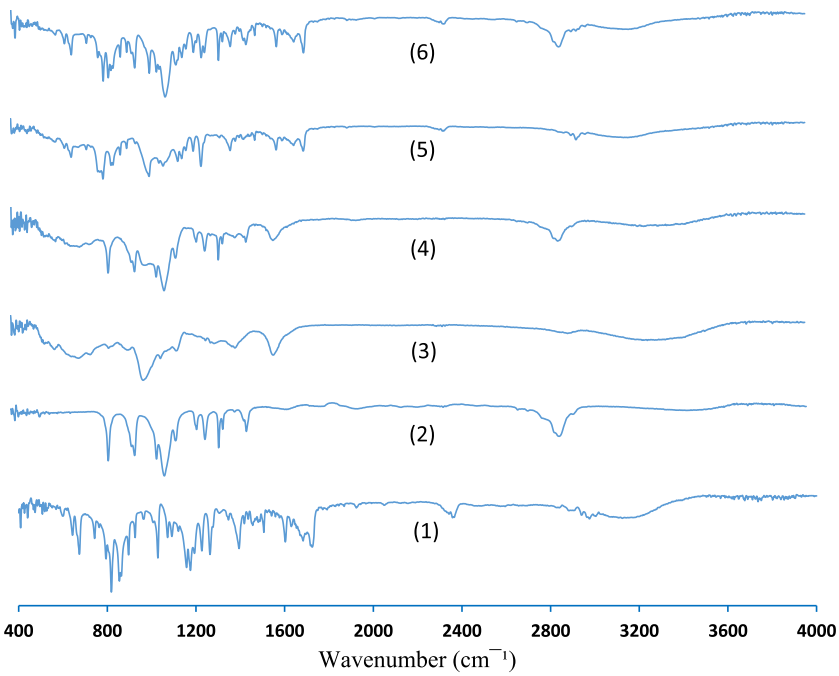

Fig. 4. FTIR spectra of (1) NPX, (2) PEG-8000, (3) sodium starch glycolate, (4) physical mixture of NPX with PEG-8000 and Na starch glycolate at a ratio of 1:1:1, (5) SDN-2 and (6) SDN-5.

3.1.4.4. SEM analysis. SEM photomicrographs of pure NPX drug, PEG-8000, sodium starch glycolate, physical mixture and solid dispersions (SDN-2 and SDN-5) are depicted in Fig. 5. Pure NPX exhibits crystals in the form of flake shapes, while PEG-8000 exhibits massive, brick-like particles as seen in SEM. SEM of sodium starch glycolate showed irregularly-shaped granules. The structure of the NPX crystal in solid dispersion (SDN-2 and SDN-5) is entirely different. This suggests that SDN-2 and SDN-5 developed a brand-new structure. Large and irregular agglomerated particles of the polymers (PEG-8000 and sodium starch glycolate) are seen in the photomicrograph of SDN-2 and SDN-5. Also, it was difficult to distinguish the presence of naproxen crystals in the photomicrograph of SDN-2 and SDN-5. Naproxen appeared to be incorporated into the particles of the two polymers. The above mentioned information confirmed that the results could be attributed to dispersion of the drug in the molten mass of the polymer.

3.1.5. Evaluation of in-vivo analgesic activity of SDN

3.1.5.1. Acetic acid-induced writhing test in mice. Table 3 display the outcomes of the acetic acid-induced writhing test performed on the SDN-2, SDN-5, and pure NPX. The tabulated findings demonstrated that, for doses of 500 mg/kg and 50 mg/kg of SDN-2, respectively, SDN-2(H) and SDN-2(L) reduced the number of writhes by 68.29% (23.85 ± 1.42) and 62.66% (28.08 ± 0.65). SDN-5 (H) and SDN-5(L) reduced the number of writhes by 72.71% (20.52 ± 0.85) and 63.11% (27.74 ± 1.13) for 500 mg/kg and 50 mg/kg of SDN-5, correspondingly whereas the reference standard (pure NPX) drug reduced the number of writhes by 59.06%

3.1.5.2. Tail immersion test. The tail immersion test outcomes at 0, 30, 60, and 90 min following oral administration of pure NPX (500 mg/kg), two doses (50 and 500 mg/kg) of SDN-2 and SDN-5 are exposed in Table 4. Treatment with the vehicle (1% Tween 80 in water) had no discernible impact on the tail immersion's latency. The latency time in seconds by SDN-2(L), and SDN-2(H) was 9.01 ± 0.38 and 10.67 ± 0.81 at doses of 50 mg/kg and 500 mg/kg, respectively, at 90 min. Following 90 min of treatment, the latency time

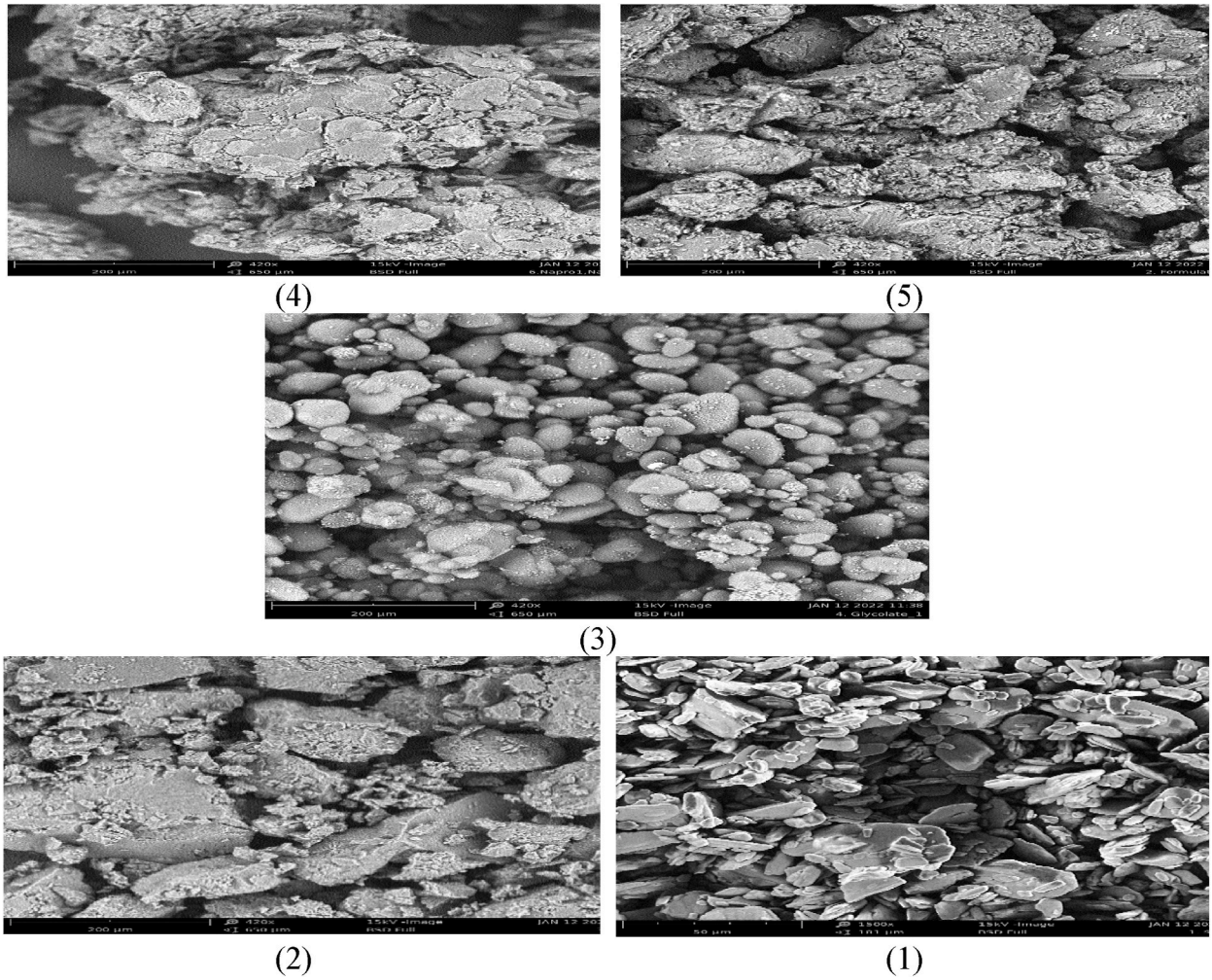

Fig. 5. Scanning electron microscopy of (1) NPX, (2) PEG-8000, (3) sodium starch glycolate, (4) SDN-2 and (5) SDN-5.

Table 3
Analgesic activity of SDN-2 and SDN-5 on acetic acid-induced writhing response in mice.

Group		No. of Writhes in 30 min (mean ± SEM)	Inhibition (%)
A	Control	75.72 ± 1.69	–
B	SDN-2 (L)	28.77 ± 1.23****	62.00
C	SDN-2 (H)	23.34 ± 0.58****$^{++}$	69.18
D	SDN-5(L)	27.49 ± 0.86****	63.70
E	SDN-5 (H)	20.45 ± 1.19****$^{++++}$	72.99
F	Standard	30.87 ± 0.98****	59.23

Values are presented as mean ± SEM, (n = 5); *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs NC;+p < 0.05, $^{++}$ p < 0.01, $^{+++}$ p < 0.001, $^{++++}$p < 0.0001 vs NPX; Dunnett's test as compared to control and standard.

by SDN-5(L), and SDN-5(H) recorded was 9.86 ± 0.40 and 10.92 ± 0.66 at doses of 50 mg/kg and 500 mg/kg, respectively, whereas, for the pure drug naproxen it was 7.58 ± 0.55. SND-2 and SDN-5 at all (low and high) tested doses revealed measurable and dose-related increases in the time-span of tail immersion when compared with pure naproxen.

3.2. Discussion

Dissolution is the rate liming step for less water-soluble medications in their absorption through the oral route. The earlier research studies demonstrated that the oral absorption and effectiveness [14,17,32–34] of a poorly soluble drug naproxen can be enhanced by manufacturing solid dispersions and subsequent augmentation of dissolution rate. Solvent evaporation technique is one of the effective methods which can be used successfully to generate [16] solid dispersions of naproxen. In our research study, the solid dispersions of naproxen were generated using solvent evaporation system through diverse kinds of carriers used individually or in combination such as Na starch glycolate, PEG-8000. Our research work focused on improving the dissolution rate of SDNs using such carrier combinations which were not exploited previously. Manogna et al. reported that solid dispersion of formulation (F3) naproxen plus urea mixture generated in a (1:3) ratio, which showed 6.2 times greater in vitro drug release rate than pure drug naproxen [33]. However, in our investigation, during the in-vitro dissolution test, the percentage naproxen release from SDN-2 and SDN-5 was between 5.4 and 6.5 fold higher at 120 min than that of pure naproxen in water medium (Fig. 1). The findings of our investigation imply that the enhanced wettability and enhanced dissolution of medicines from the SDN may be attributed to the hydrophilic qualities of PEG-8000 and the water absorption properties of Na starch glycolate. It was experimentally proved that drug in solid dispersions exists in the amorphous form [35] which gives high thermodynamic activity compared to its original crystalline form hence boost the dissolution of the drug [36]. The limited dissolution of naproxen is an effect of its poor wettability and hydrophobicity. Dissolution of naproxen in solid dispersion was improved because of its increased amorphous nature due to the anti-crystallization effect of carriers and increased surface area [18].

In our DSC experiment (Fig. 2), no endothermic peak related to the pure drug naproxen was observed for the DSC curve of SDN-2 and SDN-5 but demonstrated characteristic peaks at 69.62 °C and 58.30 °C, respectively, almost similar to PEG-8000. So, our DSC study results indicate the conversion of crystalline naproxen into an amorphous form throughout the formation of SDN-2 and SDN-5, as no new peak was found at newly formulated SDN-2 and SDN-5. Again, most of the distinctive naproxen peaks for crystalline nature were not visible within the solid dispersion pattern of the XRD spectrum (Fig. 3), signifying that crystallized naproxen had been converted toward an amorphous form. The PXRD spectra of SDN-2 and SDN-5 represented that of a typical amorphous state with no distinguishing peak. It is well understood that the absence of a clear peak in drug formulations indicates that a significant amount of the drug is dispersed inside a solid-state [37]. From the FTIR spectra (Fig. 4) of the two optimized formulations (SDN-2 and SDN-5), it was evident that the pure drug in the formulations of SDN-2 and SDN-5 had undergone no chemical reaction or interaction with any of the carriers (PEG-8000 and Na starch glycolate) used as there were all characteristic peaks at almost similar positions and no disappearing or appearing of any significant peak at all. So, it can be proved by the FTIR study revealed that the drug was stable [21] in SDNs. In a previous study, ternary SDs of NPX-PEG-6000-crospovidone [18] system for optimized formula, there was a decrease in the intensity of naproxen for the XRD spectrum however the main peaks remained in their respective locations confirming the

Table 4
Analgesic activity of SDN-2 and SDN-5 on tail immersion method in mice.

Group		Treatment	Latency time in sec			
			0 min	30 min	60 min	90 min
A	NC	Vehicle	2.49	1.73	1.56	1.89
B	NPX	Vehicle + pure NPX 500 mg	2.59	5.24	6.48*	7.99****
C	SDN-2 (L)	Vehicle + SDN-5,eq. to 50 mg/kg NPX	2.56	5.67*	7.88**	9.01****
D	SDN-2 (H)	Vehicle + SDN-5,eq. to 500 mg/kg NPX	2.55	6.79**	8.97***	10.56****$^{++}$
E	SDN-5 (L)	Vehicle + SDN-16,eq. to 50 mg/kg NPX	2.51	5.96*	7.99**	9.78****$^{+}$
F	SDN-5 (H)	Vehicle + SDN-16,eq. to 500 mg/kg NPX	2.55	6.51**	9.17****	10.82****$^{++}$

Values are presented as mean ± SEM, (n = 5); *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs NC; + p < 0.05, ++ p < 0.01, +++ p < 0.001, ++++p < 0.0001 vs NPX; Dunnett's test as compared to control and standard.

para-crystalline nature of ternary SDs. The surface morphology for SDN formulations (SDN-2 and SDN-5), using SEM (Fig. 5) was also used to investigate a specific transformation from crystalline naproxen to an amorphous structure following solid dispersion generation. In SDN-2 and SDN-5, a new (agglomerated) morphology different from pure naproxen crystalline structure was identified, which improved water retention and therefore increased naproxen's dissolution rate [38], suggesting that the pure drug naproxen was mixed well with carriers PEG-8000 and Na starch glycolate devoid of phase separation and appeared as amorphous nature. In a prior study, in contrast [39] with pure naproxen powder, which had the appearance of flat flakes, the morphology of the PVP-infused naproxen significantly changed and grew dendritically, which was in charge of improving the solubility and dissolving rate of pure naproxen. The aforementioned DSC thermograms, PXRD spectra, FTIR spectroscopy, and SEM indicated the complete alteration of naproxen's crystalline structure into the amorphous phase accomplished with SDN-2 and SDN-5 due to the addition of carrier or mixtures comprising PEG-8000 and Na starch glycolate. Among the optimized two formulations (SDN-2 and SDN-5), SDN-5 exhibited a more significant drug release than SDN-2. Because, in SDN-5, combination of Na starch glycolate and PEG-8000 were used. Na starch glycolate, a widely utilized super-disintegrant, might be used to speed up the dissolution and solubility of the drug naproxen throughout this study [40]. The incorporation of PEG-8000 as a meltable hydrophilic polymer carrier in the formulation of SDN could have been a potential strategy to increase its dispersion, disintegration, and absorption [41].

Furthermore, an experimental animal model proved the safety and effectiveness of recently created SDNs (SDN-2 and SDN-5). In this study, the in-vivo analgesic effect of naproxen was explored as one model to demonstrate the efficacy of naproxen solid dispersion formulations SDN-2 and SDN-5 based on the acetic acid-induced writhing test and tail immersion test. Studies on acetic acid-induced writhing test revealed that the percentage inhibition of the number of writhes with solid dispersions SDN-2(H) and SDN-5(H) is 68.29% and 72.71%, respectively, on the other hand, 59.06% with the pure drug naproxen. Both the lower and higher dose treatment groups of SDN-2 and SDN-5 showed greater percentage inhibition compared to the pure drug naproxen. The percentage inhibition of the number of writhes showed significantly greater ($P < 0.01$), and ($P < 0.0001$) analgesic activity for the higher dose treatment groups SDN-2(H), and SDN-5(H), respectively, when contrasted to the pure drug naproxen. On the other hand, the percentage inhibition of the number of writhes with solid dispersions SDN-2(L) and SDN-5(L) is 62.66% and 63.11%, respectively which were comparable to the pure drug. In the tail immersion method, the duration of the latency time in all of the treatment groups of SDN-2 and SDN-5 was significantly higher compared to naproxen-treated animals. The highest reaction time for the treatment group SDN-2(H) and SDN-5(H) was 10.67 and 10.92 s, correspondingly, at 90 min, while it was 7.58 s for the naproxen-treated group. In comparison with the pure naproxen treatment group, the increase in latency time at 90 min was significantly greater ($P < 0.01$), ($P < 0.05$), and ($P < 0.01$) for treatment groups SDN-2(H), SDN-5(L), and SDN-5(H), respectively [4]. The enhanced biological (analgesic) activities of solid dispersions were due to the enhanced dissolution rate of the drug from the solid dispersion pattern. As the risk of naproxen oral toxicity due to its poor solubility which can initiate severe side effects in the gastrointestinal tract such as upper gastrointestinal tract bleeding [11]. Therefore, solid dispersions of naproxen could be considered suitable alternatives for drug delivery after further pharmacological evaluation of this research study.

4. Conclusion

It can be concluded that the conversion of crystalline to amorphous nature of naproxen in the prepared SDN occurred due to the enhancement of dissolution that is authenticated by DSC, PXRD, FTIR, and SEM. Again, the administration of the newly formulated SDN-2 and SDN-5 (both 500 mg/kg and 50 mg/kg) showed greater analgesic activity in mice. In fact, low dose of SDN (50 mg/kg) might be safe, profitable, handy, and effective option to traditional dosage form of NPX (500 mg/kg) in patients with pain because the effects of SDN-L (50 mg/kg) were comparable to that of pure naproxen (50 mg/kg) due to the solubility and dissolution increment. So, SDNs can play a vital role in relief of pain due to its improved analgesic effects. These findings could provide a rationale for the use of these prepared SDNs as pain relief medication. Further pharmacokinetic studies should be performed for the greater comprehension of the mechanism of action of SDN in pain reduction purpose.

Author contribution statement

Monia Akter Nupur: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Mst. Mahfuza Rahman: Conceived and designed the experiments; Analyzed and interpreted the data; contributed reagents, analysis tools or data, Wrote the paper.

Khurshida Akter, Khadiza Binte Hanif, Jinat Fatema Sharna: Analyzed and interpreted the data; Wrote the paper.

Md. Shahin Sarker, Mir Imam Ibne Wahed: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Ethical statement

In this study, all animals were cared according to the guidelines for animal experimentation of our institute. The study protocol was approved by Ethical Review Committee, Faculty of Biological Science and Technology, at the Jashore University of Science and Technology, Jashore-7408, Bangladesh (ERC/FBST/JUST/2021–122).

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