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SOLUBILITY AND DISSOLUTION IMPROVEMENT OF POORLY SOLUBLE DRUG USING SOLID DISPESION TECHNIQUE

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ABSTRACT

A number of modern drugs are poorly soluble in water and aqueous fluids. Their absorption and bioavailability require an improvement in the dissolution rate and efficiency. Among the various methods for improving the dissolution rate and bioavailability, solid dispersion technologies were found to be very successful with a number of drugs. Rofecoxib, a selective COX-2 inhibitor is indicated for the treatment of osteoarthritis and is superior to other NSAIDS due to lower incidence of bleeding and other gastrointestinal toxic effects. However, it suffers from a drawback of having a very low solubility in water (17 µg/ml), a factor affecting the drugs bioavailability. Solid dispersions of Rofecoxib were prepared with polyvinyl pyrrolidone by kneading and with polyethylene glycol 6000 and Tween 80 mixture by fusion technique. The prepared dispersions were characterized by DSC studies. Phase solubility studies between the drug and these carriers revealed the formation of 1:1 complexes. In-vitro release profile of the various dispersions showed enhanced dissolution rate when compared with plain drug. Amongst the various carriers used for solid dispersions the order of enhancement of dissolution rate was found to be PVP K-30 > PEG – Tween 80 (60:40)> PEG – Tween 80 (80:20) for both 1:1 and 1:2 ratio of drug to carrier. All the dispersions in the ratio of 1: 2 exhibited superior dissolution rates as compared to dispersions in the ratio of 1:1. Hence PVP K – 30 appears to be the most promising agent for improving the absorption and bioavailability of Rofecoxib and can be evaluated further for in-vitro in-vivo correlation.

KEYWORDS: Dissolution rate, Rofecoxib, Solid Dispersion, Solubility.

INTRODUCTION

Aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic molecules, especially those belonging to the Biopharmaceutics Classification System (BCS) class II and IV, dissolve slowly, poorly and irregularly and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability.

Many solubilization techniques have been described that either change the nature of the solvent environment (co-solvent systems, emulsions, micellization) or the chemical identity of the dissolved solute (salt formation, complexation, pro-drugs). Alteration of the solid state at the particle or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility. Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits. This solubility benefit can be further enhanced by preparing solid dispersions. Solid dispersions contribute by slowing devitrification, enhancing wettability and modulating the properties of the solvent [1]. Solid dispersions of a number of poorly soluble drugs such as carbamazepine[2], meloxicam[3], furosemide[4], acceclofenac[5], valdecoxib[6], gliclazide[7] etc., exhibited faster dissolution rates and improved bioavailability.

Most of the Non-steroidal anti inflammatory drugs belong to class II category under Biopharmaceutical Classification System (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. They need enhancement in solubility and dissolution rate for improving their oral bioavailability. [8]

Rofecoxib, a selective COX-2 inhibitor is indicated for the treatment of osteoarthritis and is superior to other NSAIDS due to lower incidence of bleeding and other gastrointestinal toxic effects.[9] However, it suffers from a drawback of having a very low solubility in water (17, µg/ml) , a factor affecting drugs bioavailability.[10]

Efforts have been made to enhance the solubility and dissolution rate of rofecoxib by forming inclusion complexes with β-cyclodextrin.[11,12] In the present investigation, an attempt has been made to prepare solid dispersions of Rofecoxib with hydrophilic carriers such as PVP K -30, PEG 6000 – Tween 80 in various ratios with an aim of improving the solubility and dissolution rate.

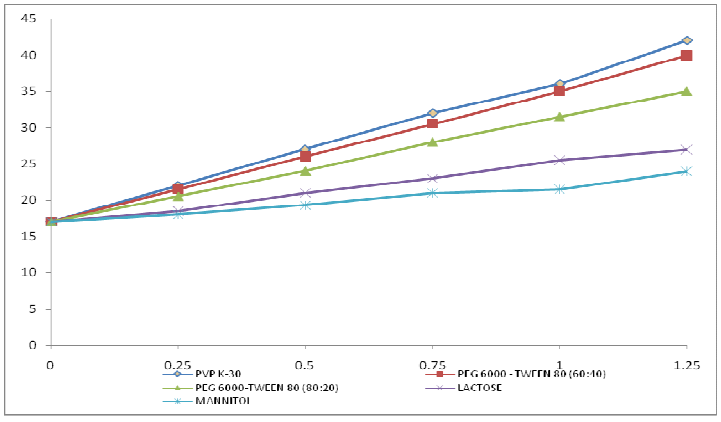
MATERIAL AND METHOD

Rofecoxib was obtained as a gift sample from Mepro Pharmaceuticals, Gujarat. Polyvinyl pyrrolidone (PVP K- 30), Polyethylene glycol 6000 (PEG 6000) and Tween 80 were purchased from Loba Chemie, Mumbai. All other chemicals used were of analytical grade. Differential Scanning Calorimetry studies were carried out on (DSC model 220 C Seiko, Tokyo, Japan), In vitro dissolution studies in dissolution rate test apparatus (Veego, Mumbai) and absorbance measurements were done on UV-1601 (Shimadzu, Japan) spectrophotometer.

Phase Solubility Studies:

Solubility studies were made according to method of Higuchi and Connors. [13] Excess amount of Rofecoxib (10mg) were added to 25 ml of distilled water containing various concentrations (0.25, 0.5, 0.75, 1.0, 1,25 % W/v) of hydrophilic carriers like PVP K – 30, PEG 6000 – Tween 80 (80:20), PEG 6000- Tween 80 (60 :40), lactose and mannitol and shaken for 3 h at room temperature on rotary flask shaker . The solutions were filtered through Whatman No. 1 filter paper and the filtrates were analyzed spectrophotometrically at 268 nm [14] with reference to a suitably constructed standard curve. The results are depicted in Figure I.

Figure I: Phase solubility studies Diagram.



Preparation of Rofecoxib-PVP K-30 solid dispersions:

A mixture of Rofecoxib and PVP K-30 (1:1 and 1:2 by weight) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. [15] The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 60 and stored in a dessicator until further evaluation.

Preparation of Rofecoxib-PEG 6000-Tween 80 solid dispersions:

Solid dispersions of Rofecoxib were prepared with PEG-6000 and Tween 80 mixture by fusion technique [16] taking the ratio of drug to carrier as 1:1 and 1:2 on weight basis. Accurate weighed amount of carrier with their concentration mentioned above was melted in a porcelain dish at 80-85^{0}C and to that calculated amount of Rofecoxib was added with thorough mixing for 1-2 min, followed by instant cooling to obtain dry granules, which were passed through 120 mesh sieve.

Characterization of solid dispersions:

DSC Studies:

The various solid dispersions were characterized by Differential Scanning Calorimetry studies with a DSC model 220 C (Seiko, Tokyo, Japan). The samples were sealed in aluminum pans and the DSC thermo grams were recorded at a heating rate of 5 ° C/ min from 40° C to 3000 ° C.

In Vitro Release Studies:

In Vitro dissolution studies of various solid dispersions were carried out in 900 ml of distilled water containing 0.5 % sodium lauryl sulphate [17] using USP XXII Type II rate test apparatus with a paddle stirrer. Sample equivalent to 50 mg of Rofecoxib, a speed of 100 rpm and a temperature of 37 ° C ± 1 ° C were used in each test. The samples were withdrawn at an interval of 5, 15, 30, 45, 60, 75 and 90 minutes, filtered and analyzed spectrophotometrically at 268 nm. (Figure III).

RESULTS AND DISCUSSIONS

The phase solubility diagram for the Rofecoxib and the hydrophilic carriers is shown in Figure I. The solubilizing ability of the carriers was found to be in the following order:

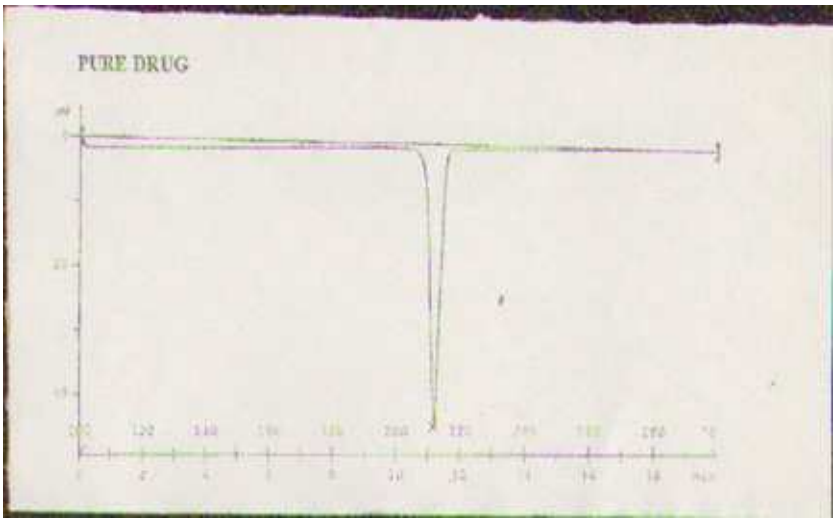
PVP K – 30 > PEG – Tween 80 (60 – 40) > PEG – Tween 80 (80:20) > Lactose > Mannitol.

In all cases, solubility of Rofecoxib increased linearly as a function of carrier concentration and the solubility curve could be classified as Higuchi's type A1 which reflects the stoichiometry of complex as 1:1.However since lactose and mannitol were not found much effective in enhancing the solubility, they were not studied further with respect to preparation of the dispersions.

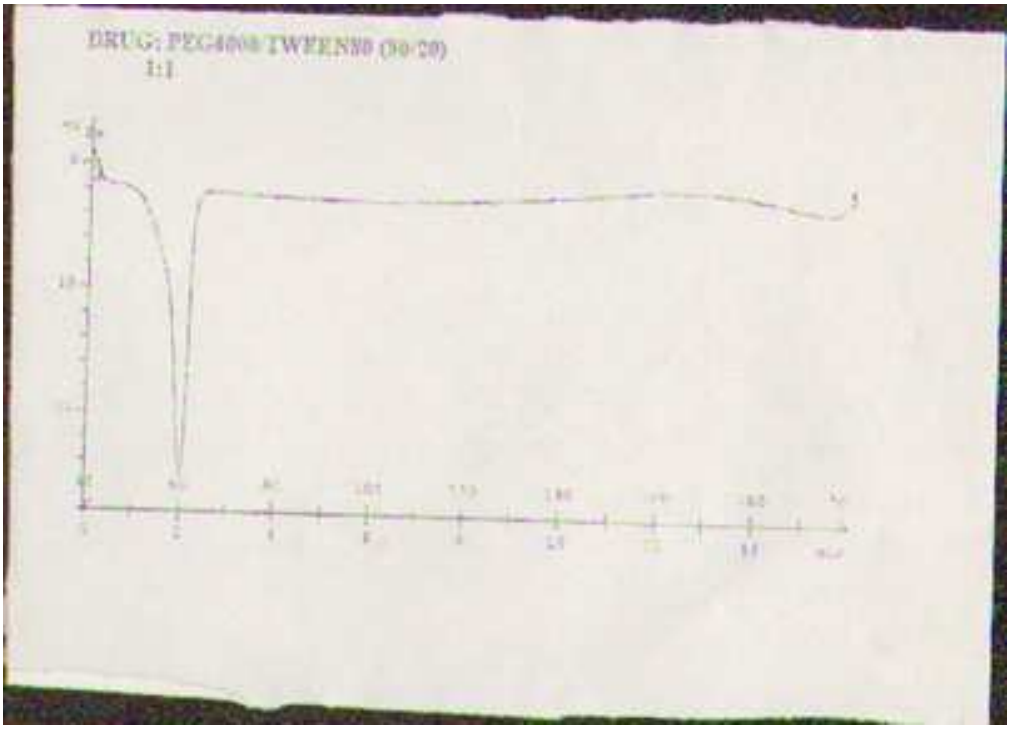
Solid dispersions of Rofecoxib were prepared with PVP K – 30 by kneading and with PEG 6000 – Tween 80 mixture by fusion methods taking the ratio of drug to carrier as 1:1 and 1:2 on weight basis. The DSC thermo gram of Rofecoxib exhibited an endothermic peak at 209°C corresponding to its melting point. The thermograms of the various dispersions were different from the pure drug thereby giving the clear evidence for the formation of dispersions. (Figure II).

Figure II: DSC Thermograms of rofecoxib and solid dispersions.

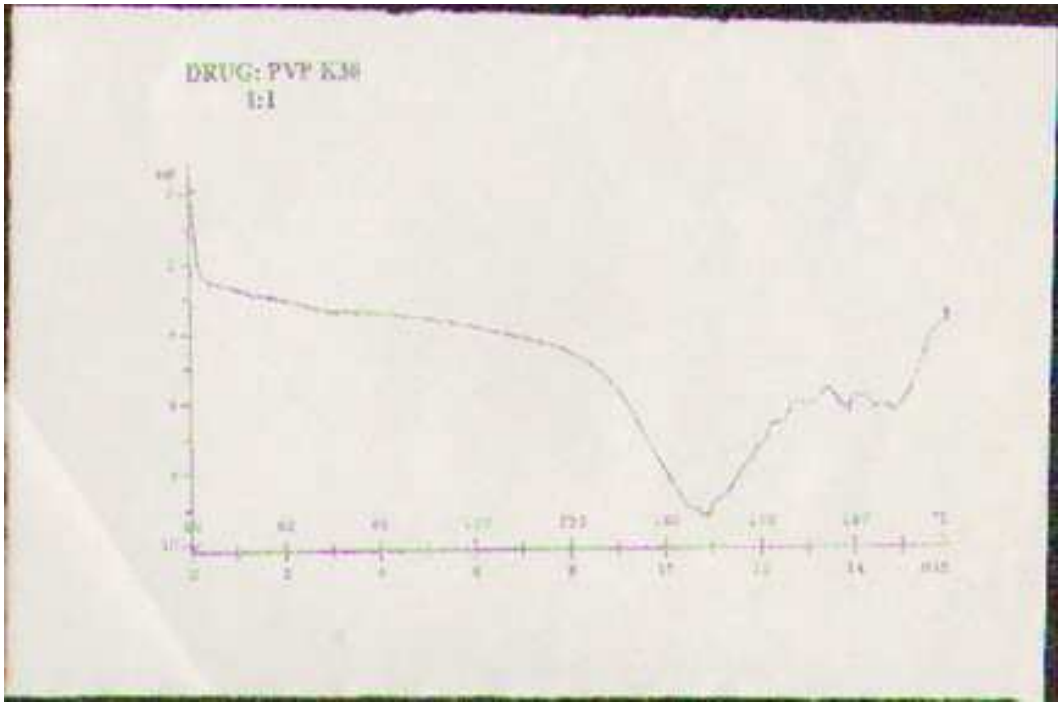
a) DSC of pure drug



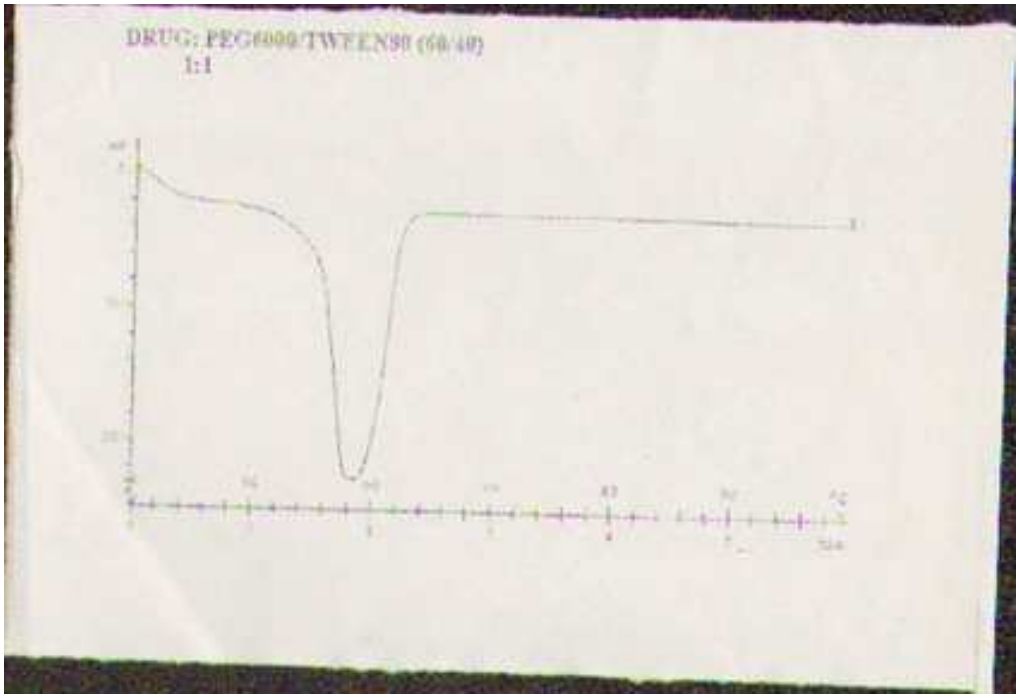
b) DSC of Drug:PEG 6000/Tween (80:20) 1:1



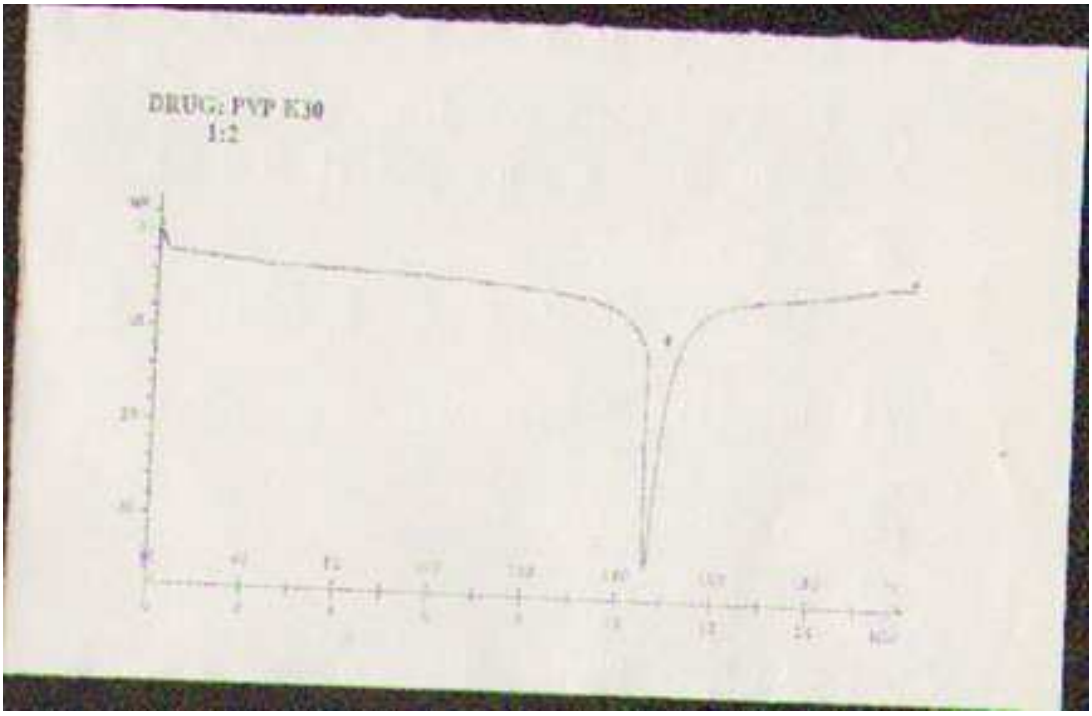
c) DSC of Drug: PVP K-30 1:1



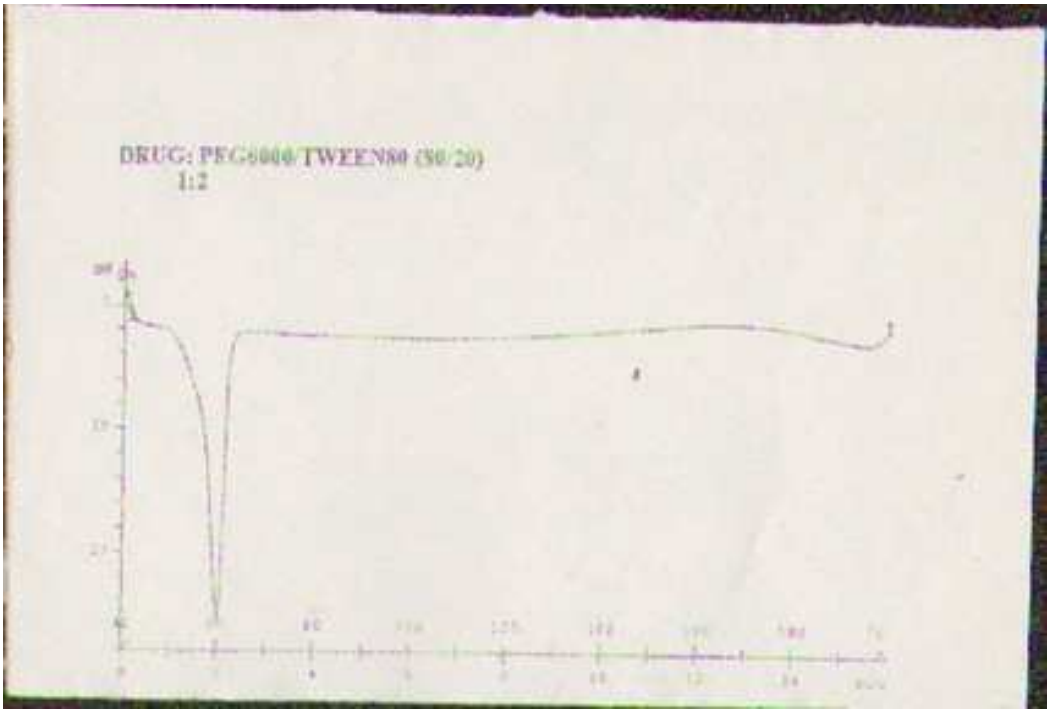
d) DSC of Drug:PEG 6000/Tween 80(60:40) 1:1



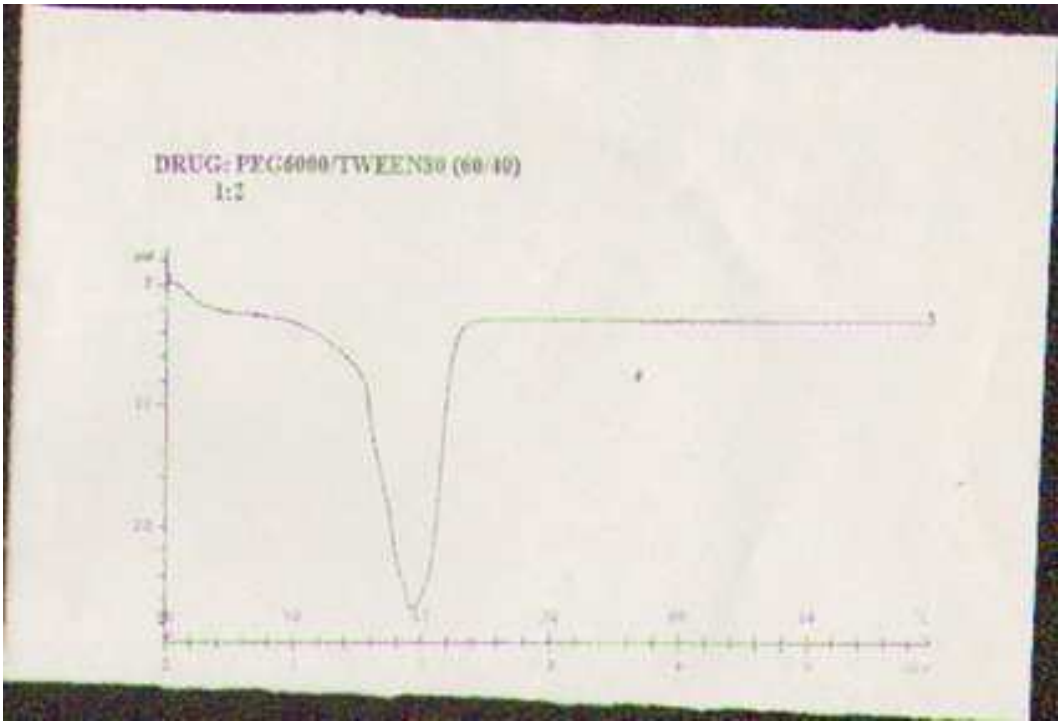
e) DSC of Drug:PVP K-30 1:2



f) DSC of Drug:PEG 6000/Tween 80(80:20) 1:2

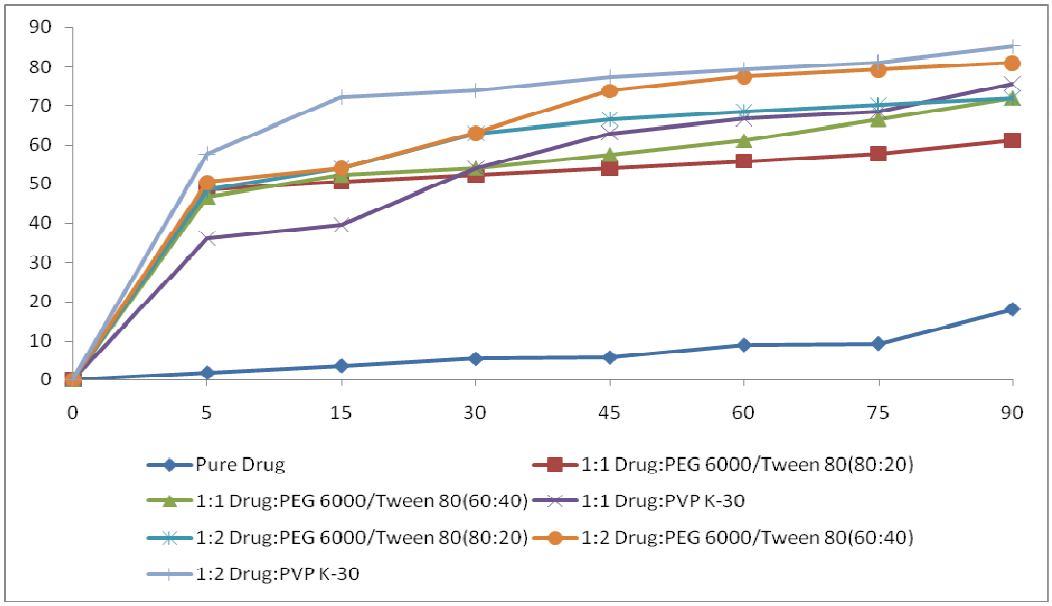


g) DSC of Drug:PEG 6000/Tween 80 (60:40) 1:2



The dissolution studies revealed that all the dispersions showed an increased dissolution rate as compared to plain drug. The results of dissolution studies have been given in figure III. Among the various carriers used for solid dispersions the order of enhancement of dissolution rate was found to be PVP K-30 > PEG – Tween 80 (60:40 0 > PEG – Tween 80 (80:20) for both 1:1 and 1:2 ratio of drug to carrier. All the dispersions in the ratio of 1: 2 exhibited superior dissolution rates compared to dispersions in the ration of 1:1. Thus PVP K – 30 appears to be the most promising agent for improving the absorption and bioavailability of Rofecoxib.

Figure III: In vitro dissolution studies.



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