# Solubility Enhancement of Poorly Water Soluble Drug Aceclofenac

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## Abstract

Solid dispersion was aim for increasing solubility and bioavailability of poorly aqueous soluble drug aceclofenac (ACE). Solid dispersion of drug aceclofenac (NSAID) was prepared by using different polymers i.e. Polaxomer 188, PVP k30, PEG 6000, in different ratios 1:1, 1:2, 1:3, by different methods of solid dispersion preparation i.e. Physical method, solvent evaporation method, melt method.

The prepared formulations was characterised by Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM), X-ray diffraction (XRD), In vitro dissolution studies, drug content estimation, saturation solubility. It was concluded that there is change in the crystalline form of drug into amorphous state during formation of solid dispersion.

Polaxomer 188 in ratio 1:3 through melt method, it shows maximum drug release which is 99.04% in 40 minutes. It was concluded that solid dispersion formation of aceclofenac drug by using polaxomer 188 is promising approach in enhancement of its absorption rate increase bioavailability and minimising its side effects.

**Keywords:** Non Steroidal Anti Inflammatory Drugs, Solid dispersion, Aceclofenac, Polaxomer 188

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## Introduction

Solubility is the major problem for various drugs result in poor bioavailability efficacy of drug response is mainly dependent on dissolution and bioavailability. Solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate, absorption and consequently the bioavailability of poorly water soluble drugs (Sekiguchi and Obi, 1961)[2]. In 1972, Monkhouse and Web suggested a new approach of increasing the d Solid dispersion term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Solid dispersions may also be called **solid-state dispersions**, as first used by Mayersohn and Gibaldi (1966).[12]

Aceclofenac, a phenylacetic acid derivative (2-{(2,6-dichlorophenyl)amino} Phenylacetooxyacetic acid), is a novel NSAID indicated for the symptomatic treatment of pain and inflammation. Maximum recommended dose is 200 mg daily: Aceclofenac is freely soluble in ethanol, methanol, acecofenac is insoluble in water. The solubility of aceclofenac in double distilled water found 3.8µg/ml. Short coming of using acelclofenac as conventional dosage forms

1. Because of its low aqueous solubility bioavailability is highly variable and its first pass metabolism.
2. The majority of side effects are of gastrointestinal system (dyspepsia, abdominal pain, nausea and diarrhoea) General: Headache, fatigue, face oedema, allergic reaction, weight increase, haemorrhagic diarrhoea, hepatitis, stomatitis.

Therefore to improve solubility and reduce side effects solid dispersion prepared using different polymer in different ratios by various methods to prepare solid dispersion were developed.

## Materials and Methods

Drug aceclofenac provided as a gift sample from Glenmark Nasik, Polaxomer 188 from BASF as gift sample, PVP K-30, PEG 6000 Purchased from CDH, all others chemicals were of analytical graded and used as received.

**Preparation of Solid Dispersion:**

Solid dispersion are prepared by the following method:

a. Physical Mixture Method
b. Solvent Evaporation Method
c. Melt Method (Melt Technique)

A. **Physical Mixture Method**: In this method drug and water soluble polymer was mixed gently in mortar pestle and then mixture passed through 60 mesh sieve for homogenous particle size, finally collected and stored in vial.

B. **Solvent Evaporation Method:** In solvent evaporation, the polymer(s) and the drug was dissolved in a suitable organic solvent (ethanol is used as common solvent) and then solvent was evaporated at an elevated temperature. Thermal decomposition of drug or polymer was prevented because of the low temperature required for the evaporation of organic solvent.

C. **Melt Method**: In Melt or Fusion Method of preparation, the polymer was heated to a temperature just above melting point and then drug was incorporated into matrix. The mixture was then cooled with constant stirring to disperse the drug throughout the matrix homogenously. The solidified masses of drug-polyethylene glycol polymer system was often found to require storage of one or more days in a desiccators at ambient temperature for hardening and case of powdering. The final mass is then crushed, pulverized and sieved.

**Saturation Solubility**

This was carried out by the taking 10ml of distilled water in each vial. To that excess amount of drug and solid dispersion were added. Then vials kept on shaker for 24 hours. Then the resulting solution was filtered, appropriate dilution were made and absorbance was measured at 274.5nm by using spectrophotometer.

**Characterisation of Solid Dispersion**

***Differential Scanning Calorimetry (DSC) Study***

Differential scanning calorimetry (DSC) measurements were carried out using Mettler ToLedo star system, Japan equipped with liquid nitrogen sub ambient accessory. Calibration was carried out using indium and Zinc as reference materials. Samples were seaded in aluminum pans and lids. DSC thermo grams were recorded at heating rate of 10°C/min. From 40-200°C temperature.

1. Approximately 5 mg crystalline aceclofenac was heated from 40-200°C with heating rate of 10°C/Min. (using nitrogen gas as effluent gas (80.0 ml./min). The determination of transition temperature and energy were done by computerized procedure.
2. Approximately 3 mg polaxomer 188, PEG 6000, PVP k-30 was heated from 40-200 with heating rate 10°C/min.
3. Approximately 9 mg of solid dispersion was heated from 40–200°C with heating rate 10°C/min.

***X-Ray Diffraction Study (XRD)***

The Crystalinity of plain drug (aceclofenac), polaxomer188, PEG 6000, PVP k-30 and solid dispersion was analyzed by using (x-ray generator and Goniometry Rigaku japan). XRD technique was carried out using X-ray diffractometer and Cu kα radiation (α-0.15418) Parallel beam optics was used with 1 mm entrance slit. The diffraction pattern was measured with voltage 30 Kv and current 100 mA in area of 10 <20 < 90 in continuous scan mode of 3θ/min (scan speed). λ = 1.54 A° was used and steps 0.02 were used for diffraction.

***Scanning Electron Microscopy (SEM)***

The surface of aceclofenac particles and formulations was studied by Scanning Electron Microscopy. The sample for SEM were prepared by lightly sprinkling. The powder on double adhesive tap stuck to aluminum stab. The tubes were then coated with gold to thickness of about 300Aº under an argon atmosphere using a gold sputter module in high vacuum evaporate. The coated sample were then randomly scanned using SEM (SEM; JSM-6100).

***Drug Content Estimation***

The percentage of drug content in solid dispersion was estimated by dissolving solid dispersion equivalent to 100 mg of aceclofenac in 10ml of ethanol. This solution was further diluted with 7.8 phosphate buffer and the absorbance was measured at 274.5nm.

***In vitro dissolution studies of solid dispersion***

The dissolution rate of plain drug and solid dispersions was determined using Tablet Dissolution Rate Test Apparatus Type-II, (paddle) 900 ml of phosphate buffer 7.8 was used as dissolution medium maintained at 37 ± 0.5ºC and 100 rpm.

Prepared solid dispersion equivalent to 100mg of aceclofenac was weighed and filled in a capsule of suitable size. One capsule was placed in the flask of the assembly and the paddle was immersed into the dissolution fluid to the specified depth, the fluid was stirred by rotating the paddle at 100 rpm. 5ml of samples were withdrawn through filter (0.45μm) at different time intervals and replaced with equivalent amount of fresh solution. Further dilution made by taken 1ml from this and diluted till 10 ml with phosphate buffer 7.8, Absorbance's of each sample was recorded at 274.5nm using spectrophotometer.

## Result and discussion

The saturation solubility was highest in case of Aceclofenac**:** Polaxomer188 solid dispersion prepared by solvent evaporation method and melt method.

Increase in wt Fraction of carrier results in increase in saturation solubility in all solid dispersions. The highest solubility enhancement was observed in 1:3, drug: polaxomer 188 solid dispersions prepared by solvent evaporation and melt method ie. 149.5 μg\ml and 143.25 μg\ml respectively.

| S. No | Solid dispersion (ratio) | Saturation solubility (µg/ml) (±S.D) |
|---|---|---|
| | Aceclofenac drug | 11.5 ±0.42 |
| 1 | Aceclofenac: pol 188 1:1 | 66.87 ±0.42 |
| 2 | Aceclofenac: pol 188 1:2 | 103.78 ±0.36 |
| 3 | Aceclofenac: pol 188 1:3 | 149.5 ±0.92 |
| 4 | Aceclofenac: PEG6000 1:1 | 49.56 ±0.12 |
| 5 | Aceclofenac: PEG6000 1:2 | 78.22 ±0.74 |
| 6 | Aceclofenac**:** PEG6000 1:3 | 106.27 ±0.46 |
| 7 | Aceclofenac: PVP k-30 1:1 | 49.25 ±0.78 |
| 8 | Aceclofenac: PVP k-30 1:2 | 86.25 ± 0.98 |
| 9 | Aceclofenac: PVP k-30 1:3 | 112.8 ±0.39 |

**Saturation solubility of drug and its solid dispersions prepared with different polymers by solvent evaporation methods**

| S. No | Solid dispersion (ratio) | Saturation solubility (µg/ml) (±S.D) |
|---|---|---|
| | Aceclofenac drug | 11.5 ±0.42 |
| 1 | Aceclofenac: pol 188 1:1 | 58.86 ±0.38 |
| 2 | Aceclofenac: pol 188 1:2 | 86.2 ±0.46 |
| 3 | Aceclofenac: pol 188 1:3 | 143.25 ±0.59 |
| 4 | Aceclofenac: PEG6000 1:1 | 42.13 ±0.78 |
| 5 | Aceclofenac: PEG6000 1:2 | 69.27 ±0.39 |
| 6 | Aceclofenac: PEG6000 1:3 | 99.25 ±0.42 |

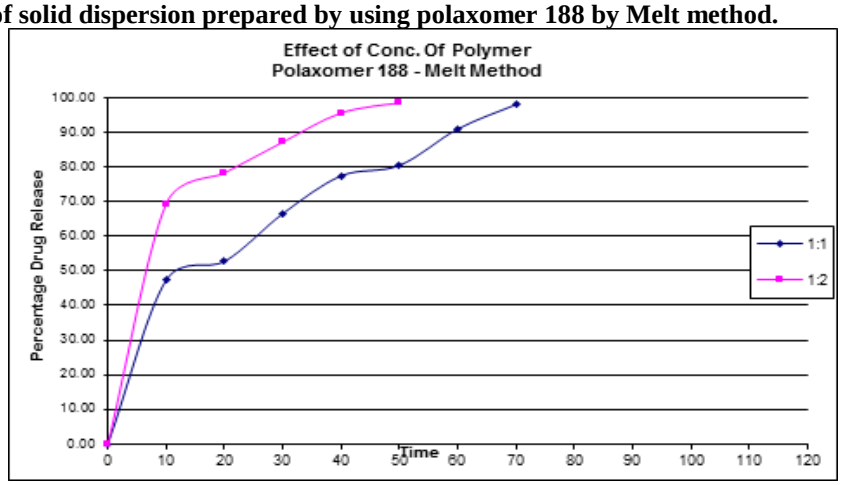
**Saturation solubility of drug and its solid dispersions prepared by different polymers by melt method**.

Enhancement solubility was observed in following order:-
Polaxomer 188>PVP K-30>PEG6000.

The solid dispersions of Aceclofenac: Polaxomer 188 in the ratio 1:3 prepared by melt method showed faster drug release i.e. 99.04% within 40 mins. Solid dispersion of above said ratio showed complete release in 50 and 60 mins. Respectively when prepared by solvent evaporation and physical mixture method.

| Time (Min) | Pure Drug | Cumulative percent drug release | | |
|---|---|---|---|---|
| | | 1:1 | 1:2 | 1:3 |
| 10 | 10.03 ±0.24 | 47.28 ±1.14 | 69.35 ±1.12 | 72.14 ±1.8 |
| 20 | 16.89 ±0.93 | 52.7 ±1.31 | 78.25 ±1.87 | 84.12 ±0.32 |
| 30 | 18.23 ±0.37 | 66.53 ±1.19 | 87.18 ±0.59 | 92.06 ±0.84 |
| 40 | 21.56 ±1.47 | 77.42 ±1.93 | 95.60 ±2.25 | 99.04 ±0.79 |
| 50 | 28.27 ±3.7 | 80.45 ±1.37 | 98.50 ±2.4 | |
| 60 | 34.22 ±0.5 | 90.99 ±3.92 | | |
| 70 | 38.05 ±0.41 | 98.06 ±3.68 | | |
| 80 | 45.7 ±1.42 | | | |
| 90 | 49.8 ±2.04 | | | |
| 100 | 53.2 ±1.89 | | | |
| 110 | 57.84 ±1.97 | | | |
| 120 | 60.2 ±1.8 | | | |
| $T_{50}$ min | 90.58 min | 15.01 min | <10 min | <10 min |
| $T_{90}$ min | >120 min | 59.06 min | 38.24 min | 27.40 min |

**Dissolution data of solid dispersion prepared by using polaxomer 188 by Melt method.**




**Effect of concentration of polymer on solid dispersion.**

In all the cases examine an increase the weight fraction of a polymer resulted in an improvement. In the rate and extent of drug dissolution.

The possible reason for this trend include facilitation of aceclofenac dissolution by dissolved carrier and a decreased in the particle size of the drug in the carrier, with an increase in the carrier concentration absence of the apparent crystillinity of drug in dispersion.

Effect of weight fraction of a polymer on dissolution of aceclofenac from solid dispersion.

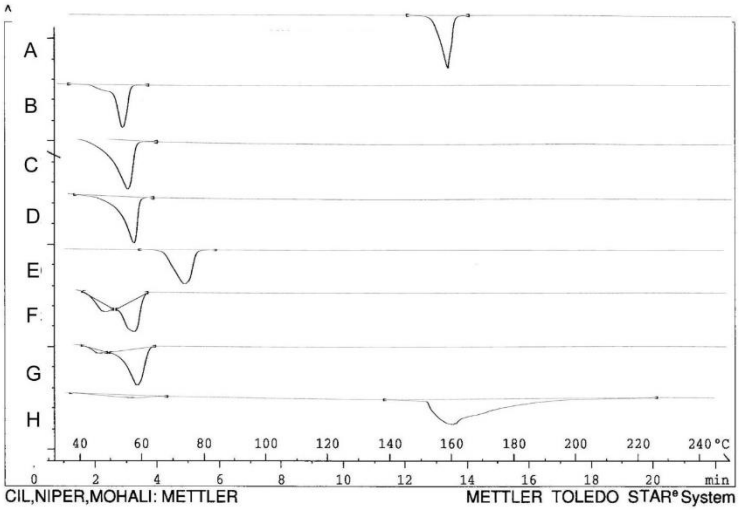
The enhancement in the dissolution rate was found in following order:

1:3>1:2>1:1

In case of Polyethylene glycols Ajeet.s Narang and anand K.Srivastava[49] reported that the improvement in the dissolution was greater with increasing the polymer weight fraction in the system. The results of the present investigation are consistent with the finding of above others.

Dissolution rate was improved when aceclofenac dispersed in polaxomer 188 against pure aceclofenac the dissolution release rate was faster amongs the PEG and PVP systems. This improvement in the dissolution rate may be attributed to mixing of drug particles with polaxomer 188, which facilitates wetting and subsequent solubilisation of the drug.

**Differential scanning calorimetric (DSC)**




Where A = Drug, B = Pol 188 1:3, C = Pol 188 (SE) 1:3, D = Pol 188 (Melt) 1:3, E = PEG (Plain) 1:3, F = PEG 6000 (SE) 1:3, G = PEG 6000 (Melt) 1:3, H = PVP (SE) 1:3

Differential scanning calorimetry thermogram of pure drug and different solid dispersions are shown in Fig. 6. The differential scanning calorimetry curve of aceclofenac was typically of crystalline anhydrous substance with sharp melting endotherm at 152°c. Where as pure polaxomer 188 shows melting endotherm at 52˚c.

The melting endotherm of PEG 6000 is observed at about 63.46˚c. The disappearance of the aceclofenac melting endotherm was assumed in all aceclofenac**:** polaxomer and Aceclofenac**:** PEG solid dispersion 1:3. These results suggest that at higher ratio of polaxomer and PEG only one peak of Polaxomer was observed. Also the melting points of both polaxomer and PEG decreased after preparation of solidified melt. This might suggest that enhancement of aceclofenac dissolution was attributed to conversion of aceclofenac to eutectic state. The solid dispersions exhibits no endotherm corresponding to the melting of pure aceclofenac, suggesting that aceclofenac is completely soluble in the liquid phase with varying amount of PEG 6000 and polaxomer upto 30%.

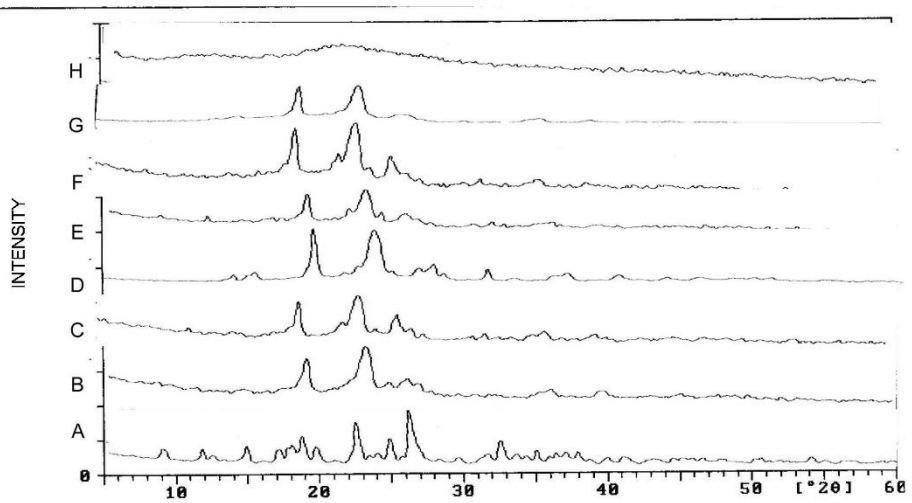
However the melting peaks of PEG 6000 and polaxomer 188 in solid dispersions were observed at slightly lower temperature than that of pure PEG6000 and pure polaxomer 188, indicating the miscibility of drug in PEG 6000 and polaxomer 188.

Absence of an endothermic peak of drug in solid dispersions has also been reported by other research group (Damian[48] et.al 2000; shin[49] et. al. 1987.)

It is speculated that aceclofenac is dissolved in melted PEG & melted polaxomer during the DSC measurement, and only one endothermic peak was observed in each solid dispersion which corresponds to the PEG 6000 or polaxomer 188.

This finding is in agreement with the report of Yamashita et. al[50] (2003) in their DSC study, absence of endothermic peak of tacrolimus in solid dispersions formulations of tacrolimus and PEG 6000 has been reported.

**X-ray Diffraction (XRD)**




Where A = Aceclofenac (Drug), B = PEG (Melt) 1:3, C = PEG (SE) 1:3, D = PEG (Plain) 1:3, E = Pol 188 (Melt) 1:3, F = Pol 188 (SE) 1:3, G = Pol 188 (Plain), H = PVP K30 (SE) 1:3
(Pol 188 = Polaxomer 188, SE = Solvent Evaporation Method)

X-ray diffraction analysis can be done to judge any change in crystallinity of drug when formulated into solid dispersion.

Aceclofenac is a crystalline drug and gives characteristic peak as shown in Fig. 7, X-ray diffraction could be used to study any change in crystallinity of drug or its precipitation in an amorphous form or conversion into eutectics, which could be one of the mechanism for improved dissolution.

Selected samples of solid dispersion i.e. 1:3 aceclofenac: polaxomer188, aceclofenac: PEG6000 and aceclofenac: PVP k-30 prepared by different methods was subjected to X-ray diffraction analysis because of their improved dissolution profile and improved saturation solubility.

X-ray diffraction, Shows that drug, polaxomer188 and PEG 6000 exhibited in crystalline form.

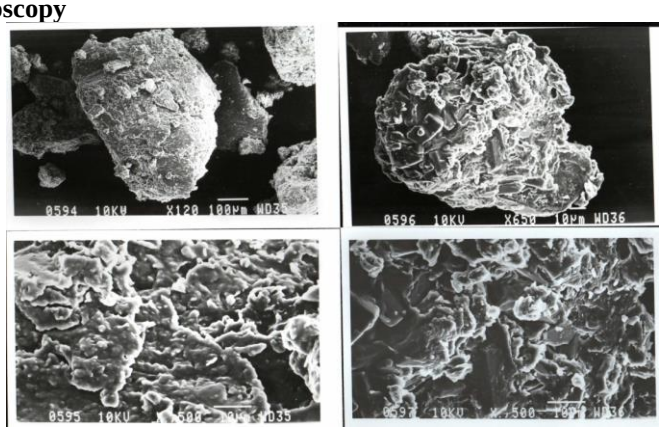
Diffraction peaks of drug, Polaxomer 188 and PEG 6000 were sharp and no amorphous hallow was observed, indicating negligible amorphous content and high crystallinity of drug as well as polaxomers.

The X-ray diffraction pattern of aceclofenac, Polaxomer 188, prepared by solvent evaporation and melt method showed absence of peaks of aceclofenac crystals at 1:3 mixing ratio this indicated that aceclofenac may be converted to an amorphous form or may have formed eutectics. Which is further confirmed by DSC studies.

X-ray diffraction peaks of drug: PEG 6000 solid dispersions also showed no peaks of drug in solid dispersions.

X-ray diffraction peaks or solid dispersions of drug prepared in PVP k-30 showed amorphous nature of solid dispersion is formed since there are no sharp peaks are observed.

**Scanning Electron Microscopy**



A) Polaxomer 188 (SE) [single partial] B) Polaxomer 188 (SE) [structure C) Polaxomer 188 (Melt) [single partial] D) Polaxomer 188 (Melt) [Structure

Scanning Electron Microscopy: Scanning electron microscopy is generally carried out for comparison of surfaces of pure polymer and loaded drug. The aceclofenac crystals appeared under the scanning electron microscopy as irregular shaped crystals with agglomerates having rough surfaces.

Solid dispersions prepared by solvent evaporation and melt method showed the uniform surfaces which proves that all the drug diffuse in the palatinate layers of polymer and possesses good attraction towards each other.

This concludes that aceclofenac molecules were dispersed uniformly in the carrier matrices. The solid dispersion techniques reduce drug aggregates and agglomerates and had an advantage over traditional particle size reduction.

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## Conflicts of interest

The author has no conflicts of interest.

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