ISSN: 2287-6898
International
Journal of Bio-Pharma Research
Volume 8, Issue 4 (2019) pp. 2523-2530
Research Article Open Access

Development and Biopharmaceutical Characterization of BCS Class II Drug – Naproxen by Two Way Complexation Solid Dispersion Technique

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Abstract: The objective of this study was to increase the solubility and bioavailability of Naproxen (NP) by fabricating ternary solid dispersion (tSDs) with water soluble polymer PEG 6000 and crospovidone. tSDs were prepared and optimized by 3^2 full factorial design with PEG 6000 level (X1) and CP level (X2) as independent variables and percent drug release (D80, (Y)) as dependent variable. The optimized tSDs were evaluated for their physicochemical properties which confirmed the formation of tSDs (DSC), SEM suggested smooth surface and compact structures. PXRD revels that drug was still present in crystalline form and was not molecularly dispersed in the complex especially in non-homogeneous part of the tSDs. The optimized tSDs revels that Dissolution rate (Y) was significantly affected by independent variable PEG 6000 (X1) while CP (X2) was insignificant. The transparent characteristics of tSDs was observed as a result of lowered Tg temperature gives higher dissolution rate up to 97.70 % for optimized formulation (F9). The pharmacokinetic study in Han Wistar rats showed that the tSDs had the greatest effect on oral bioavailability of NP *in vivo* test showed that NP (tSDs) presented significantly larger $AUC_{0\text{-}t}$, which was 1.09 folds more than that of marketed formulation. C_{max} of NP (tSDs) also increased from 120 µg/ml to 146 µg/ml compared to that of marketed formulations and generated shortened T_{max} of (1.0 ± 0.416) h, compared to marketed dosage form (2.0 ± 0.456) h.

Key words: Solid dispersion, glass transition temperature, ternary solid dispersion, level optimization, & pharmacokinetics

Introduction

Systemic availability of drug depends on the two important steps. These two steps determine the rate and extend of drug absorption, so called as Rate Limiting Steps. i. e. Drug dissolution and Drug permeation [1]. Drug dissolution is always depends on the solubility of that particular drug which is hydrophobic, poorly aqueous soluble drug like NP, falls under the category of BCS class II drug [2]. The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material [3]. Methods used to obtain solid dispersions affects the drugs crystallinity as Mooter *et al.*, revealed that with a 20/80 w/w Itraconazole/Inutec SP1 extrudate (solid solution) a dissolution of 100% could be obtained after 30 min. The same composition prepared by spray drying; however, gave rise to a dissolution of only 50% [4]. The presence of different proportions of PEG systematically lowers the degree of complexed drug NP with β-CD due to competing equilibria gives rise to ternary solid dispersions [5]. The solid dispersions and ternary complexes formed exhibits increased dissolution behaviour as result of metastable amorphous material formed which in turn cooled, it usually crystallizes below the melting temperature, (Tm). When cooling rate is sufficiently fast, the liquid fails to crystallize, and a super cooled state is attained. Further cooling to below the glass transition temperature (Tg) causes the system to fall out of structural equilibrium. Since this state is not physically stable, structural changes occur over time to achieve a more energetically favoured state leads to less dissolution rate [6]. Solid dispersions of PEG6000 and Loperamide prepared by spray drying showed deteriorated dissolution rate on storage at high temperature (40°C and 0% RH) and in conditions of higher relative humidity (25°C and 52% RH) resulting in

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progressively poorer dissolution properties [7]. This directed research scientists to look into area of Tg inhibitors and evaluated various polymers to establish their Tg temperature inhibition properties, Aso *et al.*, observed that the presence of 10% PVP slows the rate of total crystallization of amorphous NIF by a factor of 300 [8]. Low-concentration polymer additives can strongly inhibit crystal growth in the bulk of organic glasses, while having weaker effect on surface crystal growth. Ultra-thin polymer coatings can inhibit surface crystallization. Recent work has shown the importance of molecular weight for crystallization inhibitors of organic glasses, besides "direct intermolecular interactions" such as hydrogen bonding. Relative to polyvinylpyrrolidone, the VP dimer is far less effective in inhibiting crystal growth in amorphous Nifedipine [9]. Tg can be used to modify physical properties of solids. By altering the Tg of drug or polymer molecules they can be maintained in amorphous solid form at ambient or body temperatures. Improvement in handling characters, solubility and reproducibility in dissolution of solids can be achieved by increasing the Tg of solids [10]. Crospovidone is an insoluble form of polyvinylpyrrolidone, and its use in the pharmaceutical industry as a tablet excipient (a tablet disintegrant and binder) has been widely documented [11]. In the present investigation effect of crosspovidone on the NP-PEG 6000 inclusion complex was evaluated to study anti-crystallization property and level of it was optimized for its drug release pattern. The optimized formulation was further evaluated for in vivo pharmacokinetic parameters in Han Wistor rats. NP, a propionic acid derivative (Figure 1), is extensively used in non-steroidal anti-inflammatory cures. NP is poor water soluble and may show dissolution limited absorption [12].

Materials and Methods

NP was received as a gift sample from RPG Life Sciences Limited Ankleshwar, Bharuch. Crospovidone LR was purchased from Fine Chem Industries Mumbai. Poly-Ethylene Glycol (PEG) 6000, Dichloromethane (DCM) and all other pharmaceutical ingredients were purchased from Loba Chemie, Mumbai, all were of analytical grade.

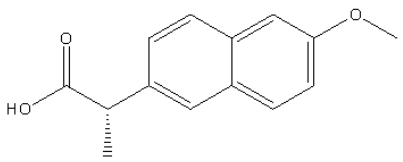

Fig. 1 Naproxen

Phase solubility study

Solubility measurement were performed in triplicate using the method reported by Higuchi and Connors [13]. An excess amount of NP was added to the aqueous solutions of PEG in different concentrations (i.e. 5, 10, 15, and 20 percent) and a blank. The flasks were sealed with aluminum foil and shaken at 37^0 C for 48 hr. in a thermostatically controlled water bath. Further the samples were filtered through a 0.45 µm whattman filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically (shimadzu 1800, Japan) at 272 nm.

Experimental Design Optimization

3^2 full factorial design (FFD) was used to examine the effect of two independent variables X_1 (PEG 6000) and X_2 (Crosspovidone) on dependent variable % drug release (Y) after 45 minutes of dissolution test time. The variable X_1 is considered at three levels 2, 4, and 6 (Gms) and coded as -1, 0, and 1. The variable X_2 is also considered at three levels 1.25, 3.75, 6.25 (percent) coded as -1, 0, 1. Three replications were taken at each of the 3^2=9 design points. The resulting data are given in Table 1. We consider that the expected response can be estimated by linear model (LM) if the response is well modeled by a linear function of the independent variables.

LM: $E(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2$ (1)

If there is curvature in the system quadratic models (QM) must be used of the form,

QM1: $E(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2$ (2)

QM2: $E(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$ (3)

QM3: $E(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$ (4)

Where Y is the measured response, β_0 is the intercept, β_1, β_2, β_{11}, β_{12}, β_{22} are the regression Coefficients whose values are to be determined. X_1 and X_2 Are variables representing factor 1 and 2 respectively. To visualize the response, surface response plots and contour plots were used. The effect of the independent variables on response parameter was visualized from the contour plots. Numerical optimization using desirability approach was employed to locate the optimal settings of the formulation variables to obtain

the desired response. An optimized formulation was developed by setting constraints on the dependent and independent variables.

Model Validity: If the model is correct and the assumptions were satisfied, the residuals should be structured less. For well fitted model residuals should be unrelated to any other variable including the predicted response. Fitting of a model can be checked by plotting residuals versus the fitted values of response.

Preparation of ternary solid dispersion (tSDs)
According to FFD, nine formulations of NP-tSDs (Table 1) were prepared by using water soluble carrier polyethylene glycol 6000 and cross povidone by solvent evaporation technique [14]. PEG 6000 and NP were separately dissolved in dichloromethane and then mixed on magnetic stirrer at low speed simultaneously cross povidone was added to get concentrated mixture of all three component. Sufficiently concentrated mixtures were frozen at -20° C followed by freeze drying at a pressure of 0.2 mbar and at −48°C for 48 hours then the lyophilized powder was stored in a desiccator at room temperature until further use.

Table 1. Independent variables and their levels with observed values of the response used in full factorial design.

Drug as a constant (1) proportion	Batch Code	Independent Variables				Dependent Variable
		PEG-6000 Level (X1)		CP level (X2)		
Drug (1)		Quantity (Ratio 1:X1)	Level Code	Quantity (%)	Level Code	% Drug Release (Y)
1	F1	6	1	1.25	-1	95.86 ± 0.65
1	F2	4	0	1.25	-1	88.35 ± 2.67
1	F3	4	0	3.75	0	89.26 ± 1.21
1	F4	6	1	6.25	1	91.86 ± 1.02
1	F5	4	0	6.25	1	93.13 ± 0.88
1	F6	2	-1	3.75	0	80.91 ± 2.01
1	F7	2	-1	6.25	1	86.55 ± 1.43
1	F8	2	-1	1.25	-1	77.91 ± 1.47
1	F9	6	1	1.25	0	97.70 ± 0.40

Table 2. Analysis of variance for dependent variables of 3^2 full factorial design

Rat No.	T_{max}[a] (h)	C_{max} (µg/mL)	AUC_{last} (µg.h/mL)	AUC_{inf} (µg.h/mL)	$T_{1/2}$ (h)	MRT_{inf} (h)
Rja0759	1.00	162	1760	2140	9.45	13.3
Rja0760	1.00	157	747	NR	NR	8.45
Rja0761	0.50	119	1330	1380	4.82	7.13
N	3	3	3	2	2	3
Mean	1.00 (0.50 – 1.00)	146	1280	1580	7.14	9.64
SD	NA	23.5	510	NA	NA	3.28
CV%	NA	16	40	NA	NA	34

T_{max} presented as median (min-max); NA: Not applicable; NR: Not reportable due to inappropriate elimination phase

Table 3. (a) Pharmacokinetic parameters of naproxen following oral gavage administration of tSD dose formulation in male Wistar rats (Dose: 100 mg/kg eq. to Naproxen) (b) Pharmacokinetic parameters of naproxen following oral gavage administration of marketed dose formulation in male Wistar rats (Dose: 100 mg/kg eq. to Naproxen)

Rat No.	T_{max}[a] (h)	C_{max} (µg/mL)	AUC_{last} (µg.h/mL)	AUC_{inf} (µg.h/mL)	$T_{1/2}$ (h)	MRT_{inf} (h)
Rja0762	1.00	133	1350	1400	5.00	6.87
Rja0763	2.00	105	1110	1160	4.82	7.02
Rja0764	2.00	122	1040	1090	5.78	7.11
N	3	3	3	3	3	3
Mean	2.00 (1.00 – 2.00)	120	1170	1220	5.20	7.00
SD	NA	14.1	163	161	0.507	0.122
CV%	NA	12	14	13	10	2

[a]T_{max} presented as median (min-max); NA: Not applicable

Pharmaceutical Characterization of the ternary solid dispersions

Fourier transform infrared spectroscopy (FT-IR): FT-IR spectra were obtained using FT-IR spectrometer (Shimadzu 4300, Japan). Pure drug, polymer and tSDs were mixed with potassium bromide separately. The potassium bromide discs were prepared by compressing the powders at pressure of 15 tons for 10 min in hydraulic press. Scans were obtained at a resolution of 2 cm−1, from 4000 to 400 cm−1.

Powder X-ray diffraction studies (PXRD): The powder X-ray diffraction patterns were determined for pure drug, polymer, and tSDs. X-ray diffractograms were obtained using the X-ray diffractometer (Siemens D500, Munich Germany) and Cu-kα radiation (λ = 1.5406). Diffractograms were run at scanning speed of 2^{o}/min and a chart speed of 0.6^{o}/min.

Differential scanning calorimetry (DSC): Accurately weighed samples (pure NP, PEG 6000, and ternary solid dispersions), were placed into the sealed standard aluminum pans with lids. Subsequently, the physical status of the NP inside the tSDs was established using the differential scanning calorimetry thermogram analysis, DSC60 (Shimadzu, Japan). The heating rate was 10°C/min and the heat flow was recorded from 25 °C to 300 °C.

SEM and morphology: The SEM photograph of NP and tSDs prepared were obtained using scanning electron microscope (Tescan, Brno, Czech Republic) operating at 15 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere using a sputter coater (SCD 005, Bal-Tec, Switzerland) prior to observation.

Dissolution (Drug Release) Studies: *In vitro* release tests were performed for the prepared tSDs as well as drug/polymer physical mixtures (all containing 100 mg NP). To analyse the dissolution samples, the calibration curves of the drug were obtained at pH 1.4 and 7.4. Both curves were linear in the range of 2.5–80 µg/ml (RSQ = 0.9987). The dissolution study was carried out by applying USP apparatus type II (Erweka, Germany), using 900 ml hydrochloric acid solution (pH 1.4) and phosphate buffer (pH 7.4) as dissolution mediums. Temperature was maintained at 37 ± 0.5 °C and agitation rate was 50 rpm. Samples were withdrawn at predetermined time intervals (0, 15, 30, and 45 min.) and filtered to remove suspended and insoluble powder particles. The sink condition was maintained by the addition of pre warmed fresh dissolution medium immediately. Samples were suitably diluted and analyzed by UV spectrophotometer at λ 272 nm.

Pharmacokinetics of ternary solid Dispersions against marketed Product

The optimized tSDs were investigated for pharmacokinetic of NP following oral gavage administration to male Han Wistar rats. The study was performed using parallel design (n=3/Group) as summarized in the Table 2. In vivo evaluation experiments of the optimized formulation in laboratory animals were all approved and performed in accordance with the guidelines of the Institutional Animal Ethics Committee (IAEC) in accordance with the requirement of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. The Test facility, Eurofins Advinus Limited, is an AAALAC approved laboratory. This protocol has been approved by Institutional Animal Ethics Committee (IAEC) of Eurofins Advinus Limited (Proposal No. ATL-42_PKR_036/June 2017). Male Han Wistar rats used as the test system for this study were procured from Envigo RMS (Israel) Limited. The age of the animals was 11-12 weeks on the day of dosing. Rats were acclimatized to the study area conditions for three days before dosing. Animals were housed (one per cage) in polypropylene cages and was maintained in controlled environmental conditions with 12 h light and 12 h dark cycles. The temperature and humidity of the room was maintained between 22 ± 3 °C and 40-70%, respectively. The room underwent 10-15 fresh air change cycles per hour. The experimental animals were provided *ad libitum* of standard pelletted food (Teklad Certified (2014C) Global 14% Protein Rodent Maintenance Diet- Rodent pellet food, manufactured by Envigo, P.O. Box 44220, Madison, WI, USA. 53744-4220. All animals were fasted for overnight prior to dosing and food was be provided at 4 h post dose. Water will be provided *ad libitum.* All study animals will be observed for clinical signs during study period.

Sample Collection and Processing

Blood samples were collected at Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post dose. At each time point, approximately, 0.25 mL of blood was withdrawn from jugular vein of the cannulated rat and transferred to a labelled microfuge tube containing 200 mM K_2EDTA (20 µL per mL of blood). Following sampling, equal volume of heparinized saline was replaced into the catheter. The blood samples were kept on wet ice at each time immediately after collection and the plasma was separated by centrifugation at 5000 RPM for 5 minutes at 4 ± 2 °C. The plasma samples were separated within 1h of scheduled time and stored below -60 °C until bioanalysis.

Bioanalysis

Bioanalysis was performed using fit-for-purpose LC-MS/MS method for the quantification of NP in rat plasma samples. The calibration curve (CC) for the method consisted of at least 6 non-zero calibration standards along with a blank and blank with internal standard samples with a lower limit of quantification (LLOQ) of 5.15 µg/mL. Study samples were analyzed along with three sets of quality control samples (9 QC samples; low, medium and high QC samples in triplicate).

Pharmacokinetic Data Analysis

The pharmacokinetic parameters for NP were calculated using the non-compartmental analysis tool (extra vascular) of the validated Phoenix® WinNonlin® software (version 6.3). The area under the concentration time curve (AUC_{last} and AUC_{inf}) was calculated by linear trapezoidal rule. The elimination rate constant value (k) was calculated by linear regression of the log-linear terminal phase of the concentration-time profile using at least 3 declining concentrations in terminal phase with a correlation coefficient of >0.8. The terminal half-life value ($T_{1/2}$) was calculated using the equation 0.693/k.

Results and Discussion

Phase solubility study

Phase solubility results reveals that the solubility of NP was 7.9 µg mL^{-1} indicating it as insoluble in distilled water. The phase solubility diagram of NP as a function of PEG 6000 concentration is given in Fig. 2. Solubility of NP linearly increased (correlation coefficient, 0.9805) as PEG 6000 concentration increased, resulting in AL type phase solubility curve according to Higuchi and Connors (1965). An apparent stability constant (Ks) was then calculated from the initial linear portion of phase solubility diagram as follows assuming that a 1:1 complex was initially formed.

$$K = \frac{Slope}{Intercept\,(1 - Slope)}$$

The intercept in the equation indicates solubility of drug without PEG 6000. The calculated slope and stability constant (Ks) were 0.0318 and 6.9974 respectively. It was obvious that PEG 6000 was useful to improve solubility of poorly water-soluble drug NP.

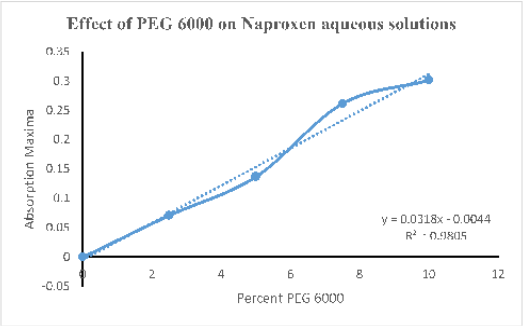

Figure 2. Phase solubility study of Naproxen in Aqueous solutions

Experimental Design Optimization

Factorial design is an effective means of discovering the relative importance of number of factorsand their interaction on responses or outcome of the study. Observed values for all nine formulations and their effect on the percent drug release are shown in Table 1.

The MINITAB14 software is used for analysis of the data, For model (1), (2) and (3) R-Sq is 77.2%, 79.0%, 88.1% and the p-value of lack of fit is <0.001 indicating that some terms are missing in the model. For model (4) R-Sq is 90.0% and the model is obtained as:

$$\hat{y} = 90.4822 + 6.675\,x_1 + 1.57\,x_2 - 3.1583\,x_1x_2 - 1.7817\,x_1^2 - 0.3467\,x_2^2$$

Analysis of variance for dependent variables of 3^2 full factorial design is given in Table 2.

R-Sq = 90.0% R-Sq 87.6%

The limited dissolution of NP is an effect of its poor wettability and hydrophobicity. Dissolution of NP in tSD was improved because of its increased amorphous nature due anti-crystallization effect of crospovidone and increased surface area. The positive sign for coefficient of X1 indicates that as the concentration of PEG 6000 increases, the % drug release (Y) also increases. The response surface plot shown in fig. 3b show that the drug release increases linearly with increasing

PEG 6000 concentration. To check the model validity residuals versus fitted values are plotted given in Fig.3.

Formulation optimization by using the desirability approach

Statistical optimization is a tool to have a systematic approach in formulations, evaluation of the effect of independent variables on the selected responses to get a robust product with desirable quality attributes. To get an optimized formulation based on the evaluations % drug release is the desirability criteria was selected as % drug release ≥ 80% (D80). Based on this desirability criteria the full factorial design using MINITAB software suggested PEG 6000 concentration of (1) level and CP concentration of (-1) level gives the optimized formulation with 96.61 ± 0.36 % drug release. Accordingly, the selected optimized formulation was prepared, and the observed values were (97.70 ± 0.40) found to be very close to the predicted values by the software.

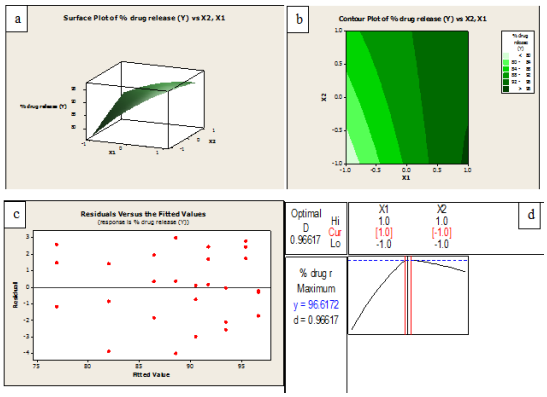

Figure 3. (a) Response surface plot, (b) Contour plot, (c) Exhibits no specific pattern indicating the model validity and (d) Response optimization

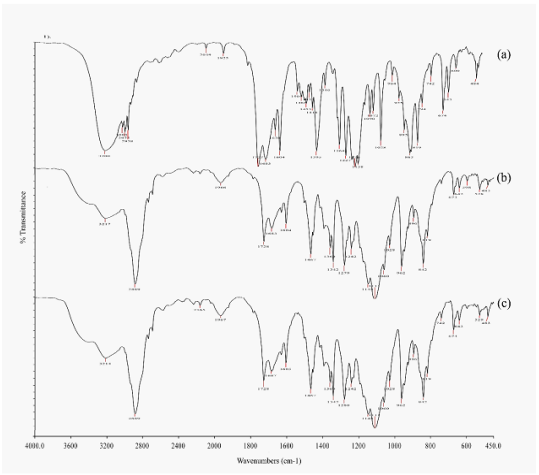

Figure 4. FTIR spectra of (A) NP and (B) PEG 6000 and (C) tSD

FTIR Fourier transform

The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug NP and in the physical mixture which confirms the absence of chemical interaction between drug and polymers Plain NP FTIR spectra showed characteristics peak at 3200 cm^{-1}indicating –OH functional group stretching, -OCH3 at 3003 cm^{-1}, 2973 cm^{-1} for –CH3 and –CO at 1727 cm^{-1}. In case of PEG 6000, the spectrum was characterized by the appearance of broad band at 2889 cm^{-1} which corresponds to the OH group. The band at 1242-1279 cm^{-1} is for C–O stretching (fig no 4). This was in good agreement with the previously recorded spectrum for the polymer PEG 6000, which reveals that there was no interaction between the drug and the carriers. There was a peak for drug at 3214 cm^{-1} and for PEG 6000 at 2889cm^{-1} which was also observed in tSDs spectra indicating the formation of inclusion complex.

X-ray powder diffraction (XRPD)

The diffraction spectrum of pure NP showed (fig.5a), that the drug is highly crystalline powder and possesses sharp peaks at 2θ equal to 18.767^0, 22.257^0. This corresponds to the Y-crystalline form of NP. Characteristic peaks of PEG 6000 (fig.5b) appeared at 2θ equal to 13.70, 19.75, 22.15, 25.60, and 29.35. In the case of tSDs of NP-PEG6000-crospovidone system for optimized formula, there was a decrease in the intensity of NP but the major peaks remained at the same positions confirms the para-crystalline nature of tSDs.

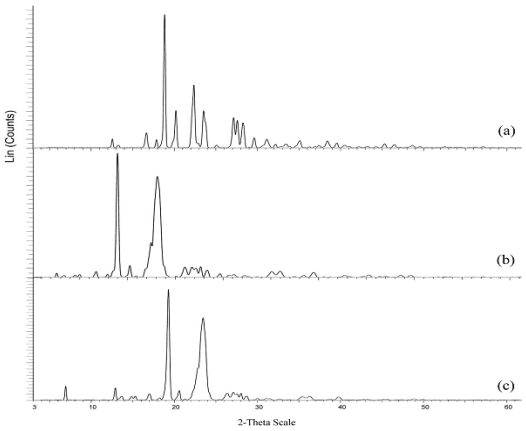

Figure 5. XRD spectra of (A) NP (B) PEG 6000 and (C) tSD.

Differential scanning calorimetry DSC

The DSC curves of NP exhibits typical of a pure crystalline anhydrous substance at 159.5, (A sharp endothermal effect of tonset at 156.4 and tpeak at 162.7) was associated with the

melting of crystals of pure NP. DSC profiles of PEG 6000 exhibits sharp endothermic peaks at 63.7 °C due to fusion at its melting point (fig no 6). The prepared optimized tSDs has showed that the sharp endothermic peak was equivalent to the addition curves of PEG 6000 and crystalline drug. The possibility of drug dissolution in the melting carrier has been previously reported Therefore, DSC results suggested that crystalline NP in the NP-PEG and CPs ternary solid dispersions were dissolved in melting PEG during the DSC scan.

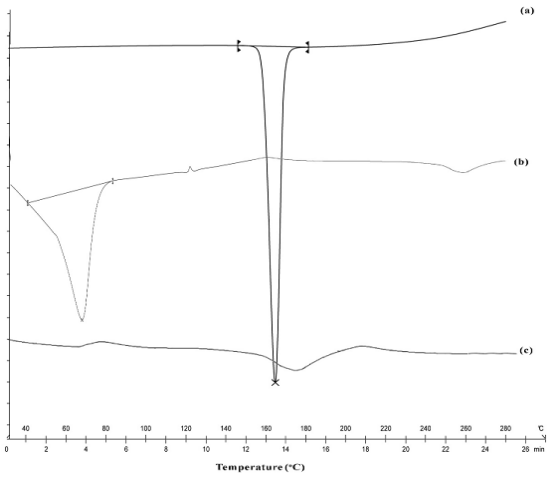

Figure 6. PXRD pattern of spectra of (a) NP (b) PEG 6000 and (c) tSD

Scanning electron microscopy

Scanning Electron Microscopy (SEM) is a method used for high resolution surface imaging which offers representation of the surface topography and distribution of elemental composition on the surface.SEM photographs showed the presence of highly crystalline nature of drug NP (Fig. 7) while tSDs SEM photograph showed it was reduced to amorphous form with smooth surface morphology.

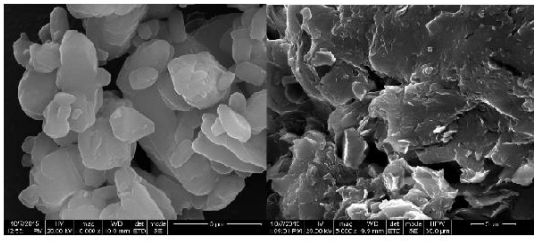

Figure 7. SEM images of (a) Naproxen (b) Naproxen, PEG 6000 and CP tSD

Dissolution (Drug Release) Studies

Table1 illustrates the time needed to release 80 % of incorporated drug (D80) at the end of 45 minutes of dissolution test time. All formulated batches showed 80% of drug release except batch (F8) which exhibits 77.91 ± 1.47 % of drug, which consists the PEG-6000 (X_1) and CP (X_2) at both (-1) levels. The maximum percent of drug release was obtained at (1) and (-1) levels of (X_1) and (X_2) respectively (97.70 ± 0.40). The mathematical projection was found to be 96.61 ± 0.36 % of drug dissolution for the same levels of independent variables.

Dissolution profiles of physical mixture and optimized ternary solid dispersion in gastric fluid at pH 1.4 ± 0.1 and 7.4 ± 0.1. The physical mixtures exhibited considerably faster initial dissolution rates than tSDs till first interval of dissolution test time. This may be due to highly water-soluble polymer 6000 which reduces the aggregation, improves wettability and local solubilisation by the carrier in the diffusion layer [15-17]. It was observed that drug in solid dispersions or ternary solid dispersions exists in amorphous form [18]. The SD and tSDs has amorphous form which gives high thermodynamic activity compared to its original crystalline form hence rapid dissolution of the drug [19]. The improved drug release rate could be attributed to the drug crystallinity reduction in tSDs prepared by PEG 6000 and CP compared to physical mixture. Fig. 8 indicated that the dissolution of NP is considerably affected by pH of the dissolution medium. The percentage of drug released at pH 7.4 ± 0.1 is remarkably higher than the amount of drug released at pH 1.4 ± 0.1. It can be correlated to NPs weak acid profile which offers grater ionization at higher pH values.

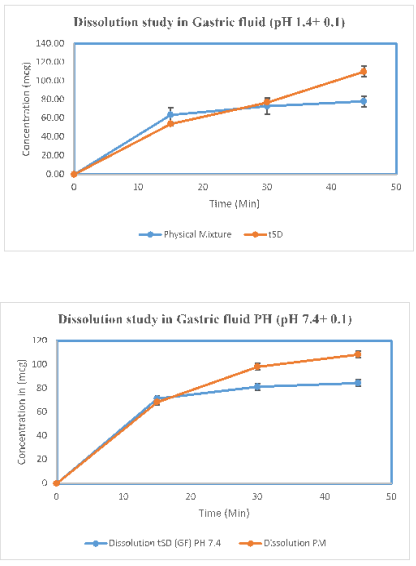

Figure 8. Dissolution profile of physical mixture and ternary solid dispersions made in gastric fluid (pH 1.4 and 7.4)

Pharmacokinetics of ternary solid Dispersions against marketed Product

Pharmacokinetic parameters of NP following oral gavage administration of optimized test formulation and reference (marketed) formulations in male Han Wistor rats are shown in table 3. The median time to reach the maximum plasma concentration (t_{max}) was found to be 1.0 h and 2.0 h, respectively. The corresponding mean peak plasma concentration (C_{max}) of was found to be 146 and 120 µg/ml respectively. The mean plasma exposure (AUC_{last}) of NP following oral gavage administration of optimized formulation and marketed formulation was found to be 1280 ± 510 and 1170 ± 163µg.h/ml respectively (Figure 9).

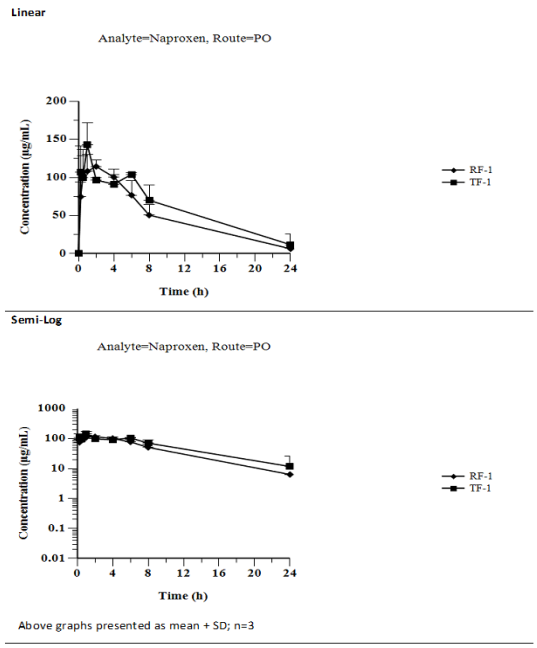

Figure 9. Plasma concentration-time data of naproxen following oral gavage administration of naproxen test and reference formulation in male Wistar rats (Dose: 100 mg/kg eq. to Naproxen)

Conclusion

In the present investigation we conclude that quality by design approach by using full factorial design can be used to prepare optimized tSD which can produce the pharmaceutical products of desired quality in terms of its biopharmaceutical properties. Two-way complexation by using crospovidone as a third component can be useful to prevent progressive recrystallization of solid dispersions. The statistical optimization of the desirability approach function of % drug release using full factorial design was promising in formulation of the naproxen tSD with desired quality.

Pharmacokinetics of naproxen following oral gavage administration to male Han Wistor rats revealed a significant increase in the oral absorption of naproxen in the optimized tSD compared to marketed dosage form. The AUC_{0-t} and C_{max} values of optimized tSD were approximately 1.09 fold and 1.21 fold greater than that of marketed dosage form, respectively. In addition to this the C_{max} obtained by the optimized tSD was half of the time taken by marketed dosage form. The enhancement of oral bioavailability of naproxen and shortened T_{max} could be explained by the improved dissolution of naproxen in presence of crospovidone in simulated gastric fluid which results in enhanced oral systemic absorption of naproxen from stomach region. Hence it can be concluded that the effect of the progressive recrystallization can be reduced by using crospovidone as a third component and preparing two-way solid dispersions for improved bioavailability and therapeutic effectiveness of naproxen. This investigation also leads to the ways to find out other possible polymeric materials which can reduce the Tg temperature of complexation and produce an amorphous material which will exhibits improved dissolution and subsequently bioavailability and efficacy without increasing the weight of the solid dispersions which is a possible limitation of prepared solid dispersions.

Acknowledgements

The authors are thankful to RPG Life Sciences Limited Ankleshwar, Bharuch (India), for providing Naproxen as a gift sample for conducting this research. Authors are thankful to Ms. Fatima Rafiq Zakariya, Chairman of Maulana Azad Educational Trust, Aurangabad (India) for providing necessary infrastructure and facilities.

Disclosure Statement

Authors declare no conflict of interest. All authors have contributed in the research.

References

1. D.M. Brahmankar, Sunil B. Jaiswal, Biopharmaceutics and pharmacokinetics A treatise, First edition, Vallabh Prakashan, New delhi, 19, 1995.

2. Giovanna Corti, Francesca Maestrelli and *et al.*, Dissolution and permeation properties of

Naproxen from solid-state systems with chitosan. Drug delivery, 15; 2008: 303-312

3. Eun-Jung Kim a, Myung-Kwan Chun and *et al.,* Preparation of a solid dispersion of felodipine using a solvent wetting method. Euro. J. of Pharm and Biopharm, 64, 2006: 200–205

4. Sandrien Janssens, Jan Van Humbeeck, Guy Van den Mooter. Evaluation of the formulation of solid dispersions by co-spray drying itraconazole with Inutec SP1, a polymeric surfactant, in combination with PVPVA 64. Euro. J of Pharm and Biopharm, 70, 2008: 500–505.

5. Margarita V, Carmen C, *et al.,* Ternary naproxen: β-cyclodextrin: polyethylene glycol complex formation. Int. J. of Pharmaceutics. 265, 2003: 141-149.

6. Kohsaku Kawakami, Modification of physicochemical characteristics of active pharmaceutical ingredients and application of super saturatable dosage forms for improving bioavailability of poorly absorbed drugs. Advanced Drug Delivery Reviews, 64, 2012: 480–495.

7. Ilse Weutsa, Dieter Kempena, Geert Verreck, *et al.,* Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying. Euro. J. of Pharm and Biopharm, 59, 2005: 119–126

8. Aso Y, Yoshioka S, Kojima S. Molecular mobility-based estimation of the crystallization rates of amorphous nifedipine and phenobarbital in poly (vinylpyrrolidone) solid dispersions. J Pharm Sci. 93, 2004: 384–391.

9. Ye Sun, Lei Zhu, Tian Wu, *et al.,* Stability of Amorphous Pharmaceutical Solids: Crystal Growth Mechanisms and Effect of Polymer Additives. The AAPS Journal, 14 (3): 2012.

10. Namdeo R Jadhav, Vinod L Gaikwad, Karthik J Nair, and *et al.,* Glass transition temperature: Basics and application in pharmaceutical sector. Asian Journal of Pharmaceutics. 2009.

11. Eugene S. Barabas and Christianah M. Adeyeye, Crospovidone. Analytical Profiles of Drug Substances and Excipients. 1996.

12. Khosro Adibkia, Mohammad Barzegar-Jalali, Hosein Maheri-Esfanjani, and *et al.,* Physicochemical characterization of naproxen solid dispersions prepared via spray drying technology. Powder Technology. 246, 2013: 448–455.

13. Camelia Nicolescu, Corina Arama, Angela Nedelcu, *et al.,* Phase solubility studies of the Inclusion complexes of Repaglinide with β-cyclodextrin and β-cyclodextrin derivatives. Farmacia, 58: (5) 2010; 620-628.

14. Sharma, C.P. Jain. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci. 5(1) 2010: 49–56.

15. M. Barzegar-Jalali, M. Alaei-Beirami, Y. Javadzadeh, G. Mohammadi, A. Hamidi, S. Andalib, K. Adibka., Comparison of physicochemical characteristics and drug release of diclofenac sodium-eudragit RS 100 nanoparticles and solid dispersions. Powder Technol, 219 (2012) 211-216.

16. N. Tiong, A.A. Elkordy, Effects of liquisolid formulations on dissolution of naproxen, Eur. J. Pharm. Biopharm. 73 (3) (2009) 373-384.

17. T. Vasconcelos, B Sarmento, P. Costa, Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs, Drug Discovery Today 12 (23/24) (2007) 1068-1075.

18. Paudel, Z.A. Worku, J. Meeus, S. Guns, G. Van den Mooter, Manufacturing of solid dispersions of poorly water-soluble drugs by spray drying: Formulation and process considerations. Int. J. Pharm.30; 453(1): 2013. 253-84.

19. G. Mohammadi, M. Barzegar-Jalali, H. valizadeh, H. Nazemiyeh, M. R. Siahi-Shadbad Alaei-Beirami, K. Adibka, M. Zare, Reciprocal powered time model for release kinetic analysis of ibuprofen solid dispersions in oleaster powder, microcrystalline cellulose and crospovidone. J. Pharm. Pharm. Sci. 13 (2) (2010) 152-161.

Cite this article as:
Milind Dharmraj Kamble, Zahid Zaheer, Rana Zainuddin, Santosh Mokale. Development and Biopharmaceutical Characterization of BCS Class II Drug – Naproxen by Two Way Complexation Solid Dispersion Technique. *International Journal of Bio-Pharma Research*, Volume 8, Issue 4 (2019) pp. 2523-2530.

http://dx.doi.org/10.21746/ijbpr.2019.8.4.1

Source of support: Nil; **Conflict of interest:** Nil.