Indonesian J. Pharm. Vol. 23 No. 4 : 209 – 215
ISSN-p : 0126-1037

Research Article

ENHANCEMENT OF DISSOLUTION RATE OF MODAFINIL USING SOLID DISPERSIONS WITH POLYETHYLENEGLYCOLS

Vyas Jigar[1*], Patel Jayvadan[2], Jain D. A.[1]

[1]Department of Pharmacy, Bhagwant University, Sikar Road, Ajmer, Rajasthan, India. 305004.
[2]Nootan Pharmacy College, Visnagar, Gujarat, India. 384315

Submitted: 20-07-2012
Revised: 29-09-2012
Accepted: 06-10-2012

*Corresponding author
Vyas Jigar

Email :
drjrvyas@yahoo.co.in

ABSTRACT

Solid dispersions (SDs) of modafinil (MDF) were prepared using polyethyleneglycols (PEGs), in 1;1, 1;2 and 1;4 proportions by fusion, solvent evaporation and physical mixing method. Differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRD) were used to examine the physical state of the drug. The data from the XRD showed that the drug was converted to amorphous form as the number and intensity of peaks were decreased in solid dispersion as compared to pure drug and physical mixture of drug and carrier. DSC thermograms also confirmed the change in physical state of the drug as the peaks were altered or disappeared. With the highest ratio of the carriers (1:4), the drug solubility was enhanced by 38.68, 34.78 and 9.29 folds in solvent evaporation, fusion and physical mixing methods respectively. Solid dispersion batch S6 containing drug:PEG6000 in 1:4, was selected to be formulated as tablet (batch TS6) and evaluated for *in vitro* drug dissolution & six month stability. An increased dissolution rate of modafinil was observed from SDs and PMs, as compared to pure crystalline drug. The dissolution rate of modafinil from its PMs or SDs increased with an increasing amount of polymer.

Key words: Fusion, solvent evaporation, physical mixture, in vitro dissolution, characterization.

INTRODUCTION

Many potential drug candidates are characterized by a low oral bioavailability. Often, poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. The relationship between dissolution rate and absorption is particularly distinct when considering drugs of low solubility. Consequently, numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption.

Among the techniques to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular ones (Chiou *et al.*, 1971; Ford *et al.*, 1986), although few marketed products rely on this concept. The interest in amorphous drug–polymer solid dispersions has grown due to the potential of improving bioavailability, particularly for poorly water-soluble drugs (Leuner *et al.*, 2000; Craig *et al.*, 2002; Hancock *et al.,* 2002*)*. The basis for this interest stems from the increased rate of dissolution, which can range from hundreds to thousands fold increase, even for the most insoluble active pharmaceutical ingredients (Hancock *et al.,* 2002*)*. For drugs whose bioavailability is limited due to poor aqueous solubility (as in BSC class II drugs), the improvement in solubility may lead to enhanced bioavailability (Ahuja *et al.*, 2007; Vippagunta *et al.*, 2007; Ambike *et al.,* 2005*)*. The SDs of drugs with PEGs may be useful to solve various problems such as stability, solubility, dissolution and bio-availability (Khawam *et al.*, 2006; Marsac *et al.*, 2006a; Marsac *et al.,* 2006b).

Solid dispersion represents a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms (Mayersohn *et al.*, 1966; Chiou *et al.*, 1969). The properties, performance, and practical applications of solid dispersions depend on factors such as: (a) the method of preparation, (b) composition, (c) selection of a suitable carrier, and (d)

physicochemical properties of the drug (Chiou *et al.*, 1971, Hajratwala *et al.*, 1974).

Modafinil is approved by the USFDA for the treatment of narcolepsy, hypersomnia, shift work sleep disorder and excessive daytime sleepiness associated with obstructive sleep apnoea and in adult it is used in attention deficient/hyperactivity disorder (ADHD). It is rapidly absorbed after oral administration with peak plasma concentrations occurring at 2-4 hours. But the oral bioavailability of the drug is very poor due to water insolubility (Minzenberg *et al.*, 2007, Jacobs *et al.*, 2002). Modafinil is BCS class II drug; hence improvement of dissolution will lead to enhancement of bioavailability.

The primary objective of the present study is to investigate the possibility of improving the release properties of modafinil via SDs with PEGs.

METHODOLOGY

Material

Modafinil was obtained as a gift sample from Alembic Pharmaceuticals Ltd. (Vadodara, India); PEG2000, PEG10000, acetone and chloroform were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India); hydrochloric acid was purchased from Loba Chem (Mumbai, India). Tablet excipients like, crosspovidone, Avicel pH101, StaRx1500, MCC and Ac-Di-Sol were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). Distilled water was freshly prepared and used for the study. All the chemicals and reagents were of Analytical Reagent (AR) grade and used without further purifications.

Preparation of solid dispersions

Solid dispersions were prepared by three different methods i.e. fusion, solvent evaporation and physical mixing method

Fusion method: Solid dispersions containing different weight ratios (1:1, 1:2, 1:4) of drug in PEG2000, PEG6000, and PEG10000 were prepared by melting the carriers in porcelain dish (at around 100º C more than the melting point of carriers on sand bath), dispersing the drug onto the molten carrier and cooling immediately on freezing mixture of ice and sodium chloride. The solid dispersions were then allowed to cool at an ambient temperature and stored in desiccators for 24 hours. The dry mass was scrapped, crushed & ground in a mortar and passed through sieve #40. The dried mass was stored in desiccator until further use.

Solvent evaporation method: Solid dispersions containing different weight ratios (1:1, 1:2, 1:4) of drug in PEG2000, PEG6000, and PEG10000 were prepared by dissolving required amount of drug and carriers in solvent system containing acetone and chloroform in 1:1 proportion. The solvent was evaporated at 40° C on water bath with continuous stirring and the resulting residues were dried under vacuum for 3 hours and stored in desiccators for overnight. The dry mass was ground in a mortar, passed through sieve #40 and stored in desiccator until further use.

Physical mixing: Drug and carriers were blended in desired proportions using spatula for 10 minutes and then ground in mortar with pestle. The co-grinding mixture was then passed through sieve #40 and stored in desiccator until further use.

Characterisation of solid dispersions containing modafinil

Saturation solubility: The saturation solubility of drug, carriers and all the solid dispersions was determined by dispersing 1g of drug, carrier or solid dispersion into 100mL of distilled water contained in glass bottle and shaken for not less than 24 hours. Solubility was then determined in mg/mL using spectrophotometer (Shimadzu 1700, Japan) with λmax at 222nm after filtration (through a 0.45µm Millipore filter) and necessary dilutions.

Melting point: Melting point of drug, polymer and all the solid dispersions was determined using precision melting point apparatus (Shimadzu MP09, Japan). Two samples were tested at a time by placing a pintch of sample into the capillary and heating at slow and consistent rate.

Stability: The prepared solid dispersions were stored in stability chamber at 45 $\pm$ 2º C with 75% RH for 6 months. The formulations were analysed for one point in vitro dissolution, solubility and melting point after 6 months and compared with the results obtained with formulations prepared and analysed immediately.

Table I. Composition of solid dispersions prepared different methods

Method	Modafinil (mg)	PEG 2000 (mg)	PEG 6000 (mg)	PEG 10000 (mg)
Fusion method	100	F1/100	F4/100	F7/100
	100	F2/200	F5/200	F8/200
	100	F3/400	F6/400	F9/400
Solvent evaporation method	100	S1/100	S4/100	S7/100
	100	S2/200	S5/200	S8/200
	100	S3/400	S6/400	S9/400
Physical mixtures	100	P1/100	P4/100	P7/100
	100	P2/200	P5/200	P8/200
	100	P3/400	P6/400	P9/400

F1-F9, S1-S9 and P1-P9 are the batches prepared by Fusion method, Solvent evaporation method and simple mixing.

Table II. Characterization of solid dispersions prepared different methods

	Fusion method		Solvent evaporation method			Physical mixtures		
Batch	SS	M_P (°C)	Batch	SS	M_P (°C)	Batch	SS	M_P (°C)
F1	1.13	135	S1	1.25	127	P1	0.43	164
F2	1.25	132	S2	1.40	124	P2	0.47	162
F3	1.57	130	S3	1.75	121	P3	0.59	161
F4	1.51	145	S4	1.68	131	P4	0.45	166
F5	1.68	143	S5	1.88	129	P5	0.51	164
F6	2.10	140	S6	2.33	125	P6	0.63	162
F7	1.84	152	S7	2.06	136	P7	0.48	166
F8	2.05	150	S8	2.27	134	P8	0.55	165
F9	2.55	145	S9	2.84	131	P9	0.68	163

SS= Saturation solubility in Mg/mL

Differential Scanning Calorimetry (DSC) Analysis: DSC scans of the powdered samples were recorded using DSC- 822e Mettler Toledo with the Stare software. All the samples were weighed (4-5 mg) and heated for total time of 40 min at a scanning rate of 5° C/min under dry air (N_2) flow (50 mL/min) at pressure of 25 psi between 50 and 250° C (furnace temperature). Aluminium pans and lids (40µL capacity) were used for the study.

X-ray diffraction analysis: X-ray diffraction (XRD) patterns were recorded on an X-diffractometer (Phillip PW 1130/00 diffractometer, Natherland), employing CuK_∞ radiation source operating at 30 mA and 40 kV. Samples were scanned from 6 to 40° 2θ at a scanning rate of 0.02° 2θ s^{-1}.

Preparation and evaluation of tablets containing modafinil

Tablets containing either solid dispersions, drug-carrier physical mixture or simple drug equivalent to 100mg of modafinil were prepared by direct compression method after mixing with required amount of different ingredients as shown in table III. All the prepared tablets were subjected to routine quality control tests like hardness, friability and weight variation before evaluating for in vitro dissolution and stability study.

In vitro dissolution study: In vitro dissolution study of modafinil was perfor-med on 8 vessel USP type II dissolution test apparatus in 0.1N HCl with constant temperature 37+2° C and speed 50rpm.

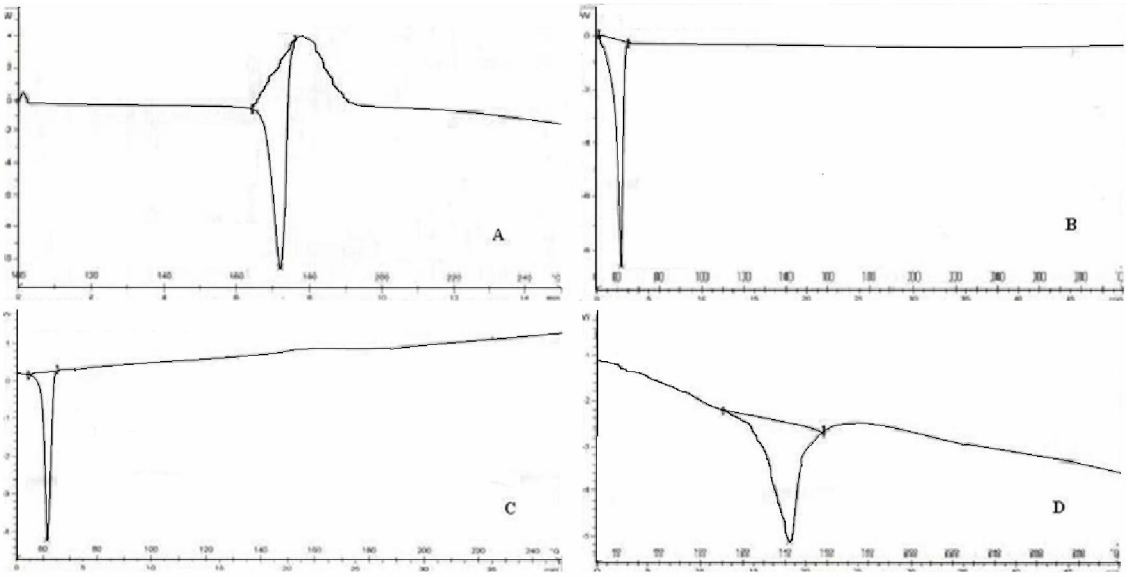

Figure 1. DSC thermogram of A) pure drug, B) pure PEG 6000, C) batch S6 & D) batch P6

Aliquots were withdrawn at predetermined time intervals, analyzed by UV-visible spectrophotometric method and cumulative percentage release of drug was recorded after one hour.

RESULTS AND DISCUSSIONS

Solid dispersions of Modafinil were prepared successfully by melting & solvent evaporation method and compared with physical mixtures of drug and carriers. All the prepared formulations were evaluated for saturation solubility & melting point; and the data of composition and evaluations of all the formulations were recorded in table I and table II.

Batch S6 was selected after comparing the saturation solubility, formulated in tablet dosage form and extensively evaluated for in vitro dissolution and stability study. Tablet containing batch P6 and pure drug were also prepared and evaluated to get better comparison of the data.

All the three tablet batches were characterised for melting point, saturation solubility and in vitro drug dissolution, as recorded in table IV, to understand stability of the formulations.

By formulating solid dispersion of modafinil, the water solubility of pure drug was increased by 6 to 45 folds and melting point was reduced by 0 to 33 % in different batches, which suggested the conversion of crystalline form to amorphous form, which was then confirmed by DSC (Fig. 1) and XRD (Fig. 2) study. While comparing different carriers, PEG 6000 was found to have higher potential to enhance the water solubility of modafinil by melting method. Hence, batch S6 showing maximum solubility enhancement was selected for extensive characterisation and compared with batch P6, as it is physical mixture of drug and PEG 8000 in the same proportion.

DSC thermogram of pure drug has shown very sharp melting endotherm at 166° C-171° C for melting and an exotherm at 174° C-190° C due to its decomposition. DSC thermogram of PEG 6000 has given a sharp endotherm at 59° C-62° C for melting. Solid dispersions batch S6 (drug:PEG6000 at 1:4 proportion by melting method) has given a sharp endotherm at 59° C-63° C that suggested that melting peak of drug was absent and melting point of the formulation was near to that of PEG 6000. Hence the DSC study also suggested alteration in state of the drug which supported the amorphisation of drug that led to increase in solubility of the drug.

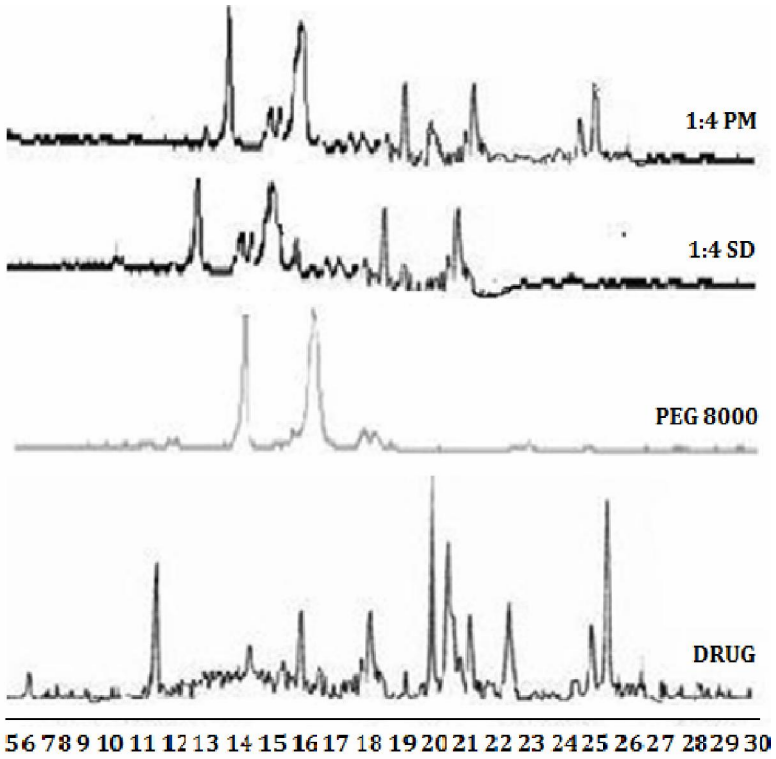

Figure 2. X-ray diffraction spectra of pure drug, PEG 6000, solid dispersion of drug:PEG 6000 at 1:4 ratio and physical mixture of drug:PEG 6000 at 1:4 ratio.

It was observed in the XRD study that pure drug is crystalline in nature showing at least three intense peaks along with several small to intermediate peaks in the spectra and pure carrier PEG 6000 is semi crystalline in nature showing two intense peaks in the spectra, but solid dispersion has no any intense peaks and showing only few peaks with lesser intensity as compared to pure drug and carrier. Hence this study confirmed that was converted in amorphous state in solid dispersion batch S6 which led to solubility enhancement. In spectra of physical mixture batch P6, reduction of number of peaks as well as intensity of peaks was observed which confirmed only partial conversion of crystalline form to amorphous form.

In the present study, it was observed that as the proportion of hydrophilic carriers was increased, the solubility also increased which might be due to the improved wetting of drug particles by carrier as the particle surface rendered hydrophilic after coating by PEGs. Higher solubility enhancement was observed with PEG 6000 than PEG 2000 & PEG 10000 due to some unknown cause but might be due to the similar melting behavior and crystalline properties which led to perfect solution of drug into carrier.

Modafinil is slightly soluble in water (Jacobs *et al.*, 2002) and its hydrophobic property prevented the powder surface from contacting the dissolution medium. In contrast, the dissolution rate of modafinil from batch TS6 was significantly higher than that of batch TP6 & batch CT. The results indicated that TS6 exhibited 92.79 % drug dissolution in 60 minutes as compared to only 57.93 % & 46.34 % from batch TP6 & batch CT respectively. The hydrophilic properties of PEG 6000 probably led to greater wetting and increased surface available for dissolution by reducing interfacial tension between the hydrophobic drug and the dissolution medium.

Table III. Composition of tablet containing pure drug, solid dispersion and physical mixture

Tablet ingredients	Amount in mg		
	Batch TS6	Batch P6	Batch CT
Drug*	500	500	100
Carbopol 974	120	120	120
Crosspovidone	24	24	24
PVP K30	40	40	40
Starch	80	80	80
MCC	20	20	420
Mg. Stearate	16	16	16
Total	800	800	800

*Solid dispersion and physical mixture are in proportion of drug:carrier 1:4, hence 500 mg of total formulation is equivalent to 100 mg of drug; batch TS6, TP6 and CT are coded for tablet of batch S6, batch P6 and convention tablet respectively.

Table IV. Data of stability study conducted for six months

Batches	Melting point			Saturation solubility			% CDR 60		
	0m	6m	% d	0m	6m	% d	0m	6m	% d
S6/TS6*	119	131	9.16	2.58	1.86	27.91	92.79	67.04	27.75
P6/TP6*	162	164	1.22	0.62	0.60	3.23	57.93	51.24	11.69
drug/CT*	166	165	0.60	0.067	0.065	2.99	46.34	43.55	6.02

% CDR 60= Cumulative percentage drug release after 60 minutes; % d= percentage difference; melting point and saturation solubility data is that of batch S6, P6 & pure drug; and % CDR 60 data is of batch TS6, TP6 & CT.

All the three tablets (batch TS6, TP6 & CT) were also evaluated for stability study for the duration of six months, where results of melting point, saturation solubility and one point in vitro drug dissolution study (% cumulative drug released after 60 minutes) were compared. It was observed that, melting point of solid dispersion (batch S6) was increase by 9.16 % as compared to 1.22 % and 0.6 % in physical mixture (batch P6) and conventional tablet (batch CT) respectively, suggested stability problem in solid dispersion. Similar results were obtained in saturation solubility study as well as in vitro dissolution study, where significant change in these properties was observed which indicated poor stability of solid dispersion or the amorphous form. Hence stabilization of solid dispersion was needed to make this formulation strategy successful.

CONCLUSION

Solid dispersions of modafinil prepared with different polyethyleneglycols (PEG 2000, PEG 6000 & PEG 10000) by melting and solvent evaporation method resulted in increased saturation solubility of drug. Based on saturation solubility study of different solid dispersion, batch S6 was selected, as it has shown better results, and formulated into tablet along with batch P6 & pure drug; and evaluated for in vitro dissolution and stability study. As demonstrated by characterization of solid dispersion by DSC and XRD Study, a decreased crystallinity of modafinil as well as the surface morphology of the polymeric particles can explain the enhanced solubility and improved dissolution rate. Tablets containing solid dispersion (batch TS6) had drug dissolution profiles that were better than those of batch TP6 and batch CT which explains that solid dispersion can be utilized successfully to enhance the water solubility of poorly water soluble drug.

ACKNOWLEDGEMENT

The authors acknowledge Alembic Pharmaceuticals Ltd. for providing modafinil as a gift sample.

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