Chapter IX

Nanoformulations of Aceclofenac and Soluplus for Improved Bioavailability
9. Nanocomposites of Aceclofenac and Soluplus® for Increased Bioavailability

9.1 Introduction

Aceclofenac is a new generational anti-inflammatory agent, belonging to the acetic acid derivative class of NSAIDs that is generally administered orally to provide symptomatic relief against a wide range of painful conditions, such as, rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. In patients with osteoarthritis of the knee, the drug decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam and naproxen. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to ketoprofen, diclofenac, indomethacin and tenoxicam in its therapeutic effect. Aceclofenac is also effective in other painful conditions such as in dental and gynaecological pains. In contrast to some other NSAIDs, aceclofenac has shown stimulatory effects on cartilage matrix synthesis. It functions by inhibiting the inflammatory mediators like the tumor necrosis factor (TNF-α), prostaglandin E2, and interleukin-1 ILβ and IL-6 together with preferential and selective cyclooxygenase-2 (COX-2) after conversion into active metabolite.

It is considered a better alternative to the popular pain-killer diclofenac, as it overcomes some of the adverse gastrointestinal and cardiac side effects associated with the latter. Diclofenac is probably the most popular NSAID prescribed for the treatment of osteoarthritis-related pain and was approved by US-FDA in 1988. The overall efficacy of the drug matches up to any of the newer approved pain-killer medications. In spite of its several advantages, diclofenac is unfortunately associated with several side effects especially concerning to gastrointestinal (GI) adversities including bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can, at times be even fatal. These adversities of a time tested drug always motivated the medicinal chemists to develop a new/modified NSAID with better safety profiles without
compromising on its efficacy. This probably motivated the design and development of Aceclofenac, which essentially is a derivatized molecule from diclofenac initially developed by Grau et al. in 1991\(^4\). Chemically, its nomenclature is 2-[[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy] acetic acid or (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid). It is the glycolic ester of the popular pain killer diclofenac(Figure 9-1) but however, has been reported to have a much better tolerability profile\(^1-3\).

![Figure 9-1: Chemical Structure of Aceclofenac. Source: Internet](image)

Preclinical studies suggest that the potential of aceclofenac to cause gastrointestinal damage is less than that of diclofenac. Most adverse events associated with aceclofenac are minor and reversible, and restricted primarily to the GI system.

However, the bioavailability of the drug remains limited due to low aqueous solubility (0.058µg/mL) and poor dissolution characteristics. Hence, improving its dissolution characteristics is of prime significance in order to establish its optimal therapeutic efficacy. Efforts towards dissolution/solubility enhancement of aceclofenac include several formulations such as spherical agglomerates\(^5\), hydrotropic mixtures\(^6,7\), solid dispersions in Avicel and Sylsysia\(^8\), lactose, mannitol, urea\(^9\), etc.,dispersions in hydrophilic polymers like PEG 6000 and PVP-K30\(^10\), inclusions in carbopol gels\(^11\), entrapment in oil-esterculia gum-alginate buoyant beads by ionotropic emulsion-gelation\(^12\) and co-grinded mixtures with Neusilin NS2\(^13\). Even as the existing techniques are progressively altered to tackle this issue, the future appears still brighter to develop novel technologies to synthesize ultrafine particles in nano-scale regime. Of late, several nanotechnology based formulations have also been explored to enhance the dissolution characteristics of aceclofenac.
Shakeel et al.\textsuperscript{14} investigated three nanotechnology based formulations namely, nanoemulsion, solid lipid nanosuspension and polymeric nanosuspension to improve solubility and dissolution of aceclofenac. They have reported highest solubility (198.53 mg/ml) as well as % dissolution (99.5) of aceclofenac with nanoemulsion formulation as compared to lipid and polymeric nanosuspension. Karthikeyan et al.\textsuperscript{14} designed electrospun composites of zein/eudragit nanofibers to co-administer aceclofenac/pantoprazole to restrict or rather compensate the adverse effects of the NSAID. They evaluated the \textit{in vitro} release efficiency as well as \textit{in vivo} efficacy of the dual delivery systems and confirmed that the co-administration of pantoprazole and aceclofenac reduced the GI toxicity induced by NSAIDs. The use of nanocarriers has not been restricted to oral delivery alone. In their study, Patel et al.\textsuperscript{15} have evaluated the use of stearic acid and oleic acid to develop nanostructured lipid carriers (NLC) for the topical delivery of aceclofenac. The NLCs were prepared by a hybrid method of melt-emulsification, low-temperature solidification, and high-speed homogenization methods. The anti-inflammatory effect of the NLC gel was assessed by the rat paw edema technique and compared with marketed aceclofenac gel.

Thus, nanosized polymeric particles have emerged as a pragmatic approach for the efficient formulation of hydrophobic drugs. The major characteristic of these systems is the rapid dissolution rate which enhances bioavailability after oral administration. They 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. Essentially they are colloidal dispersions of nanosized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer. In our study, we have explored the usage of a new amphiphilic polymeric, Soluplus\textsuperscript{®} to manufacture nanoformulations for the design and evaluation of effective oral drug administration of the poorly soluble NSAID, aceclofenac.

High shear homogenization was the method of choice for the synthesis of the nanoformulations and was achieved by ultrasonication followed by lyophilization. Homogenization using a probe ultrasonicator is very effective way of minimizing droplet size. During the process, the energy is provided through sonotrodes called as sonicator probe. It contains piezoelectric quartz crystal which can expand and contract in response to alternating electric voltage. As the tip of sonicator contacts the liquid, it produces mechanical vibration and cavitation.
occurs. Cavitation is the formation and collapse of vapour cavities in liquid. Thus, ultrasound can be directly used to produce emulsion; it is mainly used in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained\textsuperscript{16,17}. Ultrasonication has been widely used for manufacture of aqueous suspensions, lyosols, emulsions, and granulated mixtures in a variety of applications such as adhesives, cosmetics, food (sauces and dressing), plastics, polymeric blends, chemicals, paper industries for the purpose of homogenization, dispersion, as well as particle size reduction.

![Figure 9-2: (Left) Schematic showing homogenization occurring via ultrasonication. (Right) Probe sonicator. Source: Public domain.](image)

The chosen carrier Soluplus\textregistered is an amphiphilic graft co-polymer (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol), specially manufactured by BASF for formulating poorly soluble drugs. Due to its bi-functional nature, it is expected to act as an excellent matrix to dissolve the drugs in aqueous medium. Soluplus is a novel polymer specially designed for the fourth generation solid solutions towards dissolution enhancement. Soluplus can increase solubility and bioavailability of poorly soluble drugs. It is ideal for hot melt extrusion with excellent extrudability and easy processing\textsuperscript{18}.
The main objective of this work is to investigate the feasibility of synthesizing aceclofenac nanoparticles in Soluplus® matrix using the single emulsion technique in an effort to establish the enhancement of wetting characteristics, while decreasing the agglomeration of aceclofenac nanoparticles, and to evaluate their drug content and loading efficiency, IR and XRD spectral characteristics, morphology and investigate their solubility and dissolution rate.

9.2 Preparation of Aceclofenac Nanomatrix Systems

Nanoemulsion (NE) refers to an isotropic mixture of oily phase and aqueous phase that are effectively stabilized by a surfactant and/or co-surfactant molecules. They are homogenous, optically clear solutions with high free energy, greater drug penetration, better bio-availability, high absorption rate, resistant to enzymatic degradation and hydrolysis. Both hydrophilic and lipophilic drugs can be formulated depending on the type of NE formed which results in enhanced physicochemical properties and behavioral kinetics than micro/macro emulsions. They utilize only less amount of surfactant and reduce the dosage and frequency of drug. NEs can be prepared by both high energy and low energy emulsification method where former make use of devices to create dispersive forces while the latter makes use of change in parameters that affect the hydrophilic-lipophilic balance (HLB) of the system.

In the present work nanoemulsions of aceclofenac in Soluplus® were synthesized using the single emulsion technique. The single emulsion technique using oil-in-water emulsion solvent evaporation method is the oldest and most commonly used technique for microencapsulation. In this method the drug substance is either dispersed or dissolved in the polymer/solvent system. Then it is added to the aqueous phase by continuous agitation. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microsphere which contains the active moiety that is drug.
The drug and the polymer were dissolved in dichloromethane (DCM) in ratios of 1:1, 1:2 and 1:5 to form the organic phase and 20 mL of distilled water with 0.05% Tween 80® surfactant formed the aqueous phase. A conventional syringe pump was used to drop the organic phase in a slow and controlled manner into the aqueous phase (at regulated flow rate of 0.3 mL per minute). Homogenization of the two phases was achieved by using the continuous mode of operation of the probe ultrasonicator. The high-shear produced by the ultra-sonication is instrumental in dispersing organic phase containing the drug and the polymer into the continuous aqueous phase. The mixture was then magnetically stirred continuously for 24 hours for the removal of DCM and successively lyophilized (Mini Lyodel, India) at – 40°C for about 12 hours and gently ground to obtain free flowing powders. The powders were then sieved through a mesh of 200 µm sieve size and preserved under desiccation. The samples were labeled as NP AS 1, NP AS 2 and NP AS 3 to denote the nanoparticles of drug: polymer ratios 1:1, 1:2 and 1:5 respectively.
9.3 Physico-chemical Characterization

*Fourier Transform Infrared (IR) spectroscopy*

FTIR spectra of the drug, polymer and the nanoformulations (NPAS 1, NPAS 2 and NPAS 3) were obtained using an FTIR Spectrophotometer (Spectrum FTIR (Scimadzu, IRAffinity-1)). The spectra were recorded in the wavelength region from 4000 – 400 cm$^{-1}$. The procedure consisted of dispersing a sample in Potassium Bromide (KBr) by co-grinding them and compressing into pellets by applying a pressure of 6 ton for 1 min in a hydraulic press (Kimaya Pelletizer Press, India). The pellet was carefully introduced into the sample holder the spectrum was recorded. All spectra were collected as an average of 30 scans at a resolution of 0.5 cm$^{-1}$.

*Differential scanning calorimetry (DSC)*

Differential Scanning Calorimeter (TGA DSC 1, Mettler Toledo) was used to characterize the thermal behavior of the pure drug, polymer and the various nanoformulations (NPAS 1, NPAS 2 and NPAS 3). The samples were desiccated and dried till used. About 5 mg of the sample was introduced into a 70μL aluminium pan, and made to go through the thermal program. The thermal program consisted of dynamic heating at a rate of 10 °C min$^{-1}$ from ambient temperature (25°C) to 200 °C under inert nitrogen atmosphere. The evaluations were done using STARe software.

*X-ray diffraction (XRD)*

XRD patterns were recorded for drug, polymer and the nanoformulations (NPAS 1, NPAS 2 and NPAS 3) 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°.

*Field Emission Scanning Electron Microscopy (FESEM)*

Double sided carbon tapes were fixed on an aluminum stub. The powders were sprinkled onto the tape and gold sputtered for 10 mins. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (Carl Zeiss SMT- Super Ultra Model Gemini Ultra 55) operated at 4 kV. The images were scanned for drug, polymer and the nanoformulations.
Phase Solubility

Phase solubility of aceclofenac in presence of Soluplus was determined by the shake-flask method established by Higuchi and Connors\(^{23}\). An excess amount of the drug was introduced into 250 ml conical flasks containing aqueous solutions of the carrier Soluplus\(^{\circledR}\) with varying concentrations (0.5%, 1%, 1.5%, 2%, 2.5%, 3% and 4%w/v).

The flasks were suitably sealed and shaken (100 agitations/min) in orbital shaking incubator for 24 h at 37 °C. The sealed flask was left aside for equilibrium is achieved for 24 hours at 37 °C in incubator. Then 5 ml of supernatant was withdrawn and filtered using Whatman\(^{\circledR}\) filter paper. The filtrates were analyzed using a UV–visible spectrophotometer at 273 nm after suitable dilution. A double-beam Shimadzu (Japan) UV-Visible spectrophotometer, Model UV 2450, using a 1 cm quartz cuvette, with a fixed slit width (1 nm), wavelength accuracy of +0.5 nm (with automatic wavelength correction) was used. The drug analyses data were acquired and processed using UV Probe software (Version 2.3, Shimadzu, Japan), the wavelength range selected was from 300 nm to 220 nm with medium scanning speed. From the absorbance spectrum of the aceclofenac, the \(\lambda_{\text{max}}\) for aceclofenac was calculated to be 273 nm. A calibration curve was drawn by plotting absorbance and concentration of drug at the \(\lambda_{\text{max}}\). This standard curve was used to estimate the concentration of the drug in the solution.

Whether the treatment is favourable or unfavourable for drug solubilization in an aqueous medium can be obtained from Gibb’s free energy, \(\Delta G^\circ_{\text{tr}}\) value calculated from phase solubility curve. Negative Gibbs-free energy values indicate improved dissolution. The \(\Delta G^\circ_{\text{tr}}\) values of aceclofenac were calculated using the following equation:

\[
\Delta G_{\text{tr}} = 2.303RT \log (S_o/S_n)
\]

Where \(S_o/S_n\) is the ratio of the molar solubility of aceclofenac before and after treatment. The value of gas constant (R) is 8.31 J K\(^{-1}\) mol\(^{-1}\) and T is temperature in degree kelvin.

in vitro Dissolution Testing

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
50mg of aceclofenac) was introduced into the glass jar of the USP type II paddle apparatus containing 900mL of simulated intestinal fluid (phosphate buffer, 6.8 pH). This was stirred at 70 rpm for 2 hours. After predetermined regular intervals, 3 mL aliquots of the sample were withdrawn, filtered, suitably diluted and 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. Corrections for this dilution were made during the calculations. The percentage of the drug dissolved was calculated and plotted versus time. These studies were carried out three times.

9.4 Results and Discussion

9.4.1 Phase Solubility

The phase solubility studies (Figure 9-4) depict the influence of the carrier, Soluplus® on the solubility of aceclofenac in distilled water at 37 °C. At 0.7% and 1.0% w/v concentrations of the polymer, the solubility of aceclofenac was increasing by 5 times. This enhancement in solubility could be the result due to the amphiphilic nature of the polymer as well as surface adsorption of drug on the polymer.
According to Higuchi and Connors, the drug-carrier interactions follow the “A type” profile, when the solubility of the drug increases with increasing carrier concentration. Again under the A type profile, the $A_L$ indicates one molecule of drug to form a complex with one molecule of carrier exhibiting a linear relationship. The $A_P$ system indicates that one molecule of drug forms a complex with two molecules of ligand and a positive deviation from linearity is exhibited. The $A_N$ system, which is the least encountered system, shows a negative deviation which indicates a decrease with increasing carrier concentrations.

Figure 9-4: Phase Solubility profile of aceclofenac in Soluplus
Table 9-1: Phase Solubility of aceclofenac with various ratios of Soluplus®.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Concentration of Polymer</th>
<th>ΔG°_{tr}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1%</td>
<td>-103.93</td>
</tr>
<tr>
<td>2</td>
<td>0.2%</td>
<td>-461.621</td>
</tr>
<tr>
<td>3</td>
<td>0.5%</td>
<td>-962.568</td>
</tr>
<tr>
<td>4</td>
<td>0.7%</td>
<td>-1233.345</td>
</tr>
<tr>
<td>5</td>
<td>1.0%</td>
<td>-2569.615</td>
</tr>
<tr>
<td>6</td>
<td>1.5%</td>
<td>-3989.799</td>
</tr>
<tr>
<td>7</td>
<td>2.0%</td>
<td>-4143.07</td>
</tr>
</tbody>
</table>

The values of Gibbs-free energy (ΔG°_{tr}) associated with the aqueous solubility of aceclofenac in the presence of Soluplus® are presented in Table 9-1. The ΔG°_{tr} values were negative with increasing polymer concentrations, which reflect the spontaneous nature of the aceclofenac solubilization at that particular concentration of Soluplus. Also, the values decreased with increasing concentrations of polymer, thereby demonstrating that reaction became more favourable as the concentration of polymer was increased. This shows that Soluplus® can be expected to behave as a solubilizer for aceclofenac in aqueous solutions.

9.4.2 Solubility studies

An excess amount of aceclofenac was introduced into 250 ml flasks containing 25 ml of the different media (distilled water, SGF 0.1 N HCl and SIF phosphate buffer at pH 6.8). The flasks were suitably sealed and shaken for 24 h at 37±0.1 °C by an orbital shaker/incubator. The sealed flask were left aside in the incubator for 24 h at 37 °C for achieving equilibration. The supernatant
solution was withdrawn and filtered through Whatmann Filter Paper and the amount of the drug dissolved in the media was analyzed spectrophotometrically at 273 nm after suitable dilution. All solubility measurements were performed five times. The solubility of aceclofenac in water, 0.1 N HCl and phosphate buffer (pH 6.8) are shown in Table 1. The solubility of aceclofenac in water at 37 °C±1 °Cwas found to be 0.067± 0.0043mg/ml. The solubility values of aceclofenac in 0.01 N HCl and phosphate buffer (pH6.8) were observed to be approximately 0.021 ± 0.0011mg/ml and 6.233 ± 1.113 mg/ml respectively (Table 9-2). The pH of solution had a significant effect on the solubility of aceclofenac. Simulated Intestinal Fluid phosphate buffer (pH6.8) was chosen as the dissolution medium is that aceclofenac as its solubility in water and in acidic media is low and hence maintaining sink condition is harder, whereas the solubility of aceclofenac in phosphate buffer (pH 6.8) is 6.233 mg/ml, making it easier to maintain the sink condition.

Table 9-2: Solubility of aceclofenac in different dissolution media.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Solubility*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled Water</td>
<td>0.067±0.0043</td>
</tr>
<tr>
<td>Simulated Gastric Fluid (0.01N HCl)</td>
<td>0.021±0.0065</td>
</tr>
<tr>
<td>Simulated Intestinal Fluid (pH = 6.8)</td>
<td>6.233±1.113</td>
</tr>
</tbody>
</table>

9.4.3 FTIR analysis

As can be seen from the Figure 9-5, the FTIR spectrum of aceclofenac showed characteristic bands at 3319.3 cm⁻¹ (N–H stretching), 2970.2 and 2935.5 cm⁻¹ (O–H stretching), 1716.5 cm⁻¹ (C–O stretching), 1589.2 cm⁻¹ (skeleton vibration of aromatic C–C stretching), 1506.3 cm⁻¹ (in plane bending for N–H), 1380 cm⁻¹ (O–H in plane bending), 1280.6 cm⁻¹ (C–N aromatic amine), 944 cm⁻¹ (O–H out plane bending) and 746 cm⁻¹ (out plane bending for N–H). FTIR spectra of Soluplus® exhibited characteristic peaks at 2924cm⁻¹ (aliphatic – CH stretching), 1730 and 1632 cm⁻¹ (C=O stretching).
In the nanoformulations, the N–H stretching peak of aceclofenac shifted towards lower frequency 3424 cm$^{-1}$ with increasing polymer ratio and completely disappeared in NPAS 3. The reason for this observation might be the consequence of hydrogen bonding between –COOH of aceclofenac and carbonyl oxygen of Soluplus®. The presence of hydrogen bonding between the drug and polymer is indicative of the stability of the formulations because the rate of crystallization of the particles depends on the molecular mobility in the dispersed phase$^{28}$.

*Figure 9-5: FTIR Spectra for the pure drug and the nanoparticles of the drug with various Soluplus ratios.*
9.4.4 DSC Analysis

Figure 9-6 shows the thermal analysis curves for the drug alone, polymer alone and the nanoformulations. Pure aceclofenac showed a distinct melting endotherm at 154 °C. The polymer Soluplus® showed a melting endotherm (T_M) endotherm at 79 °C. All the three drug-polymer nanoformulations were devoid of the drug melting endotherm and showed decreased enthalpies of melting indicating the absence of crystalline drug moieties in the matrix of the polymer.

![DSC thermal analysis curves for the pure drug and the nanoparticles of aceclofenac with various ratios of Soluplus](image)

*Figure 9-6: DSC thermal analysis curves for the pure drug and the nanoparticles of aceclofenac with various ratios of Soluplus*

The T_M of the polymer was observed to decrease with increase in drug content of the nanoformulation. This could be because the drug-polymer interactions might be substituting the polymer-polymer interactions in the nanoformulations, thus lowering the T_M. The observed enhanced solubility of the drug was the result from 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 formulations.
9.4.5 XRD Analysis

From Figure 9-7, it can be noted that, intense crystalline peaks of aceclofenac occurred at the diffraction angles 14.4, 17.7, 18.0, 18.6 and 24.6. The polymer Soluplus® spectrum did not show any indication of crystalline structure thus confirming the amorphous nature. The nanformulations were all x-ray amorphous with no crystalline peaks of the drugs at all. This is in coherence with the thermal analysis. It can be thus concluded that aceclofenac is present as amorphous dispersions in the matrix of Soluplus®.

Figure 9-7: XRD spectra for the pure drug and the nanoparticles of the drug with various Soluplus® ratios.
9.4.6 FESEM imaging

The FESEM images (Figure 9-8) of the nanoparticulate system showed a beaded network of Soluplus® and aceclofenac composites. The absence of distinct drug crystals in the SEM images indicate that no crystallization occurred during the freeze drying process and that the drug is present as an amorphous solid or as low crystalline moieties in the formulations. The loss of crystallinity was also confirmed by DSC and XRD analyses.

Figure 9-8: FESEM images of the formulation of aceclofenac and Soluplus® nanoparticles of NP AS 3 formulation at various magnifications.
9.4.7 *Dissolution Studies*

The dissolution profiles of the pure drug and the various nanoformulations are given in Figure 9-9. Pure aceclofenac has a saturating dissolution profile at 40% even at the end of 2 hours. Clearly, it can be seen from the figure that dissolution profiles of the nanoformulations at all drug-polymer ratios are much higher than that of the pure drug. This could be attributed to the dispersion of the drug as highly amorphous particles in the matrix of Soluplus® and increased wettability on account of the hydrophillicity of the polymer.

![Dissolution Analysis](image)

*Figure 9-9: Dissolution Analysis of the pure drug, physical mixtures of drug and polymer and the nanoparticles with various ratios of the polymer.*
The nanoformulations NPAS 1 and NPAS 2 showed similar dissolution profiles reaching 70.1% dissolution achieved in a span of 10 minutes and saturating at 65.3% release by the end of 2 hours. The formulation NPAS 3, with the drug to polymer ratio of 1:5 showed maximum dissolution of 95.2% in 5 minutes (Figure 9-10), though the dissolution profile saturates at 86.6% by the end of 2 hours. Even with the physical mixture of aceclofenac and Soluplus® a marginal enhancement in the solubility with increase in polymeric content could be seen. This could be due to surface activity and its solubilizing wetting characteristics arising from the amphiphilicity of the polymer.\(^{29}\)

![Figure 9-10: Plot of Dissolution Efficiencies with variation in carrier content at early and late phase of dissolution.](image)

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 \textit{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). 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 9-11 depicts the %DE values obtained with variation in the carrier content at two times representing an early and a late phase of dissolution. By increasing the polymer content in the formulation to 66%, the efficiency achieved was about 85% (142% enhanced efficiency compared to the pure drug.

The possible mechanism of solubilization of the aceclofenac nanoparticles could be explained in the following manner. The drug nanoparticles were well dispersed in the polymer matrix as a result of the proper miscibility of the drug with the caprolactam (hydrophobic) part of the polymer. As the drug-polymer composite came in contact with water, the ethylene glycol (hydrophilic) part of the polymer hydrated rapidly into solution, solubilizing the dispersed drug nanoparticles as well. Also, the reduction in particle size increases the surface/volume ratio and the surface interactions, thus resulting in proper drug-polymer miscibility and enhancement of the dissolution rate and solubility and consequently the bioavailability of the drug.

9.4.8 Stability Studies

The stability of the formulations is of prime significance to pharmaceutical industry and needs to be assessed. However, the instability of the formulations becomes detectable only after a considerable storage time has elapsed. So, to reduce the time required for assessing the degradation kinetics and hence the storage stability, the drug product is evaluated for its shelf life under accelerated degradation conditions of temperature and humidity.

The physical stability of the resulting amorphous state of the drug after nanoformulation with Soluplus was monitored using XRD. The samples were stored in vials at 40°C and 75% RH for 4 weeks. After storage of the NF powders at 25°C and 75% RH for 4 weeks, it was evaluated for changes in the drug crystallinity and morphology. The amorphous state and morphology of
aceclofenac from NP AS 3 appears to be physically stable. The formulation NPAS 1 however showed the appearance of some crystallinity. XRD did not show any significant difference in the peaks of the stored sample for NPAS 3 indicating the absence of any significant reversion to the crystalline state (Figure 9-11).

![XRD plots](image)

*Figure 9-11: XRD plots used to assess the stability of the formulations.*

### 9.5 Conclusions

The present study shows the utility of a novel amphiphilic carrier Soluplus® in synthesis of aceclofenac nanoparticles to enhance its solubility and dissolution. The single emulsion method was adopted to convert crystalline form of drug to a more energetic amorphous form in stable nanoparticles. The phase solubility studies depicted the influence of the carrier, Soluplus® on the solubility of aceclofenac in distilled water at 37 °C. At 0.7% and 1.0% w/v concentrations of the polymer, the solubility of aceclofenac was increased by 5 times. The presence of hydrogen bonding between the drug and polymer through hydrogen bonding between – COOH of aceclofenac and carbonyl oxygen of Soluplus is indicative of the stability of the formulations because the rate of crystallization of the particles depends on the molecular mobility in the dispersed phase. The
enhancement in solubility could be the result due to the amphiphilic nature of the polymer as well as surface adsorption of drug on the polymer.

The absence of crystalline drug moieties in the matrix of the polymer can be inferred from the decreased enthalpies of melting in the nanocomposites. The reduction in the $T_M$ of the polymer in the presence of the drug could be because the drug-polymer interactions substitute the polymer-polymer interactions in the nanocomposites. Hence enhanced solubility of the drug is known to result from 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 formulations.

The nanocomposite powders were all x-ray amorphous without any indication of crystallinity of the drugs at all which is supported by the present thermal analysis thus indicating that aceclofenac is present as amorphous dispersions in the matrix of Soluplus. The absence of distinct drug crystals in the SEM images indicative of no crystallization during the freeze drying process and that the drug is present as an amorphous solid or as low crystalline moieties in the formulations.

The dissolution profiles of the nanoformulations at all drug-polymer ratios are much higher than that of the pure drug. This could be attributed to the dispersion of the drug as highly amorphous particles in the matrix of Soluplus® and increased wettability on account of the hydrophilicity of the polymer. The formulation NPAS 3, with the drug to polymer ratio of 1:5 showed maximum dissolution of 95.2% in 5 minutes, though the dissolution profile saturates at 86.6% by the end of 2 hours. By increasing the polymer content in the formulation to 66%, the efficiency achieved was about 85% (142% enhanced efficiency compared to the pure drug).

The dissolution results indicate that Soluplus enhances the dissolution of aceclofenac and also provides physical stability by preventing reversion of drug from crystalline state to amorphous state after lyophilization. The drug release from the nanoparticles was far superior to that of pure aceclofenac as well as the physical mixtures. This can be due to particle size reduction and the loss of crystallinity of the drug as nanoparticles, and also the increased wettability of the drug in the matrix of the amphiphilic polymer. This approach can be further extended for dissolution enhancement of other poorly soluble BCS class II drugs.
9.6 References


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Aceclofenac-Soluplus® Nanocomposites for Increased Bioavailability

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Abstract
Aceclofenac is a new generational Non-Steroidal Anti-Inflammatory Drug (NSAID), and is considered a better alternative to the popular pain-killer diclofenac, as it overcomes some of the adverse gastrointestinal and cardiac side effects associated with the latter. However, the bioavailability of the drug remains limited due to low aqueous solubility (0.058 µg/mL) and poor dissolution characteristics. Hence, improving its dissolution characteristics is of prime significance in order to establish its optimal therapeutic efficacy. In an effort to tackle this issue, we report the use of novel Soluplus®-based nanocomposites, prepared from emulsion templates, as effective drug loading agent for aceclofenac. Nanoemulsion templates were prepared by high-shear homogenization using a probe sonicator. The emulsions were subsequently lyophilized to obtain free flowing powders. The amorphization of the drug with increasing polymer content was clearly observed from powder X-ray diffractogram, while the drug-polymer interaction was explored by FTIR spectroscopy. The phase purity and homogeneity of the formulation was characterized using Differential Scanning Calorimetry. The dissolution profiles of the formulations were established by an USP paddle apparatus. Phase solubility study was conducted to evaluate the effect of polymer concentration on aqueous solubility of aceclofenac. The values of Gibbs-free energy (ΔG°r) associated with the aqueous solubility of aceclofenac in the presence of Soluplus was used to optimize the polymer content. The in vitro dissolution rates of aceclofenac from the nanoparticles were significantly higher compared to the pure drug. Thus, Soluplus nanoparticles provide promising formulations for the improvement of the dissolution profiles and thus, the bioavailability, of aceclofenac.

Keywords
Aceclofenac, Soluplus, Nanocomposites, Dissolution, Emulsion