Research Article

Solid dispersions of modafinil in poloxamer 188: Physicochemical characterization and *in vitro* properties

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ABSTRACT

The rationale of the research work was to increase the solubility, hence dissolution rate of a poorly soluble drug preparing its solid dispersions. Solid dispersions of modafinil a BCS class II were prepared and evaluated for its physicochemical characteristics. Saturation solubility of modafinil was conducted using various concentrations of poloxamer 188. The Gibb's free energy (ΔG_{tr}^{0}) values were all negative for carrier at various concentrations, indicating the spontaneous nature of drug's solubilization. The Gibb's free energy (ΔG_{tr}^{0}) values decreased with increased concentrations of carrier, showing that the reaction became more favorable as the carrier concentration increased. Solid dispersions of modafinil were prepared by physical mixing and melting techniques at 1:0.5, 1:1, 1:2 and 1:3 (w/w ratios of drug: carrier). The dissolution profiles of solid dispersions were compared with that of the pure drug. The solid dispersions showed improved dissolution rates than modafinil pure drug. Characterizations of solid dispersions were done by differential scanning calorimetry (DSC), X-Ray diffraction (XRD) studies and Fourier transform infra-red spectroscopy (FTIR).

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INTRODUCTION:

Low solubility of drug candidates creates key challenges in oral drug delivery and their formulation development, as affects the bioavailability. With the onset of high throughput screening in drug discovery and development, the number of poorly soluble drug candidates has increased notably [1]. The solubility and permeability of drug(s) through biological membranes are the main physicochemical parameters that limit the bioavailability of a drug molecule. Various methods are proposed to enhance aqueous solubility of poorly soluble drugs that includes: chemical modifications (e.g., pro drugs or salt derivatives), physical modifications (e.g., solid dispersions, size reduction, loading on porous carriers, co crystals), alteration of solvent compositions (e.g., pH adjustment, use of co solvents, addition of surfactants), and use of carrier systems (e.g., cyclodextrins, micelles, liposomes). Among various techniques, solid dispersions of drugs have been the most successful approach [2, 3].

Solid dispersion is defined by Chio and Riegelman 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" [4] . The reasons for improvement of drug solubility or dissolution from solid dispersion may be attributed to particle size reduction of the drug molecules, reduction of aggregation, wetting effect of the carrier, and specific molecular interactions between the drug and the polymer [5].

Chemically modafinil is 2-[di(phenyl)methyl sulfinyl]acetamide (Figure 1). It is a wakefulness promoting agent used in the treatment of narcolepsy and the other sleep disorders for oral administration. Being a BCS class II drug, its systemic availability are controlled by dissolution rate in the gastrointestinal fluids. Hence, improving solubility may lead to an enhancement in plasma drug concentration[6]. The solid dispersion technique is the successful approach in increasing the solubility, hence dissolution and plasma concentration of poorly soluble drugs. Moreover it is easy and economic[7]. In this study, solid dispersions of modafinil were prepared by physical mixing and melting techniques. Poloxamer 188 as hydrophilic carrier was used to improve dissolution rates and thus plasma drug concentration. Characterization solid dispersions were done by FTIR, XRD and DSC studies. The drug structure is given in Figure 1.

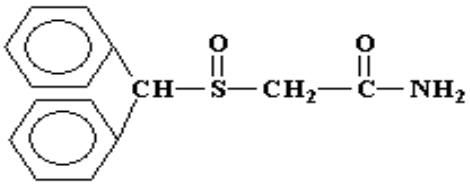

Figure 1. Structure of modafinil

MATERIALS AND METHODS

Materials:

Modafinil was received from Alembic Ltd, Baroda, India as gift sample. The chemicals and reagents used were of analytical grade. Distilled water was prepared freshly and was used in the work.

METHODS

Analytical Method:

Linear plot for estimation of modafinil:

A series of standard solutions of modafinil i.e., 5-40 µg/ ml were prepared from the stock solution of 50 µg/ ml. The drug was made dissolved in 2-3 ml of methanol as co solvent and the volume was adjusted to get various concentration of solutions using 0.1 N HCl. The linear plot was obtained at 258 nm, using UV-Vis spectrophotometer (UV spectrophotometer, Shimadzu 1800).

Equilibrium solubility studies

An excess of drug was added to 20 ml of distilled water containing various concentrations of poloxamer 188 (0.25%, 0.5%, 0.75% and 1% w/v) in a series of glass vials. The vials containing drug-hydrophilic polymer carrier mixtures were shaken at 37 ^{0}C ± 0.1 ^{0}C for 48 h in a water bath shaker (Remi Pvt Ltd, Mumbai) in order to achieve equilibrium solubility. The filtrate was suitably diluted and analyzed using UV spectrophotometer (Shimadzu 1800, Japan) at the corresponding $\lambda_{max.}$ The equilibrium solubility of drug in pure water without the hydrophilic carrier was also determined. The study was done in triplicate (n=3)[8].

The Gibbs free energy of transfer (ΔG_{tr}^0) of modafinil from pure water to the aqueous solution of carriers was calculated using following Equation 1

$\Delta G_{tr}^{0} = -2.303\ RT \log S_0/S_s$ .....Equ 1

Where So/Ss = the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water [9, 10].

Preparation of solid dispersions

By melting or fusion method

The solid dispersions of modafinil with poloxamer 188 at different weight ratios of drug and polymer (1:0.5, 1:1, 1:2 and 1:3) were prepared by melting or fusion method. The prepared solid dispersions were shifted through 40 mesh sieve and stored in a screw-cap vial in a desiccator until further study [11].

By physical mixing

The physical mixtures were prepared by simple physical mixing. The resulting mixture was passed through 40 mesh sieve and stored in a screw cap vial in a desiccator until use.

Table 1: Formulation table for solid dispersions by physical mixing and melting method

Formulation Code	Carrier	Drug: Carrier	Method Employed
F1	Poloxamer 188	1:0.5	Melting method
F2		1:1	-do-
F3		1:2	-do-
F4		1:3	-do-
F5	Poloxamer 188	1:0.5	Physical Mixing
F6		1:1	-do-
F7		1:2	-do-
F8		1:3	-do-

Drug content study (assay) of the solid dispersions:

All the prepared solid dispersions were assayed for the drug content by UV- Vis spectroscopy at 258 nm.

Dissolution rate study

Dissolution study was conducted using dissolution test apparatus type-2 (Lab India Disso 2000) at the paddle rotation speed of 50 rpm in 900 mL of 0.1N HCl, as dissolution medium at 37 ± 0.5 $^{\circ}$C. Solid dispersion equivalent to 200 mg of modafinil was added to the dissolution medium. At predetermined sampling intervals, 5 mL samples were pipette out, filtered and then assayed by measuring the absorbance at 258 nm. The sink condition was maintained by volume replacement with dissolution medium, throughout the test. Studies were conducted in triplicate (n=3). The mean values of cumulative drug release were used while plotting the dissolution profile.

Fourier transform infra-red spectroscopy (FTIR)

Fourier-transform infrared **(**FT-IR) spectra were obtained by using an FT-IR spectrometer (Schimazdu) by potassium bromide (KBr) pellet method. The samples (pure drug or solid dispersions) were previously ground and mixed thoroughly with potassium bromide, at 1:5 (Sample: KBr) ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 minutes in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Measurements were performed on a DSC-6100 (Seiko Instruments, Japan) with a thermal analyzer. Accurately weighed samples (about 2 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 $^{\circ}$C min^{-1} from 50 to 300 $^{\circ}$C. An empty aluminum pan was used as reference.

X-Ray diffraction (XRD) studies

The X- ray powder diffraction studies were obtained using a PW 1710 X- ray diffractometer (Philips, Holland) with copper as anode and graphite monochromatic, operated at a voltage of 35kV, current 20mA. The samples were analyzed in the 2θ angle range of $5^{\circ} - 70^{\circ}$ and the process parameters were set as: scan step size of 0.02° (2θ), scan step time of 0.5 seconds.

RESULTS AND DISCUSSION

Results:

The linear plot for modafinil is given under **Table 2.**

Table 2: Linear plot for modafinil

Concentration (µg/ml)	Absorbance (at 258 nm)
10	0.032
20	0.063
30	0.093
40	0.122
50	0.153
60	0.183
70	0.211

The plot showing the correlation between concentration and absorbance for modafinil is given under Figure 2, showing the regression equation and the value of coefficient of determination.

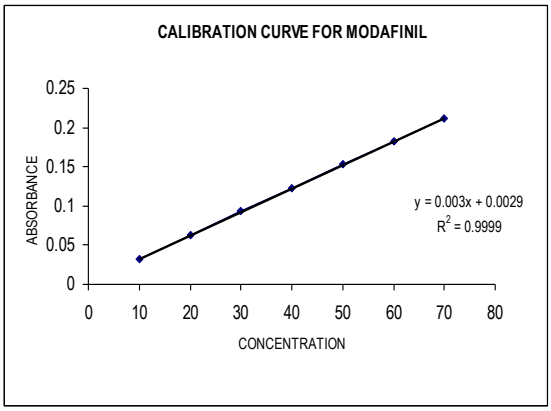

Figure 2: **Linear plot showing the regression equation and the value of coefficient of determination**

Table 3: Equilibrium solubility data of modafinil with poloxamer 188

Poloxamer 188 (%w/v) in water	Gibb's Free Energy ΔG_{tr}^{0} (J/mol)	Solubility (mg/l)
0	-	28.1
0.25	-2711	84.1
0.5	-2734	84.75
0.75	-2746	85.1
1	-2837	88.4

The dissolution profile of modafinil for 60 min is shown under **Table 4.**

Table 4: Dissolution study of modafinil

Time (mins)	% Drug Release
10	66.179
20	62.568
30	64.98
45	64.36
60	72.47

The dissolution studies of modafinil with poloxamer 188 solid dispersions prepared by melt/fusion methods are shown under **Table 5.** Solid dispersions prepared by physical mixing showed better rate of dissolution than the pure drug modafinil but lower than the solid dispersions prepared by melting or fusion method.

Table 5: Dissolution study of modafinil with poloxamer 188 by melting technique at different ratios.

Time (mins)	Percent Drug Release			
	1:0.5	1:1	1:2	1:3
0	0	0	0	0
10	67.98	58.96	61.02	59.6
20	72.33	70.92	72.04	67.76
30	74.57	78.77	79.51	75.26
45	79.26	80.21	83.35	77.26
60	84.58	85.94	88.11	82.93

Discussion:

The absorbance maximum for modafinil was found to be 258 nm. The linear regression equation obtained after regression analysis was used for calculation of drug concentration in further study. The coefficient of determination was found to be more than 0.999.

Drug Content study:

The drug content studies were carried out preparing its 10 and 20 µg/ml solutions. The absorbance values were checked and are compared with the absorbance value of the standard solutions. of 10 and 20 µg/ml. The % drug content varied from 90 - 92 %.

Equilibrium phase solubility studies

Equilibrium phase solubility study showed a linear increase of drug solubility with increase of carrier concentrations. The enhancement of the drug solubility could be well explained by the co solvent effect of the carrier. It has been found that hydrophilic carriers mainly interact with drug molecules by electrostatic bonds, even though other types of forces, such as van der Waals forces and hydrogen bonds, can commonly play a role in the drug-carrier interaction [12]. The acquired values of Gibbs free energy give the information regarding the increased solubility of drug in the presence of carrier.

Dissolution studies

The dissolution curves are shown in the **Figure 3.**

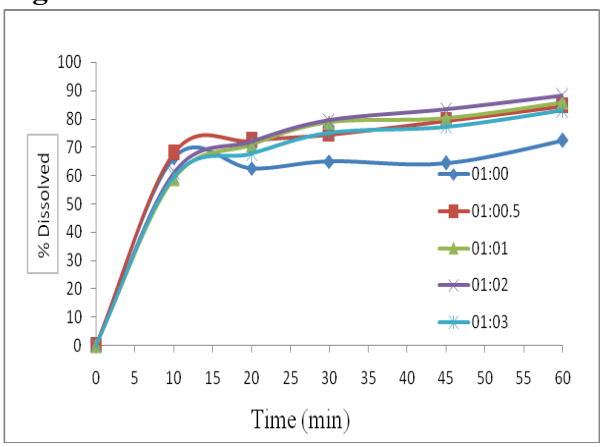

Figure 3: Dissolution study of modafinil with poloxamer 188 (SDs) by melting technique at different ratios.

According to these results, all solid dispersion formulations showed higher rates of dissolution values than the pure drug. The result may be due to amorphization, increased wet-ability and dispersibility and particle size reduction of drug in solid dispersions. Simple physical mixtures of the drug with the hydrophilic polymer increased the solubility of drug to some extent but formulation of solid dispersions by melting technique further improved the solubility and dissolution rate. The pure drug showed nearly 70 % of dissolution over a time of 60 min, but its solid dispersions prepared showed dissolution of more than 80 % over a time of 30 min. Among various ratios of drug to poloxamer 188, ratio at 1:1 w/w showed better improvement of solubility and it is observed increased polymer weight ratio has no significant benefit towards enhancement of solubility of the drug.

Fourier transform infra red (FTIR) spectroscopy

The IR spectra of solid dispersions were compared with the standard spectrum of modafinil. IR spectra of modafinil is having a characteristic peak at 1683 cm^{-1} for carbonyl (CH_2-C=O-NH_2) and stretching of amide functional group. Amide functional group is confirmed by presence of doublet at 3309 cm^{-1} for $–NH_2$ (As, S). Peaks at 2984 cm^{-1} indicates the 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. With poloxamer 188, the appearance of a broad peak in the range of 3822-3100 cm^{-1} indicates hydrogen bonding stretching. Peak at 1685 cm^{-1} is for C=O stretching of amide functional group. The IR spectrum shows no significant change of characteristic peaks for the functional groups, indicating no significant interaction between the drug and carrier used. The IR spectra are given under Figure 4 and 5.

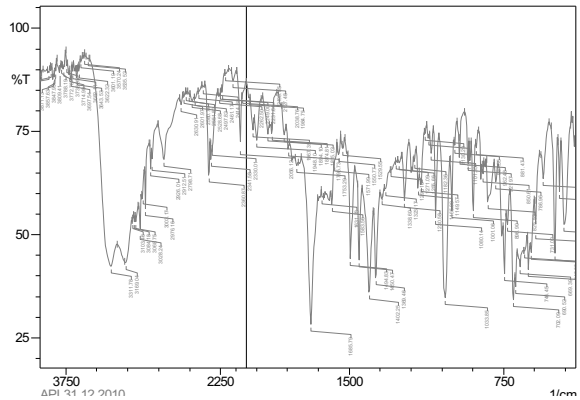

Figure 4: FTIR spectrum of modafinil

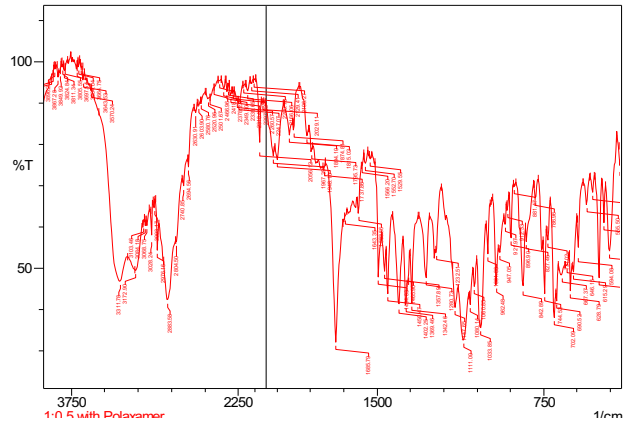

Figure 5: FTIR spectrum of modafinil SD with poloxamer 188 (1:1 w/w)

Differential scanning calorimetry (DSC)

The DSC thermogram of modafinil revealed a sharp endothermic peak at 174.59 °C corresponding to the melting point of the drug. The onset of melting was observed at 171.25 °C. Solid dispersions of drug with poloxamer 188 revealed the drug present in amorphous form in the formulation, assumed due to lack of peaks in the DSC thermogram. The DSC thermograms are given under Figure 6 and 7.

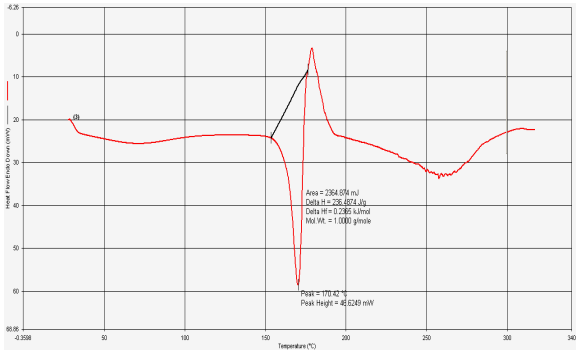

Figure 6: DSC thermogram of modafinil

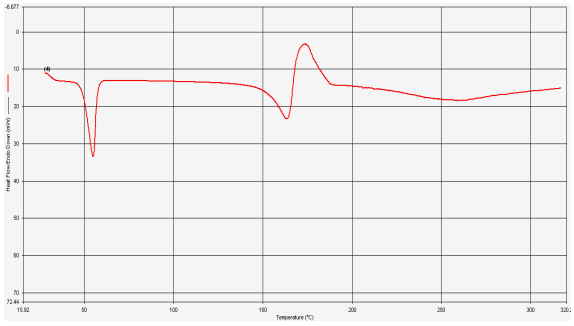

Figure 7: DSC thermogram of modafinil SD with poloxamer 188 (1:1 w/w).

XRD Studies

XRD studies revealed some change in crystal properties of the drug in its solid dispersions. There may be some fractional conversion of crystalline drug to its amorphous form in the solid dispersions. The XRD analysis results are given under Figure 8 and 9.

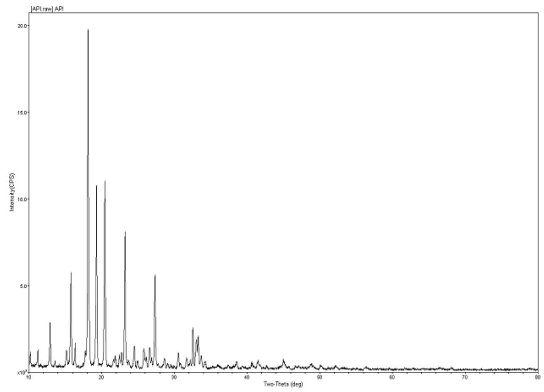

Figure 8: XRD study of modafinil

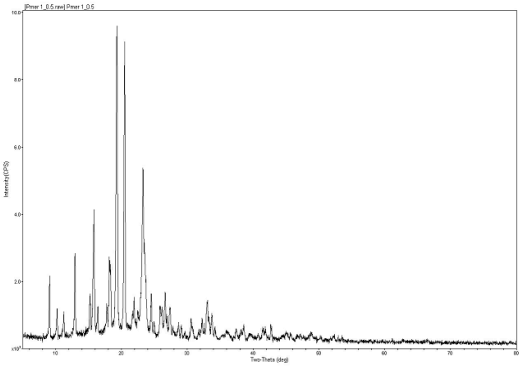

Figure 9: XRD of modafinil SD with poloxamer 188 (1:1 w/w)

CONCLUSIONS

Formation of solid dispersions is the most promising method for improving the solubility and promoting dissolution rate of poorly soluble drugs. Among various ratios of drug to poloxamer 188, ratio at 1:0.5 w/w showed better increase of solubility. Further increase in polymer weight ratio had no significant benefit towards the enhancement of dissolution

rate. The IR spectrum showed no significant interaction between the drug and poloxamer 188. The DSC thermogram revealed that the drug was present in amorphous form in the formulation which was assumed due to lack of peaks. XRD studies indicated the presence of significant proportion of modafinil in crystalline form.

CONFLICT OF INTEREST:

The author(s) herewith declare that there is no conflict of interest for publication of this manuscript.

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