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Naproxen-Soluplus® Nano formulations for Enhanced Oral Bioavailability

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ABSTRACT

Naproxen-Soluplus Nanoformulations (NFs) prepared via wet milling, using a conventional Retsch Planetary ball mill have been studied for their phase solubility behavior, physico-chemical characteristics, cytotoxicity, and morphology and dissolution enhancement. The highest dissolution enhancement of 172% over that of pure the drug was achieved for the formulation with Naproxen-Soluplus® ratio of 1:4. The ability of amphiphillic surfactant carriers to accelerate in vitro dissolution of poorly water-soluble drugs has been attributed to wetting, miceller solubilization, and/or deflocculation. The Korsemeyer–Peppas model most aptly fits the in vitro dissolution data and gives an insight into the possible drug release mechanisms predominated by anomalous non-Fickian diffusion which improves the physicochemical characteristics of naproxen towards its dissolution enhancement and the increase in the oral bioavailability of the drug without any adverse cytotoxic consequences.

Keywords: Soluplus, Naproxen, Nano formulations, Phase-stability, Dissolution, Bioavailability

INTRODUCTION

Naproxen is one of the most popular NSAIDs, widely administered against a wide range of inflammatory and analgesic disease conditions such as fever, inflammation, and pain related to a variety of muscular and skeletal disorders including osteoarthritis, bursitis, rheumatoid arthritis, kidney stones, ankylosing spondylitis, psoriatic

arthritis, gout, menstrual cramps, tendinitis, and migraine. It was first synthesized from the starting material 2-methoxynaphthalene (nerolin) [1]. The cost competitiveness of the current manufacturing process of naproxen has continuously undergone several processes research and development during the past 20 years. Currently, Naproxen is predicted to be one of the fastest-growing APIs among the adult systemic analgesics, is expected to reach nearly US$1 billion in retail value sales by 2018 [2].

The API is pale white in color and is an odorless, crystalline substance. Though a very old drug, it is highly lipophilic and practically insoluble in aqueous media. The drug, when orally administered, has quite some undesirable side effects like hemorrhage and ulceration of the stomach. And as a consequence of its scarce wettability and very poor water-solubility (0.025 mg/ml at 25^{o}C), it exhibits low and/or variable bioavailability after oral administration. Several approaches have been conducted in order to adequately improve the naproxen dissolution properties, low and/or variable bioavailability after oral administration. An improved naproxen formulation with the quick drug release pattern could be exceedingly useful in the treatment of inflammatory and painful states of the body, like rheumatoid arthritis.

In order to tackle this issue, solid dispersions with polyethylene glycol or polyvinylpyrrolidone or complexation with cyclodextrins and liquisolid technique have been reported. In fact, the first bi-component formulations of the drug involved complexation with 2-hydroxylpropyl-β-cyclodextrin. Lee et al. reported these complexes to have increased dissolution characteristics as well as decreased gastrointestinal toxicity when administered orally. Several polymers that have been used to dose naproxen include HPMC and PVP have also been demonstrated to improve the dissolution characteristics of naproxen [3-7]. Binary co-ground mixtures with drugs like cimetidine and ibuprofen have also been explored for improved solubility of naproxen [8,9].

Liversidge et al. have demonstrated using *in vivo* rat models that by reducing drug particle size to 270 nm and stabilizing the particles in suspension with pluronic F-68, the gastric irritation induced by oral administration of naproxen decreased, while the rate of absorption increased [10]. The reduction in irritation is attributed to a decrease in the local high and prolonged concentration of naproxen attributable to reduced crystal size, while the increase in the rate of absorption was attributed to an increase in surface area for dissolution for the Nano Crystal formulation. Nanosuspensions have been reported to be advantageous due to the features such as easy industrial scalability, economic viability, high drug loading efficiency, and low excipient side effects [11,12]. A simple top down approach explored for drug nanoformulations (NFs) is the use of a planetary ball mill to fracture the drug crystals into smaller drug particles [13-15].

Soluplus® a novel amphiphilic graft co-polymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol, manufactured by BASF to solubilize poorly soluble drugs [16]. Its dual functionality is claimed as an advantage to make it an excellent matrix to dissolve drugs as well as prevent their recrystallization [17]. These polymers form water-soluble complexes with many drug molecules, depending on the chemical structure of the Active Pharma Ingredients (APIs) [18]. The objective of this study was to synthesize evaluate Naproxen-Soluplus® nanoformulations using wet ball-milling approach with different drug-polymer ratios and study the characteristics of the Naproxen-Soluplus NFs in terms of their phase solubility behavior, physico-chemical characteristics, cytotoxicity, morphology and dissolution enhancement of the poorly water soluble drug, naproxen and arrive at the best Nanoformulation for adoption.

Synthesis of naproxen nanoformulations (NFs)

The NFs were prepared via wet milling using a conventional Retsch Planetary ball mill in various ratios of drug to polymer (1:1, 1:2, 1:3, 1:4). The Retsch planetary ball mill consists of a grinding jar positioned unconventionally on a sun wheel. This sun wheel moves in a direction opposite to that of the grinding jar. The grinding balls (agate balls, diameter 10 mm) in the milling jar are subjected to superimposed rotational movements, also known as the Coriolis forces. The interplay between the resultant forces produces the high and dynamic energy which results in effective size reduction.

The drug and polymer (in the required ratios) were introduced into an agate milling chamber containing 1 mm agate balls (Figure 1). 40 mL of 0.5% aqueous solution of Tween 80 was added to fill the chamber. The samples were co-milled at 500 rpm for 6 hours. Regular breaks of 5 minutes were provided after every 15 minutes of milling to avoid overheating caused due to the high energy involved in the milling process. The high shear force generated by the collision of the agate balls with the solid drug particles fractures the drug crystals into smaller particles and thus nanosuspensions were formed.

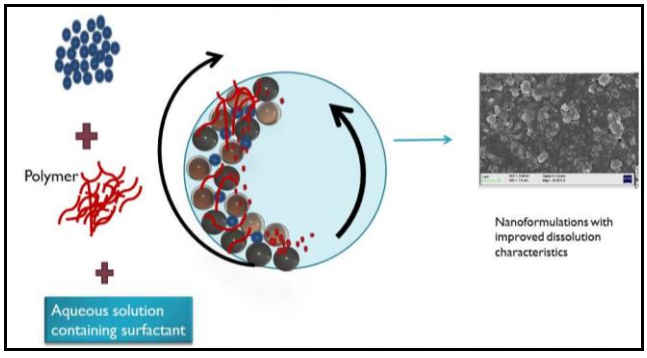

Figure 1: Schematic of Aqueous Ball Milling used to synthesize the nanoformulations

The nanosuspensions thus formed by co-milling were lyophilized for about 24 hours and gently powdered to obtain free flowing powders. To protect the nanoparticles from damage, due to ice formation and to minimize the particle size growth during lyophillization, mannitol (0.1% by weight) was added as a cryo-protectant prior to lyophillization. The several formulations of naproxen designed and studied are listed in Table 1.

Table 1: Different Naproxen Formulations studied

Formulation Label	Polymer	Drug-Polymer ratio	Percentage of carrier
NS1	Soluplus	1:1	50
NS2	Soluplus	1:2	66
NS3	Soluplus	1:3	75
NS4	Soluplus	1:5	80

Phase solubility studies

The phase solubility studies have found their usage to determine the suitability of carriers for solubility enhancement and the spontaneity of the drug solubilization process in the presence of the polymers in solution [19]. Phase solubility profiles of naproxen in various concentrations of the polymer Soluplus were established by the method established by Higuchi and Connors [20,21]. The procedure used was as follows:

To Erlenmeyer flasks (250 mL) containing 25 mL of the various polymer solution (0.1%, 0.25%, 0.5%, 0.75% and 1%, w/v), an excess amount of drug (1 g) was added. The flasks were suitably sealed and shaken at 100 rpm in orbital shaker-incubator for 48 hours at 37°C. They were left in the incubator for another 24 hours for equilibrium to be established. 5 ml of the supernatant solution was withdrawn and filtered. The amount of drug in the filtrate was photometrically analyzed spectrophotometrically at 278 nm for determination of the naproxen content using the calibration curve illustrated in Figure 2. The studies were repeated 5 times.

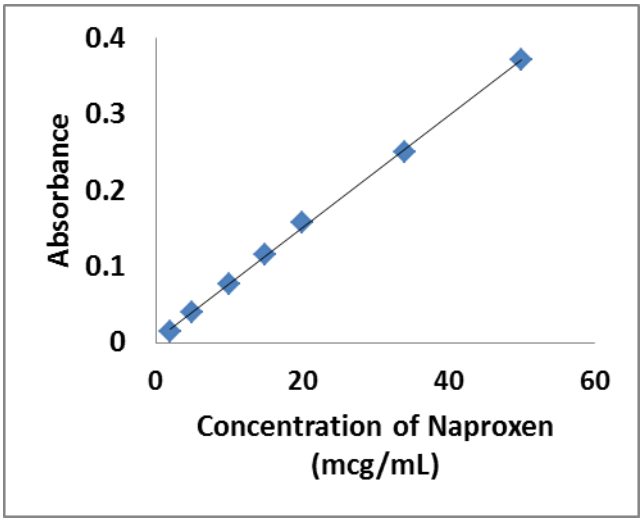

Figure 2: Calibration Curve used for spectrophotometric determination of naproxen using Beer Lambert's Law

Gibbs free energy of transfer ($\Delta G°_{tr}$) values indicate whether the particular treatment is favorable for the solubilization of the drug in an aqueous medium. The more negative the value, the more the spontaneity of the solubilization process. The $\Delta G°_{tr}$ values of Naproxen were computed from the data obtained from phase solubility studies using the following equation.

$$\Delta G^0_{tr} = -2.303\, RT \log \frac{S_0}{S_s}$$

Where;

S_o = molar solubility of Neproxen in distilled water

S_s = molar solubility of Neproxen in the presence of Soluplus®

R = 8.31 $JK^{-1}mol^{-1}$

T = temperature in degree kelvin.

Figures 3-6 shows the influence of increasing concentration of the carriers on the solubility of naproxen in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8). Pure Naproxen exhibited higher solubility in SIF (49.12 µg/mL) than in SGF (2.42 µg/mL). This could be attributed to the fact that naproxen is a weak acid with a pK_a value of 4.15. So, percentage of naproxen ionized would be much more in SIF than in SGF. The drug, thus, exhibits pH dependent solubility. The phase solubility data show a linearly increasing trend in naproxen solubility with increasing carrier levels. The high solubilizing effect of the block copolymer Soluplus® could be attributed to the multiple interaction sites in its chain and its surface active properties. The solubility of a drug in dissolution media can be influenced by altering different physicochemical properties, like hydrophobicity/hydrophilicity, viscosity, chemical structure and polarity etc. Soluplus® contains

hydrophobic as well was hydrophilic moieties in its polymeric chain. The amphiphillic nature of these carriers is responsible for their superior surface active properties in solution.

The ΔG^{o}_{tr} values obtained from the phase solubility curves with several carriers are listed in Table 2. The most negative value of ΔG^{o}_{tr} is obtained for the solution with Soluplus® which is indicative of fact that the process of transfer of naproxen from the bulk medium to its aqueous solutions was most favorable for Soluplus® than other carriers.

Table 2: ΔG tr (joules/mol) obtained from the phase solubility studies for the carrier Soluplus®

Percentage of Polymer (W/V)	ΔG_{tr} (joules/mole) for the different carriers at 37^{0}C in SGF.	ΔG_{tr} (joules/mole) for the different carriers at 37^{0}C in SIF
0.1	-2186.471	-350.717
0.25	-4539.736	-640.407
0.5	-5564.670	-1093.34
0.75	-6191.089	-1366.64
1.0	-6687.629	-1624.05

FTIR analysis

FTIR spectra of pure naproxen, all the NFs and the carriers were recorded using an FTIR Spectrophotometer (Spectrum FTIR (Scimadzu, IRAffinity-1)) in the range of 4000–400 cm^{-1}. The sample was in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 0.15 cm^{-1} and scan speed was 20 scans per second. As can be seen in Figure 3, the polymer Soluplus® showed peaks at 3450 cm^{-1} (O-H stretching), 2924 cm^{-1} (aromatic C-H stretching), 1736 cm^{-1}, 1635 cm^{-1} (C-O stretching), and 1477.21 cm^{-1} (C-O-C stretching). The carbonyl peaks of the vinyl acetate (VAC) and vinyl caprolactam (VCL) is located at 1733 cm^{-1} and 1634 cm^{-1}, respectively. The VCL carbonyl band can be observed to be split into two distinct bands at 1634 cm^{-1} and 1595 cm^{-1}. Considering that carbonyl absorption bands are shifted to lower wavenumbers when H-bonds are formed, the new band at 1595 cm^{-1} can be assigned to the VCL component that is H-bonded to the drug. This finding suggests that naproxen interacted with Soluplus® predominantly by hydrogen bonding. It is important to mention here that this kind of interaction between drug and carrier is an additional benefit for the nanoformulations, since besides increasing the solid solubility of the drug in the carrier they would also inhibit the (re)crystallization of drug.

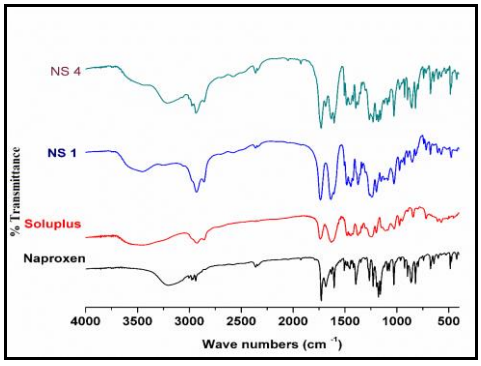

Figure 3: FTIR spectra of Naproxen, Soluplus and the nanoformluations

XRD analysis

As evident from Figure 4, the spectrum of the Soluplus® contains broad indistinct peaks resulting from the anisotropic scattering of X-rays indicating its amorphous nature, while distinct peaks of naproxen appeared at 14.50, 17.73 and 27.45. The X-ray spectra of the nanoformulations are observed to show reduction in the intensity of diffraction peaks. This reduction in the intensity of peaks compared to pure naproxen indicates the decrease in crystallinity or partial amorphization of the drug in the NS 1 and NS 2 formulations. NS 4 formulation showed absence of any of the crystalline peaks of naproxen indicating that complete amorphization was achieved at this drug to carrier ratio.

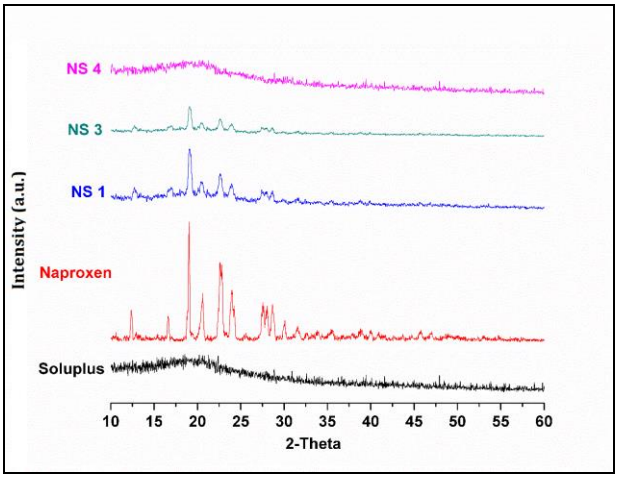

Figure 4: XRD spectra of Naproxen, Soluplus and the nanoformluations

DSC analysis

As evident from Figure 5, the DSC of Naproxen showed a sharp endotherm (T_{onset} = 147.6°C, $T_{Melting}$ = 157.5, and ΔH_{fus} = 144.2 J/g) attributed to the melting of the drug. The Thermal analysis (TA) curves of Soluplus® depicts a broad melting endotherm which begins with a prominent decrease just as the temperature crossed the ambient conditions (25°C) with a peak maximum at 83°C. The TA curves of the nanoformulations with lower polymer content (NS 1 and NS 2) showed decreased onset drug melting point temperature and reduced intensity of the drug melting endothermic peak. This could be due to the reduced lattice energy in the formulations. Also, $T_{Melting}$ the polymer was observed to reduce in the presence of the drug. This could be because the drug-polymer interactions substitute the polymer-polymer interactions in the nanocomposites, thus lowering the $T_{Melting}$. The melting point of naproxen was hardly detectable in the nanosuspension NS4 indicating the transformation of the stable crystalline state of the drug to the high disorder and high energy semi-amorphous or complete amorphous state in the formulation. This is in coherence with the XRD analysis.

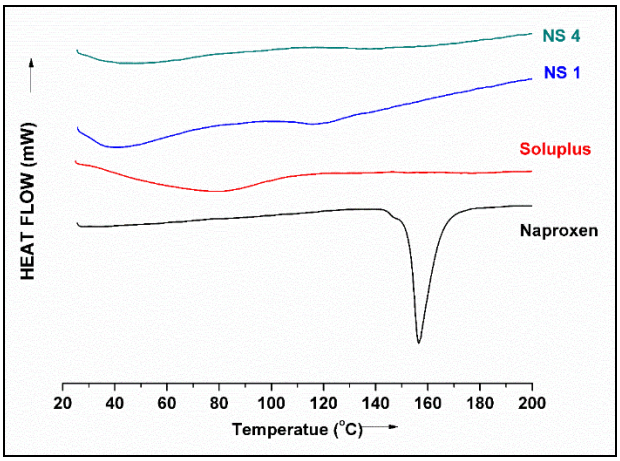

Figure 5: DSC curves of Naproxen, Soluplus and the Naproxen-Soluplus nanoformluations

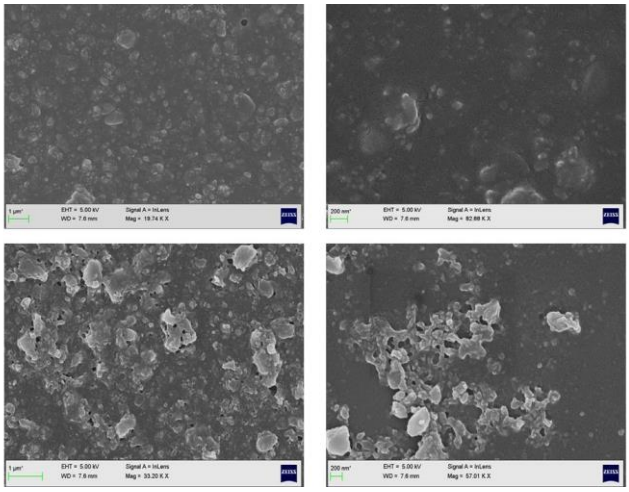

Figure 6: FESEM images showing the morphologies of Naproxen- Soluplus Nanoformualtions NS1 (Top) and NS 4 (down)

FESEM analysis

Figure 6 shows the FESEM images of two representative formulations corresponding to low (NS 1) and high polymer content (NS 4) at different magnifications. Both the formulations showed irregular morphologies. Since ball milling is brute force top down approach it offered little control over the particle size distribution (PSD) for both the formulations. NS 1 showed smooth rounded irregular particles while NS 4 showed more or less irregular shapeless mossy morphology probably due to presence of the excess amount of polymer**.**

Dissolution studies

The *in vitro* dissolution tests were performed using a USP type II paddle apparatus (DBK Dissolution Tester, Mumbai, India). An accurately weighed amount of sample (equivalent to 100 mg of naproxen) was introduced into the sample jar of the paddle apparatus (USP Type II) containing the dissolution medium. The studies were carried out in Simulated intestinal fluid without pancreatin (pH 6.8) as well as simulated gastric fluid without pepsin (pH 1.2) containing no surfactant. This was stirred at 70 rpm for 2 hours. At regular predetermined intervals, 3 mL aliquots of the sample were withdrawn, filtered and suitably diluted. The concentrations of the withdrawn solutions were determined using a UV spectrophotometer (Schimadzu, UV 2450) at 231 nm. To maintain the volume, 3 mL of solution was replaced into the glass jar after every withdrawal. Corrections were made up for this dilution during the

calculations. The percentage of the drug dissolved, thus obtained, and was plotted versus time. These studies were carried out three times.

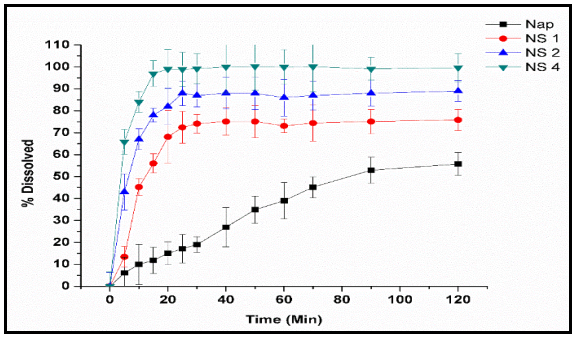

Figure 7: Dissolution Profiles of the nanoformulations of Soluplus

The dissolution of the naproxen nanoformulations was significantly faster than that of the pure drug in SIF Figure 7. Also, increase in the polymer content in the fomulations had an enhanced effect on the dissolution of naproxen. During the dissolution testing experiment, the drug was observed to leave the surface of the dissolution medium almost instantly and disperse into the bulk of the medium indicating the occurrence of rapid wetting.

There was no visible decline in the supersaturation in case the nanoformulations of even at the end of two hours. The formulation NS4 was observed to get supersaturated achieve near 100% dissolution in 15 minutes. This was a 155% enhancement achieved when compared to the dissolution pure drug at 15 minutes. The high and sustainable solubility enhancement from Soluplus® could be attributed to miceller solubilization (amphiphillic nature of the carriers), improved wetting characteristics and reduced crystallinity of the drug in the carrier systems.

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It is calculated by the following equation:

$$\%\,D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100$$

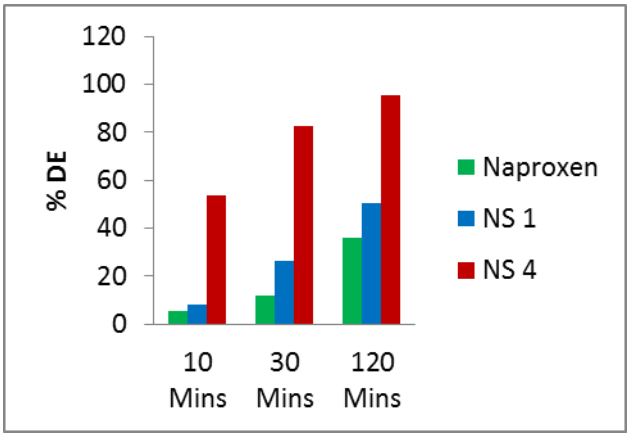

Figure 8: The comparison of Dissolution Efficiencies calculated from the dissolution plots of Naproxen and the nanoformulations NS1 and NS4

Table 3: Percentage dissolution efficiency

Formulation	% Dissolution Efficiency					
	5 min	10 min	20 min	30 min	90 min	120 min
Pure Naproxen	3.051	5.556	8.871	11.607	29.542	35.740
NS 1	4.051	7.806	15.621	26.107	48.553	50.373
NS 2	21.033	45.003	56.231	69.235	88.010	92.231
NS 4	32.937	53.943	74.086	82.399	94.040	95.377

Figure 8 and Table 3 show the % DE values of the nanoformulations NS 1 and NS 4 in comparison with that of the pure drug at three different time scales representing early and late phase of dissolution. At t = 10 minutes, the % DE of Soluplus is only about 7%. NS 1 shows a slight enhancement compared to the pure drug, while NS 4 shows an enhanced D.E value of 54%. This is an 8-fold

enhancement of the efficiency compared to that of pure drug. Similarly, at t = 120 min, an increment of 177% was achieved by NS 4 in comparison with the pure drug.

Cytotoxicity studies on naproxen nanoformulations

Caco-2 cells were used as *in vitro* models to assess the cell viability characteristics of the carrier Soluplus® and the nanoformulations of Naproxen. The assessment of cell viability was done using the tetrazolium salt based MTT assay. Duration of 12 hour exposure was selected because scintigraphic gastric transit studies in humans suggest they are physiologically relevant average and maximum exposure times, respectively, in the gastrointestinal tract. All the NFs were observed to follow the cytotoxicity trend of the polymers. Our results show that no significant decrease in cell viability was seen until 0.01% concentration of Soluplus for 12-h exposure. The NFs as well as the polymer alone had no significant effect on the viability of Caco-2 cells below 0.01% concentrations. Here it is important to note that intact intestinal membranes (*in vivo*) often are found to be more resistant to the cytotoxic effects of excipients than are cell culture models (*in vitro*). The intestine has a protective mucous layer, whereas the cell culture monolayers do not. The intestinal tissues also

have more capacity to recover from trauma than the cultured cells. Hence the present NFs can be expected to show lesser cytotoxicity when subjected to *in vivo* studies.

The dissolution of naproxen from all the NFs with Soluplus was significantly faster than that of the pure drug in both the dissolution media. Also, increase in the polymer content in the fomulations had an enhanced effect on the dissolution of naproxen. The release from Soluplus based NFs visually revealed the tendency of the drug to leave the surface of the dissolution medium instantaneously and disperse in the bulk of the medium indicating the occurrence of rapid wetting. There was no visible decline in the supersaturation in case of the NFs even at the end of two hours. The high and sustainable solubility enhancement from Soluplus could be attributed to miceller solubilization and/or reduction of activity coefficient of the drug through reduction of hydrophobic interaction(s). The Noyes–Whitney equation is often used explain the dissolution results [20].

$$\frac{dC}{dt} = DS\frac{(C_s - C)}{h}$$

where dC/dt is the dissolution rate, D is the diffusion coefficient of the dissolved drug particles, which is a parameter viscosity of the dissolution medium; S represents the exposed surface area to dissolution; h is the thickness of the diffusion layer, which is a parameter affected by agitation; Cs is the saturation solubility of the drug in solution in the diffusion layer, the term C is the concentration of the drug in the dissolution medium. Since the dissolution tests were performed under the same stirring conditions (70 rpm) and the dissolution media was prepared with same viscosity, the parameters in the equation h and D can be assumed to be constant. Thus, the only terms affecting the dissolution rates of the nanoformulations can be assumed to be (Cs - C). It can, therefore, be concluded that the wettability of the drug particles were increased and the particle size decreased. The enhancement in the dissolution of the nanoformulations could thus be attributed to a combined effect of decrease in particle size of the drug well as improved wetting characteristics of the polymer. For a comparative analysis of the drug release from the formulations, %DE values at several times, representing the various phases of dissolution study.

Dissolution efficiency (DE) is the area under the dissolution curve within a given range of time. Lower %DE values observed for NS1 could probably be attributed to slow emulsification process leading to slower dissolution in the initial time periods. At the end of 120 min NS4 achieved an improvement of 167%. Lower %DE values observed for NS1 could probably be attributed to slow emulsification process leading to slower dissolution in the initial time periods.

Table 4: Mathematical Models for Studying the Drug Release Kinetics from Dissolution Profiles

S.No	Model	Equation	Plot
1.	Zero order	$\ln(M_o/M_t) = k_0 t$	Cumulative amount of drug released versus time.
2.	First order	$M_o - M_t = k_1 t$	Log of percentage of drug remaining unreleased versus time.
3.	Higuchi	$M_t = K \sqrt{t}$	Cumulative percent release versus square root of time.
4.	Hixson-Crowell	$(M_o)^{1/3} - (M_t)^{1/3} = k_{1/3} t$	Cube root of drug percentage remaining in the matrix versus time.
5.	Korsemeyer-Peppas	$M_t/M_\infty = kt^n$	Log of the cumulative percent drug release versus log of time.

Mathematical modeling

The dissolution profiles from formulations have been treated with several mathematical models to describe release rates and mechanisms, their utility being dependenton the nature of dosage. When drug release rate is proportional to the drug remaining in the dosage form, dissolution can be rates and mechanisms, their utility being dependenton the nature of dosage. When drug release rate

is proportional to the drug remaining in the dosage form, dissolution can be said to follow first order release kinetics. The data obtained from the dissolution analysis were fitted into various mathematical models listed in Table 4 to describe the drug release mechanism from the different formulation. The release kinetics of a drug can be influenced by several parameters. For a poorly water-soluble drug, like naproxen, release kinetics should be predominantly guided by erosion of the matrix. The analysis of the data obtained from the dissolution studies with mathematical formulae helps relating the results as a function of the formulation characteristics. The analysis of the data has been done on some empirical drug release equations.

Table 5 lists the slopes and R2 values obtained from fitting the experimental in vitro dissolution data into the various release kinetic models. The fittings were carried out for the data obtained till 40 minutes for the quick release formulations NS4. Considering only the data points till superstauration was achieved, the data fit well into the first order and the Korsemeyer-Peppas models. According to the regression values, the drug release data were observed to best fit into kinetic models in the order: Korsemeyer-Peppas ≈ First order > Higuchi > Hixon-Crowel > Zero order.

Table 5: Slopes and R^2 values obtained from fitting the experimental *in vitro* dissolution data into the various release kinetic models

Formulation	Zero Order		First order		Higuchi		Hixson-Crowell		Korsemeyer-Peppas	
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
NS1	-0.076	0.662	-0.032	0.977	44.771	0.776	0.012	0.873	0.558	0.870
NS2	-0.05	0.053	-0.044	0.986	33.920	0.884	0.091	0.776	0.966	0.986
NS4	-0.05	0.053	-0.044	0.986	33.920	0.884	0.091	0.776	0.966	0.986

This model describes the release of the drug from polymeric matrices based on the release exponent factor 'n' which is calculated as the slope when log of the percentage of the drug released is plotted versus the log of time. This n value characterizes the nature of different release mechanisms for Fickian diffusion (n=0.5) or non-Fickian/ anomalous release (for 0.5< n <1). Since the values of diffusional exponent '*n*', obtained from the fitting, ranged from 0.545 to 0.966, the release phenomena may be regarded to follow a non-fickian model. The highest dissolution enhancement was achieved for the formulation with Soluplus® with ratio of 1:4. This is a 172% enhancement when compared to that of the pure drug. The ability of amphiphillic surfactant carriers to accelerate *in vitro* dissolution of poorly water-soluble drugs has been attributed to wetting, miceller solubilization, and/or deflocculation. Thus, the nanoformulations studied can help improve the physicochemical characteristics of Naproxen towards its dissolution enhancement and possibly will increase the oral bioavailability of the drug without any adverse cytotoxic consequences.

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