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Solubilization and Solid-State Characterization of Modafinil Solid Dispersions using PVP K 30

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ABSTRACT

The objective of the present study was to improve the dissolution rate of Modafinil by solid dispersion (SD) systems in PVP-K 30. Drug contents were determined by UV Spectrophotometry at λ_{max} of 259.5 nm. The phase solubility behavior of Modafinil in presence of various concentrations of carriers in distilled water was obtained at 37±2°C. The dissolution of Modafinil increased with increasing amount of carriers. Gibbs free energy (ΔG°_{tr}) values were all negative, indicating the spontaneous nature of Modafinil solubilization. The SDs of Modafinil with the carrier was prepared at 1:1, 1:3 and 1:5 (Modafinil: carrier) ratio by lyophilization method. The FTIR spectroscopic studies and Differential Scanning Calorimetry (DSC) showed the stability of Modafinil and absence of well-defined drug polymer interaction. The dissolution rate increases with increasing the ratio of PVP-K 30.

Keywords: Modafinil, Solid dispersion, PVP-K 30 and Dissolution.

INTRODUCTION

It is one of the major challenges to synthesize any new molecule, which is pharmacologically active for the researchers and pharmaceutical companies. It not only takes a long time but also consumes a lot of money. Out of this research around 40% of lipophilic drug candidates fail to reach market although exhibit potential pharmacodynamic activities [1].

The sparingly water-soluble drugs often show an erratic dissolution profile in gastrointestinal fluids, which consequently results in variable oral bioavailability [2]. From an economical point of view low oral bioavailability results in wasting of a large portion of an oral dose and adds to

the cost of drug therapy especially when the drug is an expensive one [3]. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [4].

The pharmaceutical factors effecting absorption of drugs are solubility, pka, particle size, surface area, shape, plasma protein binding, polymorphism, first pass effect etc. Solubility is the amount of drug that must be available at the site of absorption as aqueous solution which is important for drug absorption. Two main proposed approaches to enhance the solubility of solute are by chemical modification or solid state manipulation and modification in the formulation process. Modification in formulation process involves Co-solvency, Solubilisation, conversion to its salt form, Solid dispersion, Complexation, Inclusion of buffer, Solid solutions and Lyophilization [5].

The dissolution characteristics of the formulation are to be evaluated over the physiologic pH range of 1.2 to 7.5. The Drugs that are practically insoluble in aqueous medium (≤0.01%) are of increasing therapeutic interest, particularly due to the problems association with their bioavailability when administered orally. [6]

The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250mL water over a range of pH from1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 per cent absorption of the administered dose. In contrast, compounds with solubility below 0.1mg/mL face significant solubilisation obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilisation during formulation. [7]

Modafinil [2-[di (phenyl) methyl sulfinyl] acetamide, provigil] is used for the treatment of day time sleepiness in narcolepsy and the other sleep disorders (Fig 1). It is only slightly soluble in water i.e. 0.622 mg/mL at 20 °C.

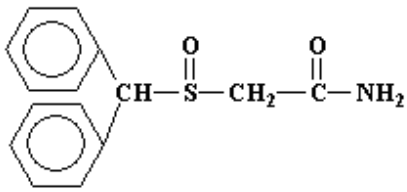

Fig 1: Modafinil

According to McBain, solubilization has been defined as the spontaneous passage of poorly water soluble solute molecule into an aqueous solution of soap or a detergent in which a thermodynamically stable solution is formed [8].

The enhancement of oral bioavailability of such poorly water-soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the

limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction [9].

One technique that can be applied to increase the dissolution rate is the formation of the solid dispersion (SD) with polymeric carriers, such as polyethylene glycol (PEG) derivatives, polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose [10].

MATERIALS AND METHODS

Materials

A gift sample of Modafinil and Poly vinyl pyrrolidone (PVP-K 30) was received from Alembic Ltd., (Baroda, Gujarat, India), PEG 4000 was received from Clariant (Germany). All other chemicals used were of analytical grade and used as such.

Methods

Phase solubility study

Solubility measurements were performed according to the method of Higuchi and Connors (1965). In brief, various (0.25%, 0.5%, .75%, and 1% w/v) aqueous solutions of PVP-K 30 were prepared, and 20 ml of these solutions were taken into separate glass vials. An excess amount of drug was added to these vials. The vials containing drug-hydrophilic polymer carrier mixtures were shaken at $37^0C \pm 0.1^0C$ for 48 h in a water bath shaker (Remi Pvt Ltd, Mumbai). After 48 hr, samples were filtered through a 0.45 µm filter paper and analyzed spectrophotometrically at using UV spectrophotometer (Shimadzu 1601PC, Japan). Solubility studies were performed in triplicate (n=3) [11].

The saturation solubility of drugs in pure water with out taking hydrophilic carrier was also determined. An indication of the process of transfer of Modafinil from pure water to the aqueous solutions of carrier was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG_{tr}^0) of Modafinil from pure water to the aqueous solution of carrier was calculated using following Eq.

$$\Delta G_{tr}^0 = -2.303\ RT \log S_0/S_s$$

Where So/Ss = the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water [12-13].

Preparation of SDs

The SDs of Modafinil with PVP-K 30 (hydrophilic polymer) containing three different weight ratios of drug and polymer (1:1, 1:3 and 1:5) were prepared by lyophilization method.
Lyophilization Formulations with PVP-K 30 were processed using Ultra-Rapid Freezing technology. PVP-K 30 was dissolved in methanol, to this Modafinil was added and dissolved. The resulting organic solvent, hydrophilic carrier and drug ternary system was freeze dried by filling the solutions in glass vials and fitting to the vials in position to the lyophilizer (Yorco, New Delhi). During operation, freeze drier was maintained at -45^0C and at a compressional pressure of 0.5 torr. After complete drying the vials were taken out and the dried products were scrapped out from the vials. The formulations were powdered and packaged in glass vials [14].

The physical mixtures (PMs) having the same weight ratio as SDs were prepared by thoroughly mixing the required amount of drug and carrier for 10 minutes in a mortar. The resulting mixtures were sieved through a 60 mesh sieve. The mixtures were stored in a screw-cap vial at room temperature until further study [15].

***In vitro* dissolution studies**

Dissolution studies of the Modafinil, in powder form, SDs, and PMs were performed by using the U.S. Pharmacopoeia (USP) model digital tablet dissolution test apparatus type-2 (Lab India, Mumbai) at the paddle rotation speed of 50 rpm in 500 mL 0.1N HCl as a dissolution medium at 37±0.5^{o}C. The SDs or PMs equivalent to 90 mg of the Modafinil was weighed using a digital balance (Sartorius, Japan) and added into the dissolution medium. At the specified times (every 15 minutes for 1 hour), 10 mL samples were withdrawn by using syringe filter (0.45 µm) (Sepyrane, Mumbai) and then assayed for the Modafinil, content by measuring the absorbance at 259.5 nm using the UV-Visible spectrophotometer (Shimadzu UV-1700, Pharm Spec). Fresh medium (10 mL), which was maintained at 37^{o}C, was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves [12].

Fourier-Transform Infrared Spectroscopy

The FTIR spectra were obtained by using an FTIR spectrometer-430 (Shimazdu, Japan). The samples (Modafinil or SDs) 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}.

Differential Scanning Calorimetry

The DSC measurements were performed on a DSC- 6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 1 mg of Modafinil or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10^{0}C min^{-1} from 50 to 300^{0}C. An empty aluminum pan was used as reference.

RESULTS AND DISCUSSION

Phase-solubility diagram (Fig 2) showed a linear increase of drug solubility with an increase of the concentration of each examined carrier. Analogous results have been found for these same carriers and several other kinds of drugs and have been attributed to the probable formation of weak soluble complexes. On the other hand, the enhancement of the drug solubility in the aqueous carrier solution could be equally well explained by the cosolvent effect of the carrier. It has been found that hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as Van der Waals forces and hydrogen bonds, can frequently play a role in the drug-carrier interaction [16]. The drug solubility increased linearly with increasing polymer concentration indicative of the A_L type of solubility phase diagram [17]. The ΔG_{tr}^{o} values were all negative for carrier at various concentrations indicating the spontaneous nature of the drug solubilization

(Table 1). The values decreased by increasing carrier concentration, demonstrates that the reaction became more favorable as concentration of carrier increased [12]. No attempt has been made to calculate the stability constant since the exact stoichiometric ratio of drug-polymer is not known.

The phase solubility diagram for Modafinil with PVP-K 30 (0.25-1.0 % w/v) showed that, there was four fold increase in solubility at 1% w/v of carrier.

Table 1: Thermodynamic parameters of the solubility process of Modafinil in PVP-30-water solutions at 37^0C

% (w/v) of carrier in water	Gibb's Free Energy ΔG_{tr}^0 (J/mol)
	PVP-K 30
0.25	-3322
0.5	-3419
0.75	-3436
1.0	-3519

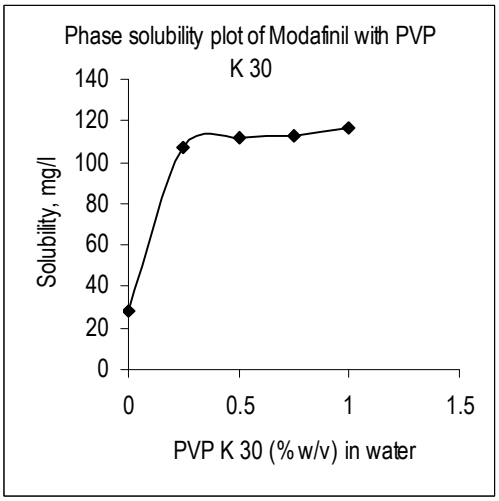

Fig 2: Phase solubility plot of Modafinil with PVP-K 30

In vitro dissolution studies of Modafinil

In vitro Dissolution studies for Modafinil SDs and PMs were carried out by the same procedure as described above by using 0.1N HCl as dissolution medium for 1 hr. Individual tests were conducted in triplicate (n= 3) and the average result was reported. Q 10 min, Q 30 min, and Q 45 min values (percent drug dissolved within 45 minutes) are reported in table 2. The dissolution study for Modafinil showed 21.43 % dissolution over a period of 60 min.

Table 2: Percent drug dissolved within 45 minutes of Modafinil- PVP-K 30 binary systems.

Sample	Drug: Polymer ratio	Modafinil Dissolved (%)		
		$Q_{10\ min}$	$Q_{30\ min}$	$Q_{45\ min}$
Pure Modafinil	-	6.76	16.43	19.76
Modafinil: PVP-K 30 SDs	1:1	25.25	61.08	63.5
	1:3	36.08	69.41	85.11
	1:5	63.58	93.76	94.06
Modafinil: PVP-K 30 PMs	1:1	12.18	31.08	34.41
	1:3	22.08	36.08	39.41
	1:5	23.58	37.75	40.25

Note: *PEG indicates Polyethylene glycol; Mean ± SD is taken with n = 3*

The dissolution rate of SDs and PMs showed enhanced results compared to that of pure drug alone. The solid dispersions showed up to a four fold increase in dissolution rate where as only up to two fold increase in dissolution was observed for physical mixtures in comparison to Modafinil alone. The SDs prepared with PVP-K 30 using lyophilization technique showed dissolution of 92 % at 1: 5 ratio within 20min (Fig 3).

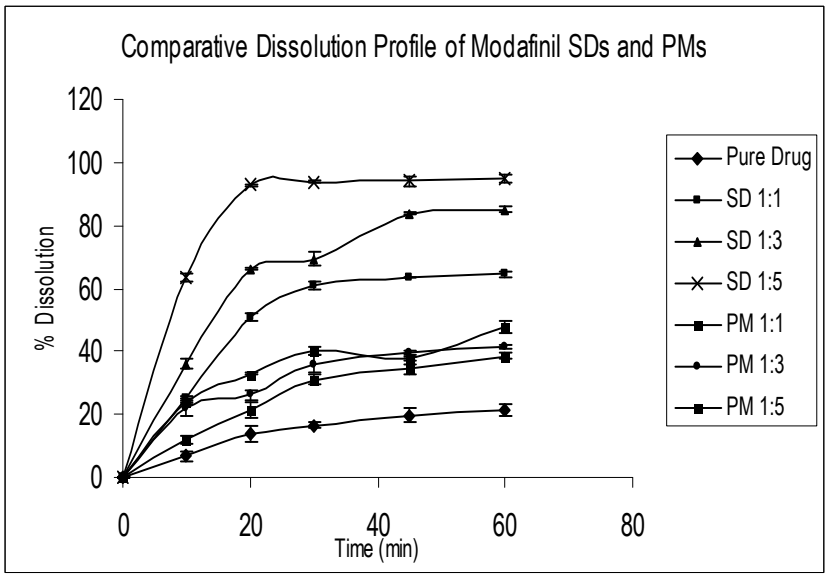

Fig 3: Comparative dissolution profile of Modafinil SDs and PMs

Possible mechanism of increased dissolution rates of SDs have been proposed by Ford [18] and include: reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability, dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the above-mentioned methods. The increased dissolution rate observed in physical mixtures can be attributed to several factors such as a solubilization effect of carriers, improved wettability of the drug and inhibition of particle aggregation.

Fourier Transform Infrared Spectroscopy

Modafinil is having a characteristic peak at 1683 cm^{-1} for carbonyl (CH_2-C=O-NH_2) and stretching of amide functional group (Fig 4). Amide functional group is confirmed by presence of doublet at 3309 cm^{-1} for $–NH_2$ (As, S). Peaks at 2984 cm^{-1} indicates presence of C-H bond. Peaks at 1402 cm^{-1} indicate presence of carbonyl group. Peaks in the range of 900-600 cm^{-1} indicate presence of aromatic rings.

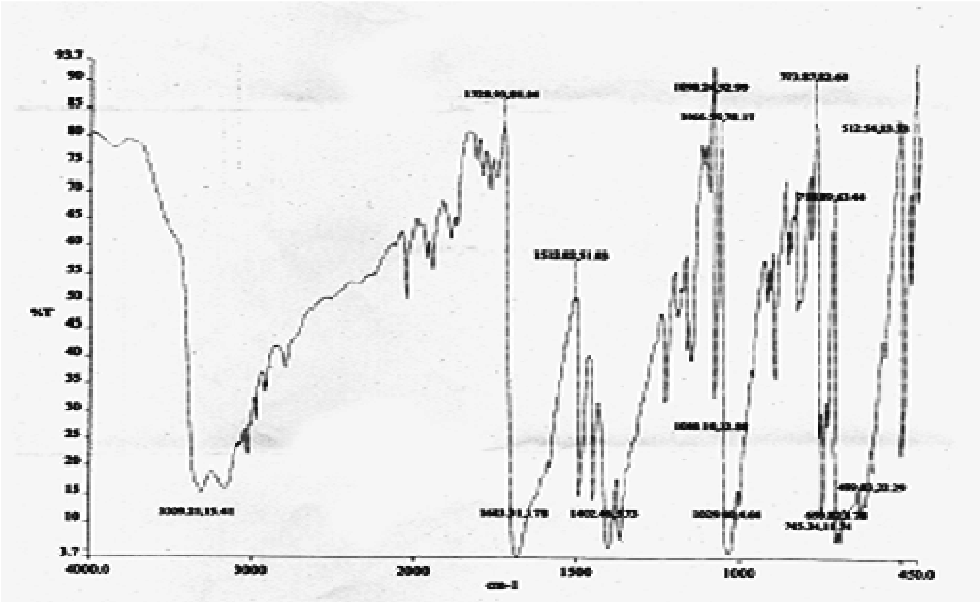

Fig 4: FTIR spectrum of Modafinil

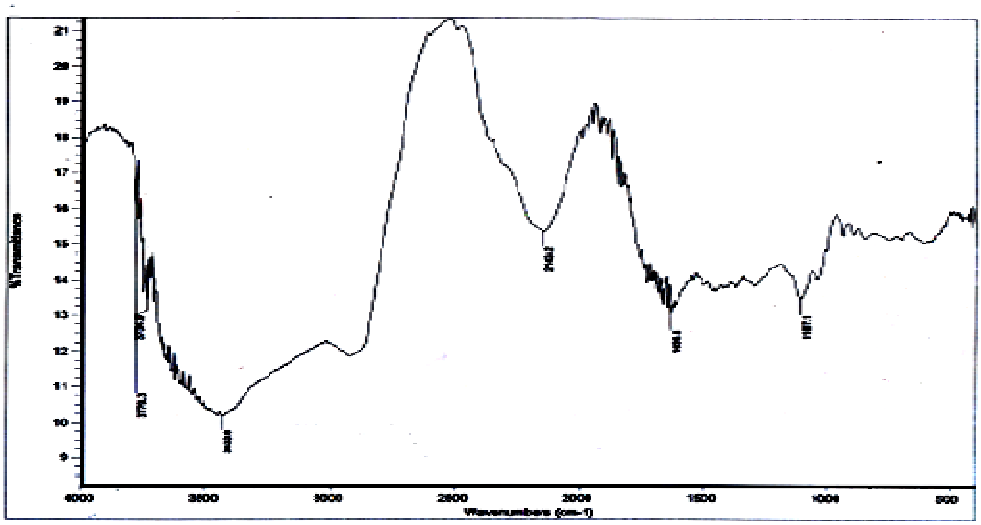

Fig 5: FTIR spectrum of Modafinil SD with PVP (1:5w/w)

The IR spectrum for the SDs of drug with PVP shows a broad peak in the range of 3734-3300 cm^{-1} indicating O-H bond stretching which overlaps the doublet of $–NH_2$ group peak in the pure

drug (Fig 5). The peaks in the range of 900-600 cm^{-1} are due to the aromatic rings present in the drug. There is no significant shift in the characteristic peaks for the drug and carrier indicating less significant interaction.

Differential Scanning Calorimetry

The DSC thermogram of Modafinil is shown in (Fig 6). The presence of a sharp endothermic peak at 174.59^0C indicates the MP of the drug. The onset of melting was observed at 171.25^0C. A broad endothermic peak ranging from 61^0C to 107^0C was observed for SD with PVP, which may be due to the presence of water. No characterstic peak was observed for the drug in the thermogram indicating that the drug was distributed homogeneously in amorphous state with in the SD formulation (Fig 7).

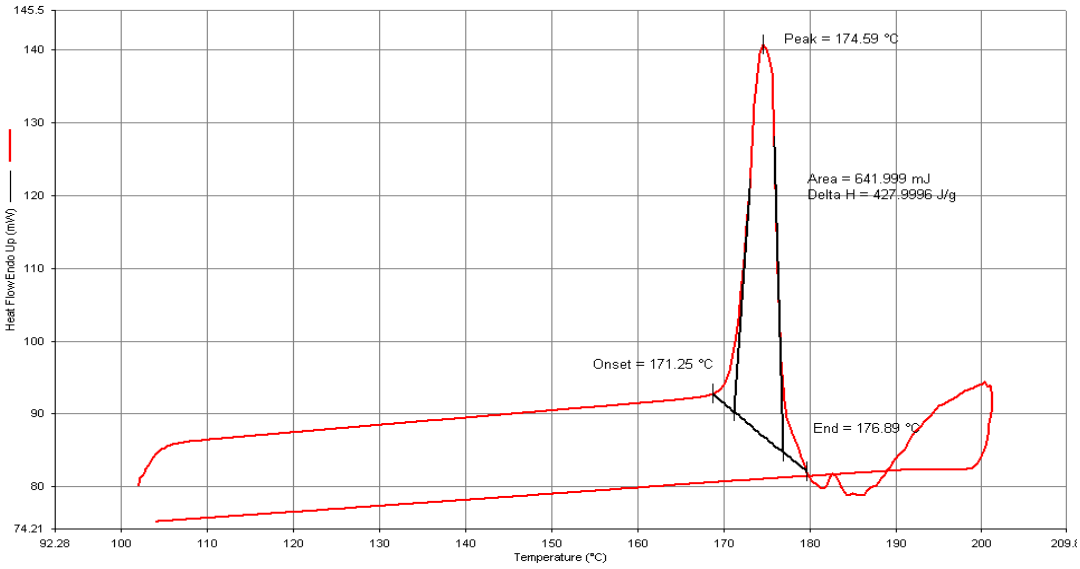

Fig 6: DSC thermogram of Modafinil

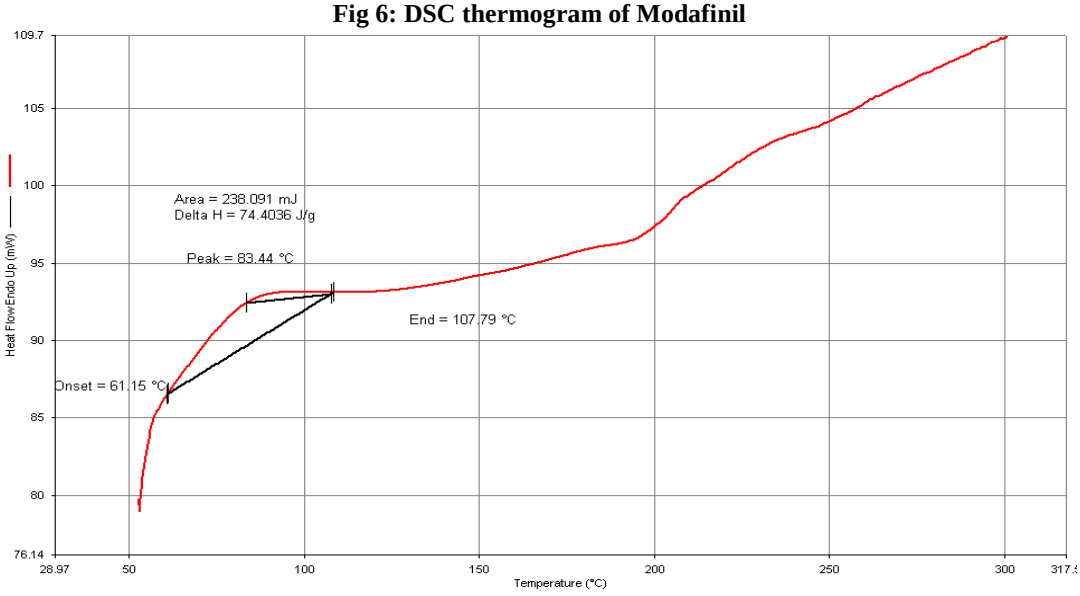

Fig 7: DSC thermogram of Modafinil SD with PVP-K 30 (1:5w/w)

CONCLUSIONS

An attempt was made in the current research work to enhance the solubility of poorly soluble drug Modafinil. Solid dispersions were prepared using hydrophilic carriers such as PEG 4000 and PVP-K 30. It was found that both the examined carriers were effective in improving the solubility of Modafinil but to different degrees. Lyophilized formulations of Modafinil with PVP showed higher rate of dissolution than PEG 4000 at 1: 5 ratio. From FTIR spectroscopy and DSC studies, it was concluded that there were no well defined chemical interactions between the drugs and the carriers studied. Thus, the polymers and the methods described above can be successfully employed for enhancement of solubility of Modafinil.

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