Research Article

Dissolution Rate Enhancement of Ganciclovir by Solid Dispersions with Polyethylene Glycol 6000

Rajib Kumar Rautray[1], Bhagaban Biswal[2], Ruchita Kumari Patra[3], Soudamini Mallik[3]
[1]Abbott Health Care Pvt. Limited, Andheri, Mumbai, India.
[2]Om Sai College of Pharmacy and Health Sciences, Berhampur-3, India
[3]Royal College of Pharmacy and Health Sciences, Berhampur-2, India

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ABSTRACT

The aim of this study was to prepare and characterize solid dispersions of ganciclovir by solid dispersion techniques. Enhancement in solubility of the drug was also tried using different techniques like co-solvency, pH alteration and micellization (cloud point technique). The phase solubility study of ganciclovir was conducted in the presence of various concentrations of PEG 6000. Negative values of Gibbs free energy value (ΔG^0_{tr}) indicated spontaneity of ganciclovir solubilization. Solid dispersions of ganciclovir-PEG 6000 were prepared by physical mixing and melting techniques in w/w ratios of 1:1, 1:2 and 1:3 (drug: carrier). Characterization of the solid dispersions was carried out by differential scanning calorimetry (DSC) and Fourier transform infra-red spectroscopy (FTIR). The dissolution profiles of solid dispersions were compared with those of the pure drug. Solid dispersion of ganciclovir with PEG 6000 prepared by melting technique at 1:3 ratio showed greater solubility compared to other formulations. FTIR and DSC studies showed no significant interaction between ganciclovir and the hydrophilic carriers PEG 6000 used.

***Corresponding Author:**
Rajib Kumar Rautray,
Abbott Health Care Pvt. Limited, Andheri, Mumbai, India.
E mail: rajib_royal03@yahoo.co.in

Introduction

Majority of the newly discovered chemical entities and most of the existing drug candidates exhibit poor solubility, presenting a challenge to the successful formulation and marketing of new drugs(1). For drugs with low gastrointestinal solubility and high permeability, drug release is a critical and limiting step in oral drug bioavailability. By improving the drug release profile of such drugs, it is possible to enhance their bioavailability and reduce side effects (2). Numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to obtain more rapid and complete absorption (3).Among the different techniques available for solubility enhancement, preparation of solid dispersions has been the most successful strategy because they can produce a solid dosage form in an amorphous state (4).

Chio and Riegelman defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method" (5). Different types of interactions occurring in solid dispersions include simple eutectic mixtures, solid solutions, glass solutions, glass suspensions, compound or complex formation between drug and carrier, amorphous precipitation of drug in crystalline carrier (6). The improvement of drug dissolution from solid dispersion is attributed to particle size reduction of the drug molecules, reduction of aggregation, solubilization effect of the carrier, and specific molecular interactions between the drug and the polymer (7, 8).

Polyethylene glycols (PEGs) with molecular weights of 1,500- 20,000 are generally used in the preparation of solid dispersions. Advantage of PEGs for formation of solid dispersions is their good solubility in water and also in many organic solvents; their low melting points which are helpful in manufacturing by melting techniques. The solid dispersions of drugs with PEG 6000 may be useful to solve various problems like stability, solubility, dissolution and bioavailability (9).

Ganciclovir which is chemically denoted as 9-[[2-hydroxy-1-(hydroxymethyl) ethoxy] methyl] guanine is an acyclic nucleoside analogue of 2'-deoxyguanosine. The structure is given as Figure 1.

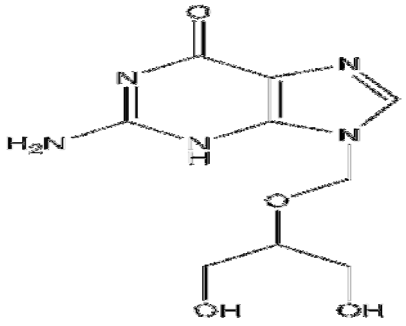

Figure 1**:** Structure of ganciclovir

It is a potent inhibitor of the Herpes virus family including cytomegalovirus and is used to treat complications from AIDS-associated cytomegalovirus infections. Ganciclovir is a white to off-white crystalline powder which is insoluble in water. Being a BCS class II drug, its rate of absorption and extent of bioavailability are controlled by rate of dissolution in the gastrointestinal fluids. Hence, improvement in its solubility and dissolution rate may lead to an enhancement in bioavailability.

In this study, solid dispersions of ganciclovir were prepared by physical mixingand melting techniques. PEG 6000 as hydrophilic carriers were used to enhance dissolution rates and thus bioavailability. Solubility and dissolution rate of the solid dispersions were compared with pure ganciclovir. The physical properties of the prepared solid dispersions were characterized by FTIR and DSC studies.

2. Materials and methods

2.1 Materials

Ganciclovir, PEG 6000 and all the chemicals and reagents used were of analytical grade. Freshly prepared distilled water was used in the work.

2.2 . Solubility studies

2.3. Phase solubility studies

Drug was added in excess (25mg) to 10 mL of double distilled water containing various concentrations (1- 8% w/v) of PEG 6000 in a series of glass vials. These mixtures were shaken on a rotary shaker at 37^{o}Cfor 48 hours in order to achieve equilibrium solubility. These samples were suitably filtered, dilutedand analyzed spectrophotometrically at the wavelength of 265nm using a spectrophotometer (Shimadzu). Phase solubility studies were conducted with and without the addition of hydrophilic carrier. The solubility experiments were performed in triplicate.

Preparation of physical mixture and solid dispersions

Physical mixtures

Required amounts of ganciclovir and the hydrophilic carriers (PEG 6000) were thoroughly mixed in a mortar and pestle in order to obtain a homogenous mixture. The resulting mixture was passed through 40 mesh sieve. The powder was stored in a screw cap vial in a desiccator until use.

Melting technique

Solid dispersions of ganciclovir with PEG 6000 were prepared by this method in the ratios of 1:1, 1:2 and 1:3. Required amounts of ganciclovir and PEG 6000 were melted in a glass container in a heating mantle with rapid stirring using a glass rod till it liquefies. The molten mixture was rapidly cooled on an ice bath. The product was pulverized and shifted

through 40 mesh sieve, stored in a desiccator till use.

In vitroDissolution studies

Dissolution studies of ganciclovir in powder form and from its solid dispersions was studied using Electro lab dissolution test apparatus with a paddle stirrer. These studies were conducted in 900 mL of simulated gastric medium (0.1N HCL of pH~1.2) maintained at a temperature of 37±0.5°C at 50rpm speed. About 20 mg of ganciclovir or its solid dispersion equivalent to 20 mg of ganciclovir was added to the dissolution medium. At predetermined sampling intervals, 5mL of dissolution medium was withdrawn using syringe filter. The withdrawn volume was replenished immediately with the same volume of the blank (37°C) dissolution medium in order to maintain a constant volume throughout the test. The filtered samples were analyzed spectrophotometrically at 265 nm. Dissolution experiments were conducted in triplicate.

Differential Scanning Calorimetry (DSC)

Measurements were performed on a DSC-6100 (Seiko Instruments, Japan) with a thermal analyzer. All accurately weighed samples (about 2 mg of ganciclovir or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of $10^{o}C\ min^{-1}$ from 50 to 300°C. An empty aluminum pan was used as reference.

Fourier Transform Infra-Red spectroscopy (FTIR)

The FTIR spectra were obtained by using an FTIR spectrometer (Shimazdu, Japan). The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (Sample: KBr) ratio respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

Dissolution Data Analysis

Phase solubility Studies

The value of apparent stability constant, Ks, between drug-carrier combinations were computed from the phase solubility profiles, as described below

$$Ks = \frac{slope}{Intercept\ (1-slope)} \quad \text{Equation…. (1)}$$

The Gibbs free energy values provide the information whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative Gibbs free energy values indicate favorable conditions. The Gibbs free energy of transfer (ΔG_{tr}^{0}) of ganciclovir from pure water to the aqueous solution of carriers was calculated using following Equation 1.

ΔG^0_{tr}= -2.303 RT log S_0/S_s Equation..2

Where So/Ss = the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water.

In vitro Dissolution Data

Dissolution studies of the drug in powder form, solid dispersions of drug and carrier can be carried out using dissolution apparatus.

Results and discussion

Solubility studies

According to the solubility studies using different solvents or co solvents the study results are given in Table 1.

Table 1: Solubility in different solvents or co-solvents.

Solvents	Solubility (mg/mL)
Distilled water	0.809
0.1N HCl	0.815
0.1N NaOH	1.008
PEG 400 10 % v/v	0.929
PEG 400 20 % v/v	0.852
Glycerin 10 % v/v	0.827
Glycerin 20 % v/v	0.980
Ethanol 10 % v/v	0.896
Ethanol 20 % v/v	0.929

The pH- solubility profile is shown in Table 2.

Table 2: Solubilitystudy in different pH range.

pH	Solubility in mg/ml
3	0.98
4	0.702
5	1.008
6	0.951
7	0.896
8	0.911

The pH solubility profile figure is given under Figure 2.

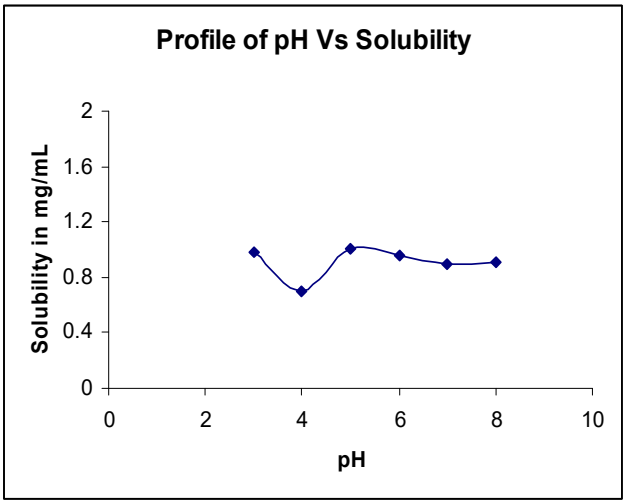

Figure 2: **pH solubility profile**

When the solubility was tested with different concentrations of polysorbate 80 (5%, 10%, 20%, 30%) by the use of cloud point technique, it was noted that the drug showed maximum solubility of 2.177mg/mLin 10% w/v of polysorbate 80, results shown in Table 3.

Table 3: Solubility study with polysorbate-80.

Concentration of Polysorbate 80 (%w/v)	Solubility(mg/mL)
5	1.859
10	2.177
20	2.040
30	2.040

Figure for micellar solubilization using polysorbate 80 is given in Figure 3**.**

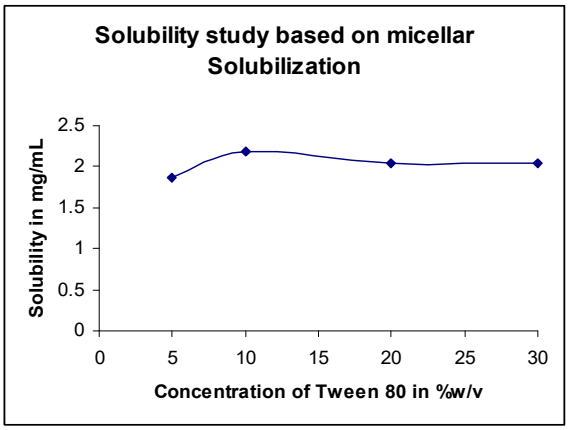

Figure 3: **Micellar solubilization using polysorbate 80**

Phase solubility studies

Phase solubility showed an increase in solubility of ganciclovir with increase in concentration of each of the carriers.An indication of the process of transfer of drugs from pure water to the aqueous solutions of carriers was obtained from the values of Gibbs free energy change.The obtained values of Gibbs free energy provide the information regarding the increased solubility of drug in the presence of carrier. The ΔG_{tr}° values were all negative for the carriers at various concentrations, indicating the spontaneous nature of drug's solubilization, and it decreased with an increase in its concentration, demonstrating that the reaction became more favorable as the concentration of carrier increased.Effect of various concentrations of PEG 6000 on ganciclovir solubility and thermodynamic parameters of the solubility process in different carrier- water solutions at 37±2 $^{\circ}$C is given in Table 4(n=3)

Table 4: Effect of various concentrations of PEG 6000 on ganciclovir solubility and thermodynamic parameters of the solubility process in different carrier-water solutions at 37±2 $^{\circ}$C is given in Table 4(n=3)

Concentration of carrier PEG 6000 in water (%w/v)	Solubility (mg/mL)	Gibb's free energy ΔG^{0}_{tr} (J/mol)
2	1.296	-1210
4	1.671	-1869
6	2.016	-2350
8	2.478	-2884

Dissolution studies

All the formulations were subjected to *invitro* dissolution studies to access various dissolution properties. The

dissolution curves are shown in the Figure 4. According to these results, all the solid dispersions exhibited higher dissolution rate than pure drug. Simple physical mixing of the drug with the hydrophilic polymers increased the solubility of drug to some extent but formulation of solid dispersions by melting technique further improved the dissolution rate of the drug.The pure drug showed up to 59.23% dissolution over a period of 30 min, while its solid dispersion prepared with PEG 6000 by melting technique at 1:3 w/w ratio showed a dissolution up to 81.58 %. This might be due to the change in the state of the drug from crystalline to amorphous, reduction of particle size, increase in wet-ability and prevention of aggregation of the drug particles by carriers.

In vitro dissolution profile of ganciclovir, its physical mixtures and solid dispersions with PEG 6000 in pH 1.2 buffer showing drug release at 10, 20 and 30 minutes interval is presented in Table 5.

Table 5: *In vitro* dissolution profile of ganciclovir, its physical mixtures and solid dispersions with PEG 6000 in pH 1.2.

Sl. No.	Formulation	% Dissolution		
		Q_{10} min	Q_{20} min	Q_{30} min
1	Drug	49.80	52.88	59.23
2	Physical mixture 1:3	54.93	58.82	63.34
3	Melting Mixture 1:1	55.13	60.36	65.38
4	Melting Mixture 1:2	60.26	67.43	74.40
5	Melting Mixture 1:3	68.77	75.74	81.58

In vitro dissolution profile of ganciclovir, its physical mixtures and solid dispersions with PEG 6000 in pH 1.2 buffer showing percent drug release for 60 minutes is shown in Figure 4.

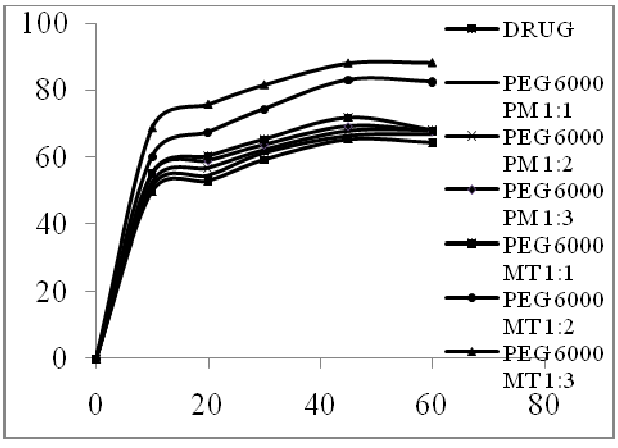

Figure 4: Dissolution profiles of PEG 6000 by melting and physical mixing techniques in 0.1N HCl

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry enables quantitative detection of all the processes where energy is required or produced (i.e., endothermic and exothermic phase transformations). The DSC curve of pure ganciclovir showed a melting endotherm at 246.50°C corresponding to its melting point, indicating its crystalline nature. But the thermogram of PEG 6000 gave a melting endotherm at 57.95 °C. Thermograms of solid dispersions of drug with PEG6000 exhibited a decrease or disappearance of thermal features of drug indicating the drug in the amorphous state. But in the case of ganciclovir-PEG6000 solid dispersion produced by melting technique in 1:1 ratio, the thermal characteristic of the pure drug was present indicating the presence of drug in the crystalline form and shows no interaction between drug and polymer. The DSC thermogram of ganciclovir and its solid dispersions are given in Figure 5-8.

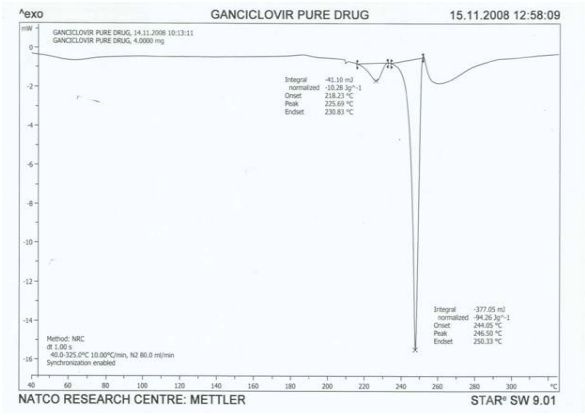

Figure 5: DSC thermogram of ganciclovir

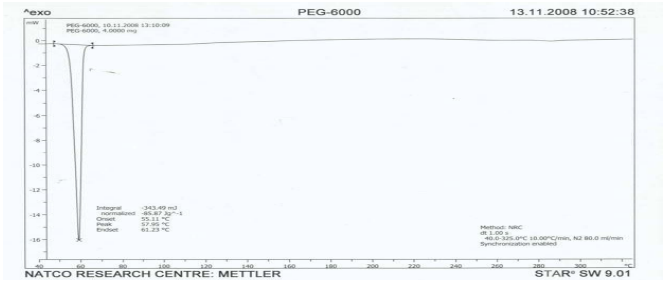

Figure 6: DSC thermogram of PEG 6000

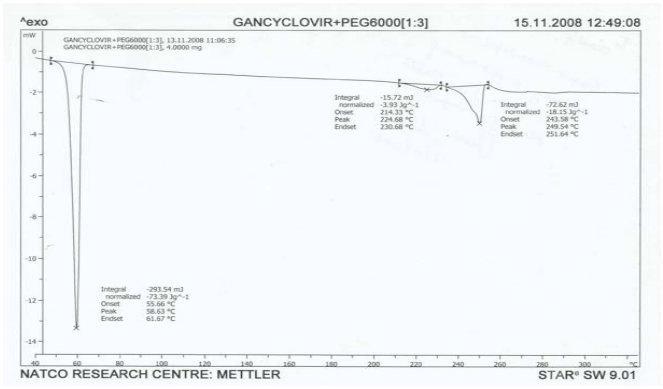

Figure 7: DSC thermogram of ganciclovir with PEG 6000 physical mixture

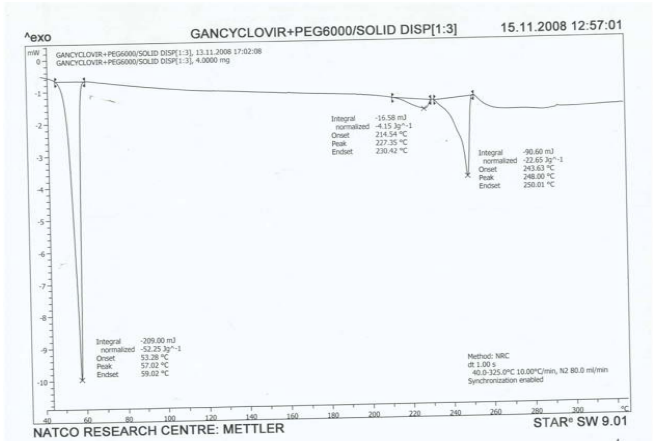

Figure 8: DSC thermogram of ganciclovir with PEG 6000 solid dispersions

Fourier transform infra-red (FTIR) spectroscopy

Comparing the IR spectra of solid dispersions with the standard spectrum of ganciclovir, it was revealed that there were no differences in the positions of the

absorption bands, hence providing evidence for the absence of any significant chemical incompatibility between pure drug with that of carrier in their formulations. The absence of any significant change in the IR spectral pattern of drug–carrier formulation indicated the absence of any interaction between the drug and carrier. The IR spectrum of ganciclovir and its solid dispersions are given in Figure 9-12.

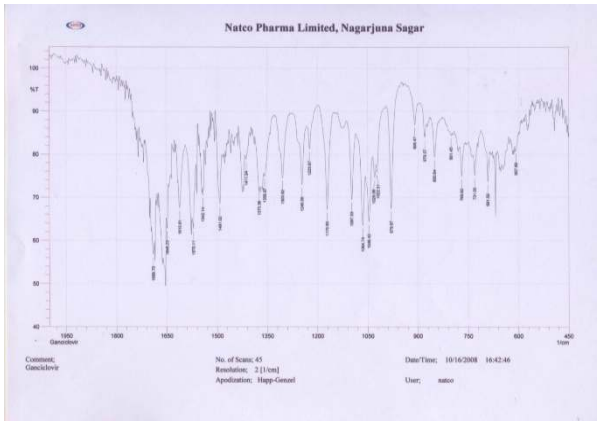

Figure 9: IR spectrum of ganciclovir

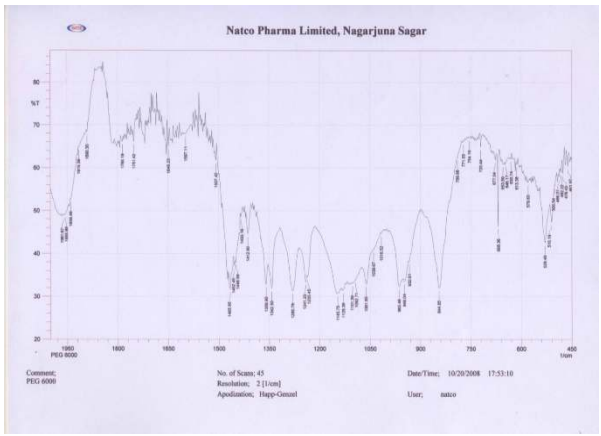

Figure 10: IR spectrum of PEG 6000

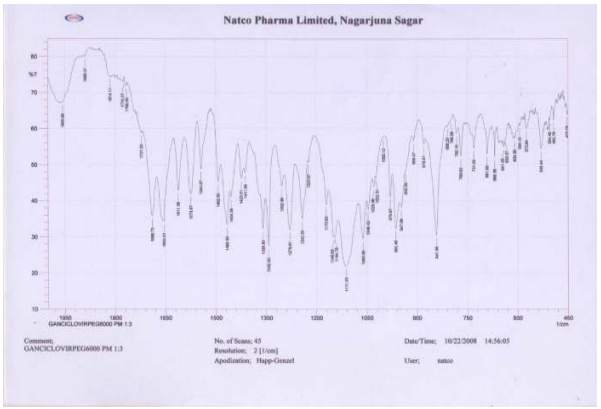

Figure 11: IR spectrum of ganciclovir-PEG 6000 solid dispersions (Physical mixture) 1:3 w/w ratio

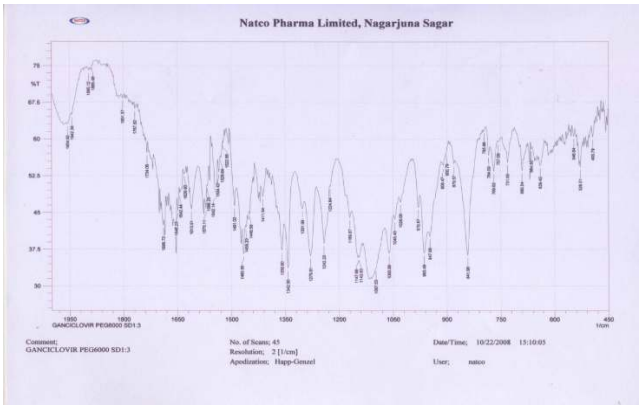

Figure 12: IR spectrum of ganciclovir-PEG 6000 solid dispersions (Melt mixture) 1:3 w/w ratio

Conclusions:

Formation of solid dispersions is the most promising method for improving the solubility and promoting dissolutionrate of poorly soluble drugs.Among various ratios of drug to PEG 6000, ratio at 1:3 w/w showed better enhancement of solubility and this indicated that any further increase inpolymer weight ratio had no significant benefit towards the enhancement of solubility.The solubilization effect of PEG 6000 may be due to reduction of particle

aggregation of the drug, formation of microcrystalline or amorphous drug, increased wet-ability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate. The IR spectrum showed no significant interaction between the drug and carrier. The DSC thermogram revealed that the drug was present in amorphous form in the formulation which was assumed due to lack of peaks.

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