Chapter VIII

Novel Nanoformulations for overcoming the poor bioavailability of Piroxicam
8. Nanodispersions and Nanosuspensions for overcoming the poor bioavailability of Piroxicam

8.1 Introduction

Piroxicam, is one of the most potent NSAID, prescribed very often for reduction of pain, inflammation and stiffness associated with joint ailments like osteoarthritis and rheumatoid arthritis. It belongs to the oxicam class of NSAIDs and reduces pain by inhibiting prostaglandin synthesis and reducing the sensitivity of the pain receptors. It also reduces fever by modulating the center of the hypothalamus responsible for heat-regulation. It inhibits thromboxane A2, the platelet-aggregating substance. Other mechanisms proposed for its anti-inflammatory properties include stabilisation of lysosomes, synthesis of kinin and leukotriene, alteration of chemotactic factors and inhibition of neutrophil activation. Chemically, Piroxicam is designated as 1,2-benzothiazine-3-carboxamide-4-hydroxy-2-methyl-N-(2-pyridyl)-1,1-dioxide and belongs to the enol-carboxamide class (Figure 1). It is weakly acidic in nature. It was first developed by Pfizer and Co. In the late 70’s, it entered into medical praxis. It is a white or slightly yellow crystalline powder. It shows polymorphism. It is practically insoluble in water, slightly soluble in dehydrated ethanol and aqueous alkaline solution, soluble in dichloromethane.

Its suitability for short term use as an analgesic as well as long term use as an anti-inflammatory drug makes its usage popular against several conditions including ankylosing spondylitis, acute gout, muscular or skeletal injury, dysmenorrhea, episiotomy, dentistry, and so on. Currently, it is distributed under the brand names Pixicam/Buxicam in Canada and Apo-piroxicam/Gen-pixicam in the US and as Dolonex in India.1

It, however, belongs to the BCS class II category. Hence, its dissolution rate in the gastro intestinal track (GIT) is the limiting step for its absorption. For poorly soluble, highly permeable drugs like piroxicam, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract. Hence, along with permeability, the solubility and dissolution
characteristics of a drug are prime determinants of its overall oral bioavailability. This undesirable property of poor aqueous solubility could also lead to increased damage of the intestinal layers, due to long duration contact of drug with the mucosal layer of the GI tract.

![Figure 8-1: Chemical Structure of Piroxicam](image)

Thus, preparation of time-stable dosage forms with finely divided piroxicam for quick drug release leading to faster initial drug absorption is a mainstay to achieve its optimal therapeutic efficacy. Several attempts in this regard include mainly solid dispersion (SD) / solid solution methods based on cyclodextrin inclusion complexes, poly vinylpyrrolidone, polyethylene glycols 4000 and 6000. SDs of piroxicam-PVP K25 have been prepared with different manufacturing techniques, namely, spray drying and precipitation with compressed antisolvent (PCA). SD prepared with the PCA technique showed about 20-fold faster dissolution rate in the first 15 min compared to the pure drug owing to the fact that the active ingredient is ‘nanodispersed’ in the polymer matrix. The basic principle of such enhancements has been attributed to either complete removal of drug crystallinity and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal (nano)particles. The drug is, thus, said to exist in a supersaturated state because of forced solubilization in the carrier. This increases surface area, and consequently the dissolution and bioavailability of the poorly soluble drugs.

In their study, Javadzadeh et al. investigated the use of novel liquisolid compacts to modify the dissolution behaviour of piroxicam in both simulated gastric fluid (SGF, pH 1.2) and simulated
intestinal fluid (SIF, pH 7.2). Their results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made. Lai et al. have explored nanocrystals of Piroxicam with poloxamer 188 as stabilizer using the high pressure homogenization technique. They designed oral disintegrating tablets (ODTs) with the nanocrystal suspensions using different excipients to study their effect on the PRX dissolution properties. PRX nanocrystal ODT prepared using gelatin or croscarmellose showed a higher PRX dissolution rate compared with the commercial formulation and ODT prepared using xanthan gum. Their overall results confirmed that improved PRX dissolution rate is due to the increased surface-to-volume ratio due to the nanosized drug particles.

In another study by Adibkia et al. designed an improved ocular delivery system for locally inhibition of inflammation of the eye. They prepared nanoformulations using the carrier Eudragit RS100 to control inflammatory symptoms in the rabbits with endotoxin-induced uveitis (EIU). The nanoparticles of piroxicam in Eudragit RS100 were formulated using the solvent evaporation/extraction technique. The in vivo examinations revealed that the inflammation can be inhibited by the nanosuspension more significantly than the microsuspension of drug alone. Thus, formulation scientists are increasingly turning to nanotechnology based solutions to improve solubility, dissolution and bioavailability of poorly soluble compounds.

This chapter gives a comparative account on two such nanoscaling based approaches Nanodispersions and nanosuspensions for tackling the poor solubility/dissolution of piroxicam.

**8.2 Nanodispersions of Piroxicam using PVP K-25 and Soluplus**

There is an increasing trend to view and report the solid dispersion systems as nanoparticulate dispersions or simply nanodispersions, since they have the ability reduce the drug particle size to nanoscale or even molecular level, to solubilize or co-dissolve the drug by the water soluble carrier and provide better wettability and dispersibility of the drug by the carrier material. In such systems, the solubility and dissolution characteristics of the carrier (or mixtures of carriers) dictate the drug release profile.

Recently, the usage of carriers possessing inherent self-emulsifying properties and surface activity or incorporation of surfactants having such properties (along with hydrophilic polymers) has gained predominance. These are termed as the new third generational solid dispersions. These
contain a surfactant-carrier, or a mixture of amorphous polymers and sometimes surfactants as carriers. They are intended to achieve a dual role; firstly, attain high degree of bioavailability improvement for the poorly soluble drugs and secondly stabilize the solid dispersion by avoiding drug recrystallization during the span of dissolution process.

The objective of our study was to compare the dissolution rate of piroxicam drugs by making their nanodispersions with the conventional PVP polymer and a newly developed graft copolymer having surface active properties, Soluplus using the solvent evaporation method.

When solvent method is chosen to synthesize the nanodispersions (NDs), during the process of evaporating the solvent(s), small variations in the experimental conditions (e.g., vacuum drying or use of a rotary evaporator, use of nitrogen stream or spray-drying, freeze-drying or super critical fluids, etc.) may cause significant changes in the product performance. The molecular weight as well as the percent of the hydrophilic polymer used obviously plays a significant role in the drug release rate from the amorphous SD. It is needless to mention that the composition or the nature of the polymer itself shall have an enormous influence on the properties of the SD and the drug release rate. Soluplus is a new amphiphilic polymer (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), specially developed by BASF for making SD of poorly soluble drugs. Due to its bifunctional nature, it is claimed by BASF to act as an excellent matrix for SD and to dissolve the drugs in aqueous medium. There have been quite a few reports on solid dispersions of class II drugs, with Soluplus® as the matrices, resulting in considerable dissolution enhancement. On the other hand, PVP K-25 is a linear polymer (K value calculated from the relative viscosity in water to indicate the viscosity average molecular weight) These polymers form water-soluble complexes with many drug molecules, depending on the chemical structure of the Active Pharma Ingradients (APIs).

The objective of this study was to compare the physicochemical characteristics and dissolution enhancement of the nanodispersions of Piroxicam with the two different polymeric solubilizers.
8.2.1 Synthesis of Nanodispersions

Nanodispersions were prepared with drug to PVP (K-25)/Soluplus in the weight ratios 1:1, 1:2, 1:3, 1:4 and 1:5 by means of the solvent evaporation method. To a solution of piroxicam in acetone (0.5 g in 30 ml), the appropriate amount of PVP was added while stirring over magnetic stirrer. The minimum amount of isopropyl alcohol (IPA) was added to solubilize the polymer PVP (for Soluplus, IPA was not necessary). These solvents were chosen because they are less toxic and are considered safer (Class 3) according to US-FDA ICH guidelines. The solvents were removed under reduced pressures of a vacuum rotary evaporator at 40 °C and dried under vacuum at about 80 °C for 2 days and then carefully stored in a vacuum dessicator. The samples were pulverized using a mortar and pestle, and the 0.05–0.25 mm particle size fractions were obtained by sieving with a sieve size of about 250 microns (50 BSS units).

Rotary evaporation is a very simple, economical and robust method for solvent removal during preparation of nanodispersions for early stage and laboratory scale studies. Since the evaporation time is relatively long in the process, the drug and carriers must be sufficiently stable in the solvent at the temperatures used. For our experiments, since the solvent used was predominantly acetone (boiling point 56 °C), the bath temperature was set to 30 °C and the vacuum was set to 25 mm Hg. Though this process is not very suitable for the industrial large scale manufacturing, development and commercialization, it is an excellent laboratory scale tool to assess the suitability of solubilizers and characteristics of dispersions.

8.2.2 Physicochemical Characterization

XRD Analysis

XRD patterns were recorded using PANalytical X’pert Pro MPD diffractometer, with the following settings: Cu Kα radiation with wavelength 1.54 Å, voltage = 45 kV, current = 40mA. Measurements were made in the 2θ range of 10 to 80°.
It can be noted that the polymers, Soluplus® (Figure 8-3) and PVP (Figure 8-3), are amorphous powders having no crystalline structure. However, for pure piroxicam crystalline peaks were
observed at at the diffraction angles 8.89, 15.7, 23.0 and 25.9. The XRD patterns of the nanodispersions were clearly different from those of the crystalline piroxicam. With an increase in the composition of the polymeric species in the dispersions, the crystallinity was found to successively decrease. The crystalline peaks, corresponding to the API, completely disappeared for the dispersions of the compositions 1:5, in case of PVP, and 1:4 in case of Soluplus®, indicating that at these ratios the drug is entrapped as high energy amorphous state in the polymeric matrices. The polymers, perhaps, interfere in the crystal formation and ‘nanodisperse’ the API, thus modifying its natural crystal habit. Under the given preparation conditions, Soluplus® was able to amorphosize the drug better than PVP.

Figure 8-4: Overlay of the FTIR spectra of Piroxicam, polymer Soluplus® and the nanodispersions in various ratios.
Information regarding drug-carrier interactions, such as hydrogen bonding, can be obtained from an FTIR spectrum. From Figures 8-4 and 8-5, it can be seen that the drug Piroxicam contains a hydrogen donor (–NH), whose characteristic stretching absorption peak is observed at 3339 cm$^{-1}$. The Piroxicam molecules have been speculated to be present in various chemical forms like the tautomeric keto-enol or the zwitterionic forms. Due to the lack of a normal absorption of conjugated ketone in the FTIR spectrum recorded, piroxicam would be present as enol or zwitterionic forms.

The spectrum of PVP portrays a broad absorption band at 3500 cm$^{-1}$ that is indicative of the –NH stretching absorption. The carbonyl stretching vibration was observed as a broad band at 1650-1700 cm$^{-1}$. In the spectrum of Soluplus®, a distinct, broad -OH peak was observed at 3300 to 3600 cm$^{-1}$. The carbonyl stretching of the amide occurred at 1650 cm$^{-1}$ while the carbonyl of the acetate gave an absorption peak at 1750. The peak at 2900-3000 can be attributed to the –NH stretching vibrations. The –C-O-C- bending vibrations, gave a peak at 1470. Nanodispersions also showed slightly different FTIR spectra in the fingerprint regions, the substantial differences were
shown in the N-H or O-H stretching regions. As the proportion of polymers is increased, the broadening of the -OH peak occurred.

The drug: PVP 1:1 showed doublets at 3341 and 3322 cm\(^{-1}\). The single absorption bands at 3337 cm\(^{-1}\) were observed in the FTIR spectra of the drug: PVP 1:2, 1:3 and 1:5. The complete loss of the N-H / O-H stretching vibration peaks of pure piroxicam in the spectra of ND 1:4, in case of Soluplus and ND 1:5 in case of PVP, suggest that the amine hydrogen of piroxicam has hydrogen bonded with the polymer, thus weakening the peak at 3339 cm\(^{-1}\). This is in coherence with the XRD data.

* Differential scanning calorimetry

![Figure 8-6: DSC Thermograms of Piroxicam, Soluplus and the Nanodispersions.](image)
DSC was used to detect interactions between piroxicam and excipients. Thermograms of pure drug, Soluplus and the nanoformulations are presented in Figure 8.5. As noticeable in the thermogram, while pure piroxicam gave a sharp melting endotherm at 203°C, indicating its crystallinity, those thermograms of Soluplus and nanodispersions showed the broad endotherms, due to water removal at about 110-150°C.

In the dispersions with lower polymeric composition, the endotherm corresponding to the melting of piroxicam was still prominent to a certain extent. However, with increase in polymer ratio, the endothermic peak for the drug shifted toward lower melting points than that for pure crystalline piroxicam. The XRD pattern of the dispersion 1:1 clearly indicates the peaks characteristic of the

Figure 8-7: Overlay of DSC TA curves of Piroxicam, and the nanodispersions of Piroxicam with PVP.
drug substance and hence 1:1 sample was not completely amorphous. As expected, the drug: Soluplus® 1:4 nanodispersion that was shown amorphous by XRD did not show a melting endotherm. Taking into consideration of the DSC scans and the XRDs, it was decided that 4 parts of Soluplus are required for each part of the drug substance to make the latter completely amorphous.

The XRD pattern of the dispersion 1:1 clearly indicates the peaks characteristic of the drug substance and hence 1:1 sample was not completely amorphous. As expected, the drug: Soluplus® 1:4 nanodispersion that was shown amorphous by XRD did not show a melting endotherm. Taking into consideration of the DSC scans and the XRDs, it was decided that 4 parts of Soluplus are required for each part of the drug substance to make the latter completely amorphous. The Figure 8-7 shows that the PVP could lower the melting of piroxicam in the nanodispersions. The broadening of the peak and reduction in the peak height could indicate that the drug is present in a high energy amorphous state in the nanodispersions.
8.2.3 Dissolution Analysis

Method

The in vitro dissolution analysis was carried out was using a USP paddle type 2 dissolution testing apparatus (DBK Dissolution Tester, Mumbai, India). A known amount of sample (equivalent to 10mg of piroxicam) was introduced into the glass jar of the USP type II paddle apparatus containing 900mL of 0.5 % (by weight) Sodium dodecyl sulphate (SDS). This was stirred for 2 hours. After predetermined regular intervals, 5mL aliquots of the sample were withdrawn and the concentration of the solution was photometrically determined. To maintain a constant volume during dissolution, 5mL of SDS solution was replaced into the glass jar after every withdrawal.
The spectrophotometric analysis of all piroxicam samples in aqueous solutions (pH 1.2) was performed at 333.6 nm (UV/visible spectrophotometer, Shimadzu, Japan).

**Preparation of calibration curves**

A suitable, accurately weighed quantity of piroxicam was dissolved in methanol to obtain a stock solution. Standard solutions were prepared by dilution of the stock solution with phosphate buffers (pH 4.5 and pH 6.8), SGF without pepsin (pH 1.2), and water in which dissolution and solubility studies would be performed. Ultraviolet absorbances of the solutions were determined at the wavelength of maximum absorbance at 361 nm for pH 4.5, 354 nm for pH 6.8, 333 nm for pH 1.2, and 359 nm for water (Shimadzu spectrophotometer UV-2450, Japan).

![Calibration Curve of Piroxicam in Dissolution Medium](image)

*Figure 8-9: Calibration Curve of Piroxicam in Dissolution Medium*

Figures 8-10 and 8-11 show the dissolution profiles of the drug polymer and the nanodispersions of piroxicam with Soluplus® and PVP respectively. In all cases, nanodispersions exhibited faster dissolution rates than the pure drug. Piroxicam yielded the slowest initial dissolution rate with only about 10% of the drug dissolved in 15 min.
The pure drug was observed to dissolve very slowly and visually settled on the surface of the dissolution medium. Its hydrophobic nature caused the powder to float on the surface of the dissolution medium and prevented its surface contacting the medium. Since piroxicam in both solid dispersions was amorphous and dispersed in the carrier, the dissolution of the API was more of a carrier controlled process. The dissolution rates increased with increase in proportion of the polymer. The dispersions with the drug: polymer weight ratio 1:4 in case of Piroxicam - Soluplus NDs and 1:5 in case of Piroxicam- PVP NDs showed maximum dissolution way above all other dispersions, reaching to near 95% dissolution in 15 minutes. This can be attributed to the drug present in high energy amorphous form in the nanodispersions.
Because PVP K-25 and Soluplus® are readily soluble they could provide larger surface area to facilitate the disintegration of the solid dispersions. According to the Noyes-Whitney equation, the drug dissolution rate of a drug is directly proportional to its concentration gradient (Cs–C) in the stagnant diffusion layer and its surface (S) available for dissolution. Cs is the saturation solubility of the drug in the dissolution medium and, thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (70 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of piroxicam from nanformulations are probably due to the significantly increased surface of the molecularly dispersed piroxicam. In addition, the saturation solubility of the drug in the microenvironment (Cs) might be increased in the amphiphilic/hydrophillic matrix of the polymers.
The enhanced dissolution rate of piroxicam from the nanodispersions might be also resulting from the increase in drug wettability and also the interactions of drug to polymer indicated in FTIR analysis. The dissolution rate of piroxicam in nanodispersion was strongly dependent on the relative concentration of the drug to polymer ratio.

8.2.4 Making of tablets

In order to provide an orientation towards pharmaceutical application, the characteristics and dissolution profiles of the dispersions would be evaluated in the most popular oral dosage form, i.e. tablets. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet needs to be formulated to deliver an accurate dosage of the drug to a specific site in the GI tract. Several excipients are used, apart from the API to formulate a tablet. The excipients include: fillers, binders, disintegrants, glidants, lubricants, etc… Though, more often taken orally, it can be administered sublingually, buccally, rectally or intravaginally.

The active ingredient/ nanodispersions (equivalent to 10 mg of piroxicam) were passed through a mesh of size 250µm (BSS units 50) and mixed with the excipients and again passed through the mesh. The lubricant, magnesium stearate was then added, and mixed well using glass rod and again passed through the mesh to ensure homogeneity. The fine mixture was then compressed to a tablet with a pressure of 5 kg/cm² (45 tons), in an 8mm die, using a hydraulic press.

The following are the excipients and their role in the tablet:
1. Piroxicam/ nanodispersion (Active ingredient)
2. Kollidon CL (Disintegrant)
3. Microcrystalline cellulose (MCC) (Binder)
4. Colloidal Silicon dioxide (glidant)
5. Magnesium stearate (Lubricant)

The tablets were designed to weigh 200mg, to deliver a dosage of 10mg of Piroxicam.

8.2.4.1 Determining the Assay of the tablets

The drug content in the tablets was determined by placing a randomly picked tablet in a 100 ml volumetric flask and filling it with the dissolution medium containing sodium lauryl sulphate. This was shaken for a while on mechanical shaker (30 min) till the tablet disintegrated and the drug
dissolved in the medium. This was filtered using suction filtration and 5mL of the filtrate was withdrawn. The concentration of piroxicam was photometrically determined. From the concentration the weight of the active ingredient was assessed. The assessment of the tablets showed that the average weight of Piroxicam in the tablets was 9.87mg.

8.2.4.2 **Hardness of tablets**

The hardness of tablets was determined by a method formulated in-house. A single tablet was held between the compressing plate and the punches of a pelletizing machine along its diameter and the force was manually increased slowly. The force at which the tablet cracked was noted down. The average value of the hardness of ten such tablets was determined to be 186N, which is appropriate hardness required for a tablet of 8mm.

8.2.4.3 **Dissolution Analysis of Tablets**

As indicated by Figure 8-12, the tablets with crystalline Piroxicam as the active ingredient, have very poor dissolution characteristics. The percentage of the drug dissolved in 0.5% SDS solution is hardly 20% after an hour. The tablets with nanodispersions of piroxicam with PVP have a greater release capability compared to the pure crystalline drug. About 80% of the drug is released within an hour. The tablets with Piroxicam nanodispersed in Soluplus as the active ingredient have the highest release rates, with about 90% dissolution taking place in a span of an hour.
8.3 Nanosuspensions of Piroxicam and Soluplus by Wet Ball Milling

There is a growing need for a unique strategy that can tackle the formulation-related problems associated with the delivery of hydrophobic drugs in order to improve their clinical efficacy and optimize their therapy with respect to pharmacoeconomics. One of the nanoscience approaches that has rapidly gained a proven record within the pharmaceutical sciences is the formulation as nanoparticles. These particles have a size below 1 μm, typically a few hundred nanometers. The particles can be obtained either by particle size reduction of larger crystals (top-down approach) or by building up particles by precipitation of dissolved molecules (bottom-up approach). These production processes are conducted in liquid, hence forming a nanosuspension. Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water- and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies. As the total surface area of the
resulting nanosuspension particles is typically orders of magnitude larger compared to a coarse suspension, large quantities of additives may be necessary to ensure adequate stabilization. Therefore, whatever method is used for the production of nanosuspensions, a careful evaluation of the type and concentration of the stabilizer used is key to the successful production of nanosuspensions. Both polymeric stabilizers and surfactant stabilizers can be used for this purpose\textsuperscript{32}.

We report the usage of a very simple and scalable top down technique, wet ball milling in aqueous media, to synthesize piroxicam-soluplus\textsuperscript{®} nanosuspensions. The nanosuspensions were lyophilized and the physicochemical properties of the obtained formulations were assessed using FTIR and XRD. We have investigated the cytotoxicity of the Soluplus\textsuperscript{®} and the formulations using cell viability experiments from MTT assay on Caco-2 cell lines.\textsuperscript{,} We have also established their \textit{in vitro} dissolution rate using a USP type II paddle apparatus and explored the mechanism of drug release from the formulations by fitting the data obtained from the dissolution studies into several mathematical models.

\subsection{8.3.1 Preparation of Piroxicam Soluplus\textsuperscript{®} Nanosuspensions}

Nanosuspensions were prepared via wet milling using a conventional Retsch Planetary ball mill using the amphiphilic carrier, Soluplus\textsuperscript{®} in various ratios of drug to polymer (2:1, 1:1, 1:2, 1:3, 1:4). The drug and polymer (in the required ratios) were introduced into an agate milling chamber containing 10 mm agate balls. 40 mL of bidistilled water 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\textsuperscript{33,34}.

The nanosuspensions thus formed by co-milling were lyophilized for about 24 hours and gently powdered to obtain free flowing powders. Mannitol (0.1\% by weight) was added as a cryoprotectant during lyophilization.
8.3.2 Results and Discussion

8.3.2.1 Phase Solubility

Phase solubility of piroxicam in various concentrations of soluplus was determined using the Higuchi and Connors method\textsuperscript{35}. To Erlenmeyer flasks (250mL) containing 25 mL of the different concentrations of the polymer solution (0.1\%, 0.25\%, 0.5\%, 0.75\% and 1\%, w/v), an excess amount of drug (1g) was added. The flasks were suitably sealed and shaken at 100 rpm in an orbital shaker cum incubator for 48 hours at 37 °C. They were left in the incubator for another 24 hours for the equilibrium to be established. Then, 5 ml of supernatant was withdrawn and filtered. The amount of drug in the filtrate was photometrically determined using a UV–VIS spectrophotometer at 273 nm after suitable dilution. The studies were carried out 5 times.

Data Analysis

\(\Delta G^0_{tr}\) values of Piroxicam were computed using the following equation:

\[
\Delta G^0_{tr} = -2.303 \log \frac{S_0}{S_s}
\]

where

- \(S_0\) = molar solubility of piroxicam in distilled water
- \(S_s\) = molar solubility of piroxicam in presence of Soluplus\textsuperscript{®}
- \(R = 8.31 \text{ JK}^{-1}\text{ mol}^{-1}\)
- \(T = \text{temperature in degree kelvin.}\)

Gibbs free energy of transfer (\(\Delta G^0_{tr}\)) 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.

To assess if Soluplus\textsuperscript{®} is an ideal choice as a carrier for solubilizing piroxicam, phase solubility studies were carried out. The solubility of Piroxicam in distilled water was determined to be 1.138 \(\mu g/mL\), which implies that it is poorly water soluble. The phase solubility data (Figure 8-13) show
a linear increase in drug solubility with increasing Soluplus® concentration, \( r^2 = 0.998 \). This enhanced effect on the solubility of the drug could be attributed to the several hydroxyl groups present in the polymer chain and its surface active properties. The phase solubility diagram followed an A_L-type system at the given range of concentrations\(^{35,36}\). Moreover, the values of \( \Delta G^0_{tr} \) also varied linearly and became more negative with increasing concentrations of Soluplus® showing that the drug solubilization process is spontaneous in the presence of the polymer (Figure 8-14).

*Figure 8-13: Phase Solubility Profile of Piroxicam in different concentrations of polymer solution*
Figure 8-14: Gibbs Free Energy of Transfer Values with increasing polymer concentration.

The rapid negative increase in $\Delta G_{tr}^0$ values with the polymer concentration also indicates that the transfer of the drug from aqueous phase at the drug particle vicinity to the bulk of the carrier solution is more favorable at higher carrier concentrations. However, the stability constant $K_s$ calculated from the slope and intercept of the phase solubility curve is 4.734 mL g$^{-1}$ is indicative of the binding affinity between the drug and the carrier. The low value of $K_s$ predicts that the binding affinity between Piroxicam and Soluplus® would not be strong though the high $\Delta G_{tr}^0$ values predict spontaneous drug solubilization.

8.3.2.2 Physico-chemical Characterization

PXRD: Distinct sharp peaks of piroxicam were obtained at the diffraction angles 14.50, 17.73 and 27.45 (Figure 8-15). Thus the crystalline nature of pure piroxicam is evident from its PXRD spectrum. The spectrum of the polymer soluplus® contains broad indistinct peaks resulting from the anisotropic scattering of X-rays indicating its amorphous nature. The positions of diffraction peaks of piroxicam in the nanosuspensions were almost completely superimposable, indicating no
chemical interaction between these two components or existence or formation of any other crystal morphology. However the broadening of the peaks in the various formulations suggests decreasing crystallite sizes of the drug dispersed in the polymer with increase in the polymer to drug ratio.

![PXRD spectra](image)

*Figure 8-15: PXRD spectra of Piroxicam, Soluplus and the nanoformulations*

**Thermal Analysis:** The TA curve (Figure 8-16) of pure piroxicam shows a distinct melting endotherm at 203°C, indicating the pure crystalline form of the drug. The TA curves of the nanosuspensions showed decreased onset- melting point temperatures and reduced intensity of the melting point- endothermic peak with increasing polymer concentration. This could be attributed to the reduced lattice energy in the formulations leading to the less distinct melting point peak indicating a glass transition at around 185°C.
FTIR Analysis:

The overlay of the FTIR spectra of the drug, polymer and the nanoformulations are presented in the Figure 8-17. Soluplus® is a block co-polymer of polyethylene glycol (PEG), polyvinyl caprolactam and polyvinyl acetate. Soluplus® showed peaks at 3448.72 cm\(^{-1}\) (O-H stretching), 2924.08 cm\(^{-1}\) (aromatic C-H stretching), 1735.93 cm\(^{-1}\), 1635.23 cm\(^{-1}\) (C-O stretching), and 1477.21 cm\(^{-1}\) (C-O-C stretching). The FTIR spectrum of piroxicam shows a characteristic peak of at 3344.5 cm\(^{-1}\) corresponding to the N-H stretching. The spectra of the nanosuspensions show that there was no interaction between the drug and the polymer.
Morphology and Particle size Analysis

The SEM images of the nanoformulations of piroxicam and soluplus® in the ratios of 2:1 and 1:4 obtained from wet ball milling after 6 hours are shown in Figure 8-18. The particles were of varied morphology with particle shapes ranging from irregular, cuboidal to round. The size distribution varied from about 50nm to 300nm. Since ball milling is top down synthetic route, it offers poor control over morphology and size distribution. Both the formulations showed similar characteristics in terms of morphology and particle size.
8.3.2.3 in vitro Dissolution Studies

The in vitro dissolution analyses were performed using a USP type II dissolution testing paddle apparatus (DBK Dissolution Tester, Mumbai, India). A known amount of sample (equivalent to 10 mg of piroxicam) was introduced into the glass jar of the USP type II paddle apparatus containing 900 mL of simulated gastric fluid (0.1N HCl, pH 4). This was stirred at 70 rpm for 2 hours. After predetermined regular 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 (Shimadzu, UV 2450). To maintain a constant volume during dissolution, 3mL of solution was replaced into the glass jar after every withdrawal. In order to make up for the loss
of drug and the dissolution medium that occurs because dilution caused during this sampling, the corrections were made according to the following equation:

\[
C_i = A_i \left( \frac{V_s}{V_t} \right)^{n-1} \sum_{i=1}^{n} A_i \left[ \frac{V_t}{V_t - V_s} \right]
\]

where

- \( C_i \) = corrected absorbance of the \( i^{th} \) observation.
- \( A_i \) = observed absorbance
- \( V_s \) = Volume of the sample
- \( V_t \) = Total volume of dissolution medium

The percentage of the drug dissolved, thus obtained, and was plotted versus time. Each experiment was performed three times.

As can be seen in the Figure 8-19, the dissolution profile of piroxicam indicates that it has very poor solubility in SIF (less than 40% dissolved after 2 hours). The dissolution of piroxicam from all the nanoformulations studied was significantly faster than that of the pure drug. The dissolution profiles show that the release of piroxicam from all the nanoformulations is gradual and not of the burst release types. All the formulations achieved supersaturation by the end of about one hour. There was no visible decline in the supersaturation in any of the formulations even at the end of two hours. This negates the occurrence of any recrystallization of the dissolved drug in the dissolution medium. Increase in the Soluplus® content in the formulations had an enhanced effect on the dissolution of piroxicam. This improvement can be attributed to improved wetting characteristics, micellar solubilization, and surface adsorption of the drug on the polymer.\textsuperscript{12,28,37} The highest dissolution enhancement was achieved for the formulation with the drug to polymer ratio of 1:4 which is 95% at 90 minutes. This is a 144% enhancement when compared to that of the pure drug.

Dissolution efficiency (DE) is the area under the dissolution curve within a given range of time. It is a comparative dissolution parameter which takes the entire dissolution profile into account rather than a single point. The absorption of a drug can be assumed to be directly proportional to the
amount of drug dissolved and the time the solution is in contact with the region of absorption in the GI tract. And also since the in vivo bioavailability of a drug is estimated as the area under the blood level curve, it is more relevant to represent the dissolution data in terms of percentage dissolution efficiency (%DE). Table 8-1 lists out % DE values for different time periods with increasing polymer weight percent.

![Dissolution Profiles of Piroxicam and the Nanoformulations with different Soluplus® content.](image)

*Figure 8-19: Dissolution Profiles of Piroxicam and the Nanoformulations with different Soluplus® content.*
Figure 8-20: Comparative Dissolution Efficiencies of the Nanoformulations with increasing polymer content.

Table 8-1: Dissolution Efficiencies calculated at different times.

<table>
<thead>
<tr>
<th>Percentage of Polymer</th>
<th>% DE at t=10 min</th>
<th>% DE at t = 20 min</th>
<th>% DE at t = 30 min</th>
<th>% DE at t = 60 min</th>
<th>% DE at t = 90 min</th>
<th>% DE at t = 120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>5.99</td>
<td>8.71</td>
<td>21.49</td>
<td>14.43</td>
<td>24.01</td>
<td>27.19</td>
</tr>
<tr>
<td>20%</td>
<td>8.89</td>
<td>13.88</td>
<td>36.86</td>
<td>25.93</td>
<td>32.23</td>
<td>35.49</td>
</tr>
<tr>
<td>33%</td>
<td>9.49</td>
<td>16.02</td>
<td>41.36</td>
<td>28.79</td>
<td>36.88</td>
<td>40.98</td>
</tr>
<tr>
<td>50%</td>
<td>15.08</td>
<td>21.47</td>
<td>53.27</td>
<td>35.73</td>
<td>42.92</td>
<td>46.95</td>
</tr>
<tr>
<td>66%</td>
<td>22.00</td>
<td>33.52</td>
<td>79.80</td>
<td>54.01</td>
<td>65.88</td>
<td>72.31</td>
</tr>
</tbody>
</table>

During the initial time periods the enhancement in the DE with increasing polymer percentage is hardly significant. At t=5min, the DE values of the drug is only 4.50%. This increases gradually with increasing ratio of the polymer, reaching up to 17.02% which is a 4 fold increase compared
to that of the pure drug. The lower values of DE during the initial time periods (up to 30 minutes) could be due to slow emulsification process. At the end of 120 minutes, the DE achieved by piroxicam alone is only 27%. By increasing the polymer content to 66% in the nanoformulation, the DE increased to 72%.

8.3.2.4 Mathematical Modeling Studies:
Table 8-2 lists the slopes and R² values obtained from fitting the experimental in vitro dissolution data into the various release kinetic models. The fitting for all the formulations were carried out for the data obtained until the last sampling time i.e, 120 minutes. The Higuchi model described the drug release data of pure piroxicam the best while the nanoformulations were observed to best fit into Korsemeyer-Peppas model. Predominantly, the most befitting model describing the release mechanisms for all the formulations was the Korsemeyer-Peppas model, while, the zero order model was the least befitting.

Table 8-2: Slopes and r² values obtained from fitting of the dissolution data into various models

<table>
<thead>
<tr>
<th>% of Soluplus®</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixon-Cronwell</th>
<th>Korsemeyer–Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>r²</td>
<td>Slope</td>
<td>r²</td>
<td>Slope</td>
</tr>
<tr>
<td>20%</td>
<td>-0.015</td>
<td>0.546</td>
<td>-0.0022</td>
<td>0.739</td>
<td>4.668</td>
</tr>
<tr>
<td>33%</td>
<td>-0.016</td>
<td>0.542</td>
<td>-0.002</td>
<td>0.789</td>
<td>6.279</td>
</tr>
<tr>
<td>50%</td>
<td>-0.012</td>
<td>0.532</td>
<td>-0.003</td>
<td>0.760</td>
<td>6.396</td>
</tr>
<tr>
<td>66%</td>
<td>-0.014</td>
<td>0.536</td>
<td>-0.02</td>
<td>0.893</td>
<td>9.968</td>
</tr>
</tbody>
</table>

According to the Korsemeyer-Peppas power law, the value of ‘n’ describes the release mechanism of the drug. The values of the diffusional release exponent ‘n’ computed from the slopes of this model fell within a range of 0.640 to 0.721. Since these values fall between 0.43 and 0.85 (assuming spherical geometry), all the formulations exhibit anomalous non-Fickian release kinetics. Thus, the release phenomena may be regarded to be both diffusion and swelling controlled.
8.4 Conclusions

Nanodispersions of piroxicam with PVP K-25 and Soluplus were prepared and characterized by powder XRD, DSC, FTIR, FESEM, and dissolution tests. Looking at the results of all the characterization and dissolution studies of the nano/micro-dispersions, it is expected that the drug is dispersed as highly energetic species either as amorphous or nanosized particles. The analyses show that the drug in the dispersions with both the polymers were devoid of crystallinity and dissolved quickly in 0.1 N acidic (HCl) 0.05% SDS solution. The nanodispersions exhibited higher dissolution rates than those of pure crystalline piroxicam, resulting from the increase in drug wettability and the drug-PVP/Soluplus interactions. Tablets made out of the nanodispersion of Soluplus (1:4) showed about 20% higher release rate than that of PVP (1:5).

Aqueous based wet ball milling, an easy and scalable manufacturing top down process, was used as a synthetic route for Piroxicam-Soluplus® nanosuspensions. The solubilizing characteristics of Soluplus® were investigated using the phase solubility studies. The physico-chemical characteristics of the nanoformulations, established using PXRD, DSC, FESEM and FTIR analysis indicate that reduced drug crystallinity played a pivotal role in governing the solubility characteristics of the drug. Dissolution studies show that by increasing Soluplus content in the formulation to 66% an enhancement of 144% could be achieved in comparison to the pure drug. The Korsemeyer–Peppas model best fits the in vitro dissolution data and gives an insight into the possible drug release mechanism dominated by anomalous non-Fickian diffusion.

8.5 References


Dissolution Enhancement in Nano/Micro-Sized Dispersions of Piroxicam with the Novel Polymer Soluplus® and Polyvinyl Pyrrolidone

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ABSTRACT

Piroxicam, a Non-Steroidal Anti-Inflammatory Drug (NSAID), belongs to the class II of the biopharmaceutical classification system (BCS) and thus exhibits poor bioavailability. In an effort to tackle this issue, we report here the comparative properties of the solid dispersions of piroxicam made from a novel graft copolymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus) and the linear polymer polyvinyl pyrrolidone (K 25), both the dispersions synthesized identically using solvent evaporation method. The absence of crystallinity of drug in the solid dispersions was confirmed by Powder X-Ray Diffractometry, and Differential Scanning Calorimetry (DSC). FTIR analysis showed the presence of intermolecular hydrogen bonding between the piroxicam and the polymers. The morphology and the particle size of the dispersions were analyzed with an FESEM. The results obtained from these analyses confirm that the drug is present in amorphous state in the dispersions. The in vitro dissolution characteristics of the tablets made from these powders were studied using the USP paddle dissolution apparatus (type II). The dissolution profiles show that the nanodispersions have higher dissolution rate than that of pure drug.

Keywords: Piroxicam, solid dispersions, dissolution enhancement, polyvinyl pyrrolidone, Soluplus

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