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Preparation and characterization of solid dispersion of modafinil for enhancement of dissolution rate

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ABSTRACT

Solid dispersions of Modafinil were prepared using polyethyleneglycols, in various proportions by melting, solvent evaporation and simple mixing methods. Based on the solubility and melting point study, PEG 8000 was selected and solid dispersion batch containing drug: PEG 8000 in the ratio of 1:4 was prepared by melting method and then formulated as tablet followed by evaluation of dissolution and six month stability studies. When the results of selected tablet batch were compared with that of tablet containing physical mixture of drug:PEG 8000 in the ratio of 1:4 and conventional tablet containing plain Modafinil, it has shown significant improvement of dissolution profile of Modafinil Present study conclusively demonstrated that PEG 8000 enhanced water solubility of Modafinil by amorphization, which was confirmed by XRPD, FTIR, SEM and DSC. The melting method was found better than solvent evaporation method for enhancement of dissolution profile.

Keywords: Modafinil, solubility enhancement solid dispersion, polyethyleneglycols.

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, solid dispersion is one of the most popular techniques (Chiou, 1971; Teofilo, 2007), 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, 2000; Craig, 2002; Hancock, 2002; Ahuja, 2007; Vippagunta, 2007). For drugs whose bioavailability is limited due to poor aqueous solubility (as in BSC class II drugs), the improvement in solubility and hence increase in dissolution rate may lead to enhanced bioavailability (Ambike, 2005; Khawam, 2006; Marsac, 2006a; Marsac, 2006b). One of the underlying principles of enhanced water solubility of solid dispersion is achievement of the amorphous state which is considered to be more soluble than the crystalline state as very less energy is required to break the crystal lattice (Mooter, 1998; Habib, 2000; Law, 2000). The other fact is that particle size is reduced to its absolute minimum during entrapment of drug which causes increased surface area and effective dissolution rate (Pignatello, 2001; Babu, 2002; Hancock, 1997). The properties, performance, and practical applications of solid dispersions depend on factors such as the method of preparation, composition, selection of a suitable carrier and physicochemical properties of the drug (Chiou, 1971; Karanth, 2006). Various methods like fusion method, solvent evaporation method, Spray drying method have been extensively used for preparation of solid dispersion (Vyas, 2011; Sinha, 2010; lee, 1999; Li, 2008). Polyethylene glycols present themselves as one of the most extensively used hydrophilic carriers for preparing solid dispersions by different methods,

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) (Minzenberg, 2007). It is rapidly absorbed after oral administration with peak plasma concentrations occurring after 2-4 hours. However the oral bioavailability of the drug is poor due to water insolubility (Minzenberg, 2007). Modafinil is BCS class II drug; hence improvement of dissolution will lead to enhancement of bioavailability.

In the present study, to improve water solubility, we prepared solid dispersions of Modafinil using hydrophilic carriers (polyethyleneglycols) by two different methods i. e. melting method and solvent evaporation method. For purposes of comparison, physical mixtures were prepared by simple mixing and homogenization after pulverization of drug and carriers.

MATERIALS AND METHODS

Modafinil was obtained as a gift sample from Alembic Pharmaceuticals Ltd. (Baroda, India), PEG 4000, PEG 6000, PEG 8000, cross povidone, polyvinylpyrrolidone (PVP) k30, starch, microcrystalline cellulose (MCC), magnesium (Mg.) stearate, acetone and chloroform were purchased from S.D. Fine Chemicals Ltd. (Mumbai,India), and hydrochloric acid was purchased from Loba Chem (Mumbai,India). All other chemicals and reagents used were of AR grade and used without further purifications.

Preparation of solid dispersions and physical mixtures

Solid dispersions were prepared by two methods i.e. melting method and solvent evaporation method.

Melting method - Solid dispersions containing different mass ratios (1:1, 1:2, 1:4) of drug in PEG 4000, PEG 6000, and PEG 8000 were prepared by melting the carriers in porcelain dish (at around 10 °C above 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 and ground in a mortar and passed through sieve #40 (420 µm)**.** The dried mass was stored in desiccator until further use.

Solvent evaporation method - Solid dispersions of same compositions as discussed in previous method were prepared by dissolving required amount of drug and carriers in a solvent mixture of acetone and chloroform (1:1). The solvent was evaporated at 40 °C on a water bath with continuous stirring and the resulting residues were dried under vacuum for 3 hours and stored in desiccators overnight. The dry mass was ground in a mortar, passed through sieve #40 (420 µm) and stored in desiccator until further use.

Physical mixtures were prepared by kneading desired amount of drug and carriers for 10 minutes and then grounding in mortar with pestle. The co-grinding mixtures were then passed through sieve #40 (420 µm) and stored in desiccator until further use.

Characterisation of solid dispersions

Saturation solubility of Modafinil was determined in mg/ml using UV-visible spectrophotometer (Shimadzu, Japan) measuring maximum absorption (λmax) at 222 nm after filtration and necessary dilutions. *Melting point* was determined using precision melting point apparatus (Remi, India). *Stability study* of solid dispersions was conducted in stability chamber (Remi, India) at 45 $\pm$ 2 ºC with 75 $\pm$ 5 % RH for 6 months and stability was evaluated and compared by determining saturation solubility and melting point.

FTIR spectra of moisture free powdered samples were obtained using a FTIR spectrophotometer (Shimadzu, Japan) in potassium bromide. The scanning range was kept between 400 and 4000 cm^{-1} and the resolution was kept constant at 1 cm^{-1}.

DSC scan of powdered samples were recorded using DSC- 822e Mettler Toledo (Japan). All the samples were weighed (4-5 mg) and heated for total time of 40 min at a scanning rate of 5 °Cmin^{-1} under dry air (N_2) flow (50 mL min^{-1}) at pressure of 25 Pa between 50 and 250 °C (furnace temperature). Aluminium pans and lids (40 µL capacity) were used for the study.

X-ray powder diffraction (XRPD) patterns were recorded on Phillip PW 1130/00 diffractometer (Philips, Holand), employing CuK_α 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}.

The surface of powdered drug, carrier and their binary system, was examined by means of scanning electron microscope (JSM-6400 Jeol, Japan). The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180-200 Å) using a fine coat ion sputter (JFC-1100 Jeol, Japan). The pictures were then taken at an excitation voltage of 20 kV with magnification in the range of 118 to 245X.

Preparation and evaluation of tablets containing Modafinil

Tablets containing solid dispersions, drug-carrier physical mixture or pure drug, equivalent to 100 mg of Modafinil, were prepared by direct compression method after mixing with required amount of different ingredients.

All the prepared tablets were subjected to content uniformity test and then evaluated for *in-vitro* dissolution and six months stability.

In-vitro dissolution study of Modafinil was performed on 8 vessel USP XXVIII type II dissolution test apparatus (USP-XXVIII, 2005) in 0.1N hydrochloric acid with constant temperature of 37 $\pm$ 2 °C and paddle speed at 50 rpm. Aliquots were withdrawn at predetermined time intervals, measured at 222 nm and cumulative percentage release of drug was recorded.

Stability study of tablets was conducted in stability chamber (Remi, India) at 45 $\pm$ 2 ºC with 75 $\pm$ 5 % RH for 6 months and stability was evaluated and compared by determining cumulative percentage release of drug after 1 hour.

RESULTS AND DISCUSSION

Solid dispersions and physical of Modafinil and PEGs were prepared successfully by melting and solvent evaporation method and compared with physical mixtures of drug and carriers. All the prepared formulations were evaluated for saturation solubility and melting point (Table 1, Table 2 and Table 3).

Table 1. Composition and evaluations of solid dispersions prepared by melting method

Batch	Modafinil (mg)	PEG 4000 (mg)	PEG 6000 (mg)	PEG 8000 (mg)	SS (mg/ml)	M_P (°C)
F1	100	100	-	-	1.14	115
F2	100	200	-	-	1.27	113
F3	100	400	-	-	1.59	110
F4	100	-	100	-	1.53	119
F5	100	-	200	-	1.71	117
F6	100	-	400	-	2.12	114
F7	100	-	-	100	1.87	124
F8	100	-	-	200	2.06	122
F9	100	-	-	400	2.58	119

SS=saturation solubility, Values of saturation solubility and melting point (M_P) are average of three determinations

Table 2. Composition and evaluations of solid dispersions prepared by solvent evaporation method

Batch	Modafinil (mg)	PEG 4000 (mg)	PEG 6000 (mg)	PEG 8000 (mg)	SS (mg/ml)	M_P (°C)
F10	100	100	-	-	1.03	123
F11	100	200	-	-	1.14	120
F12	100	400	-	-	1.43	118
F13	100	-	100	-	1.37	132
F14	100	-	200	-	1.53	130
F15	100	-	400	-	1.91	127
F16	100	-	-	100	1.67	138
F17	100	-	-	200	1.86	136
F18	100	-	-	400	2.32	132

SS=saturation solubility, Values of saturation solubility and melting point (M_P) are average of three determinations.

It was observed in the present study that the solubility of Modafinil was increased with increased proportion of PEGs. This might be due to the improved wetting of surface of drug particles by hydrophilic carrier due to which the particle surface became hydrophilic. Higher solubility enhancement was observed with PEG 8000 than PEG 4000 and PEG 6000 due to some unknown cause but might be due to the similar melting behavior and crystalline properties of PEG 8000 and Modafinil which led to perfect solution of drug into carrier.

Batch F9 in melting method and F18 in solvent evaporation method has shown highest improvement in solubility of Modafinil. However batch F9 was selected for further study because the saturation solubility of Modafinil was greater in batch F9 (2.58 mg/ml) as compared to F18 (2.32 mg/ml).

Table 3. Composition and evaluations of physical mixtures

Batch	Modafinil (mg)	PEG 4000 (mg)	PEG 6000 (mg)	PEG 8000 (mg)	Ss (mg/ml)	M_P (°C)
F19	100	100	-	-	0.39	163
F20	100	200	-	-	0.43	161
F21	100	400	-	-	0.54	160
F22	100	-	100	-	0.41	165
F23	100	-	200	-	0.46	163
F24	100	-	400	-	0.57	161
F25	100	-	-	100	0.44	165
F26	100	-	-	200	0.50	164
F27	100	-	-	400	0.62	162

SS=saturation solubility, Values of saturation solubility and melting point (M_P) are average of three determinations.

Batch F9 was characterized by FTIR (Figure 1), DSC (Figure 2), XRPD (Figure 3) and SEM (Figure 4) to understand possible mechanism of solubility enhancement. Physical mixture batch F27 was also characterized and compared with batch F9 to understand the mechanism of solubility enhancement of Modafinil.

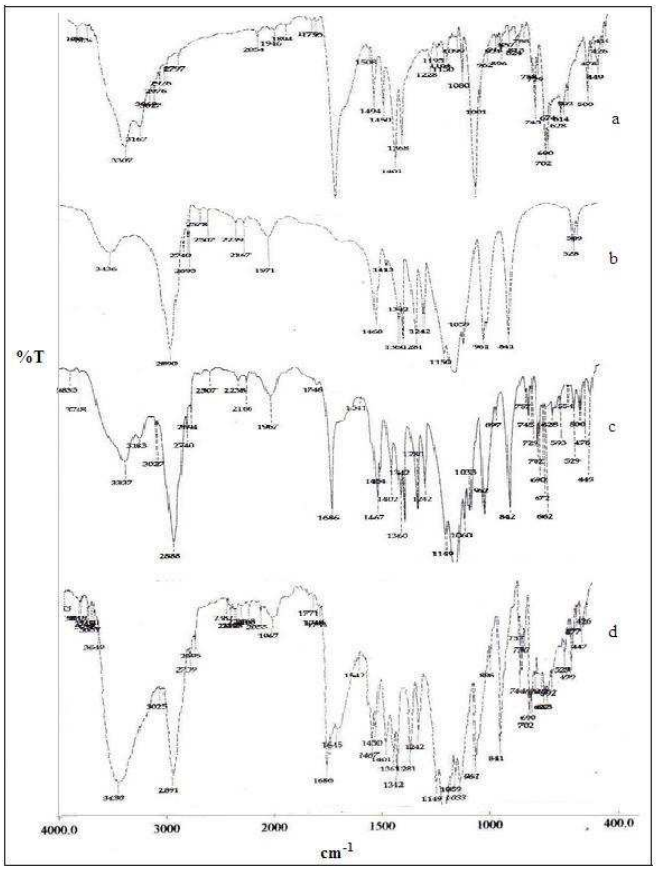

Figure 1. FTIR spectra of a) Modafinil, b) PEG 8000, c) SD batch F9 and d) PM batch F27

FTIR spectra (Figure1) showing characteristic peaks of Modafinil at 3307 and 3167 cm^{-1} for Aliphatic -NH stretching hydrogen bond; 3069 and 3027 cm^{-1} for aromatic –CH stretching; 2976 and 2926 cm^{-1} for aliphatic –CH stretching; 1685 cm^{-1} for -C=O of amide and 1080 cm^{-1} for -S=O groups. PEG 8000 showed characteristic peaks at 3436 cm^{-1} for -OH stretching and at 2890 cm^{-1} for -CH stretching of CH_2 groups. In spectra of batch F9, peaks at 3307 and 3167 cm^{-1} are absent, or rather split into 3337 and 2888 cm^{-1} due to breaking of hydrogen bond between -NH and -CH stretching to form the bond between -NH group of Modafinil with -OH group of PEG 8000. Also the intensity of peak at 1686 cm^{-1} was decreased and a peak at 1080 cm^{-1} in pure drug was shifted to 1060 cm^{-1} in solid dispersion indicating absence of free drug in solid dispersion.

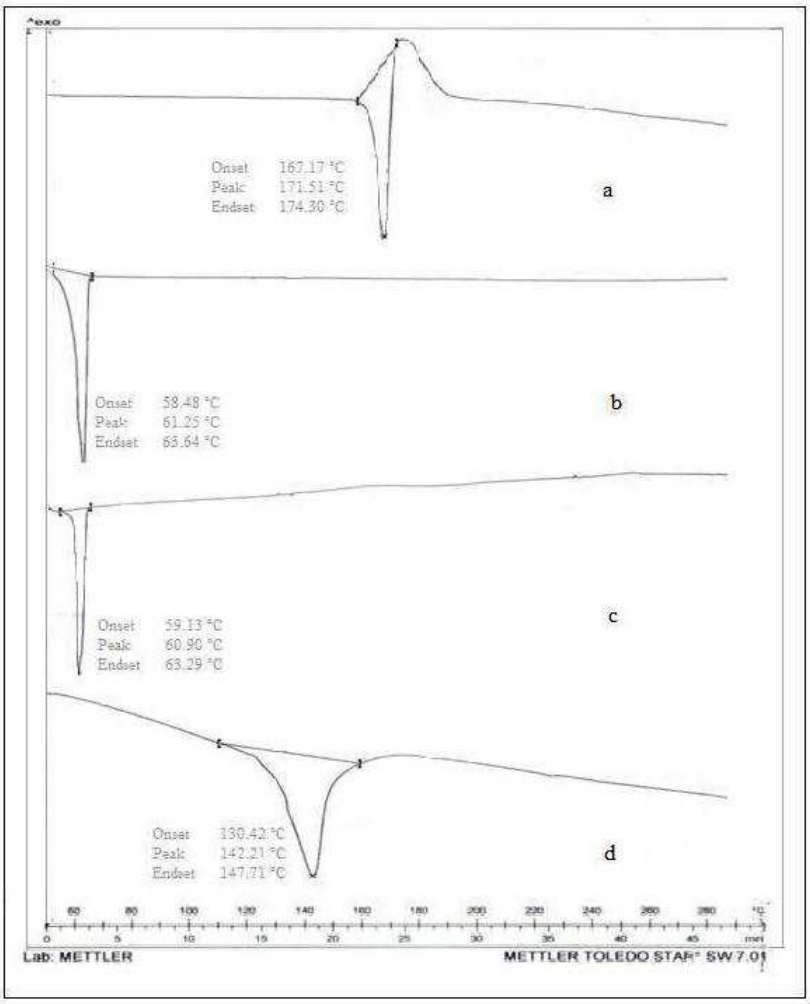

Figure 2. . DSC thermogram of a) Modafinil, b) PEG 8000, c) SD batch F9 and d) PM batch F27

DSC thermogram (Figure 2) of pure drug has shown very sharp melting endotherm at 167 °C - 171 °C and an exotherm at 174 °C – 190 °C due to its decomposition. DSC thermogram of PEG 8000 has given a sharp endotherm at 59 °C – 62 °C for melting. Solid dispersions batch F9 (drug:PEG 8000 1:4, melting method) has given a sharp endotherm at 59 °C – 63 °C that suggested that melting peak of Modafinil was absent and melting point of the formulation was near to that of PEG 8000. Hence the DSC study also suggested alteration in the state of Modafinil which supported the amorphisation of drug that led to increase in solubility.

It was observed in XRPD diffractogram (Figure 3) that Modafinil is crystalline in nature showing at least three intense peaks along with several small to intermediate peaks in diffractogram and PEG 8000 is semi-crystalline showing two intense peaks in diffractogram. Solid dispersions showed no intense peaks but only few peaks of lesser intensity when compared to pure drug and carrier. This study confirmed that Modafinil was converted in amorphous state in solid dispersion F9 which led to solubility enhancement. In diffractogram of physical mixture (batch F27), reduction of number of peaks as well as intensity of peaks was observed confirming only partial conversion of crystalline to amorphous form.

Figure 4 shows SEM images of the pure components, solid dispersion and physical mixture. PEG 8000 (Figure 4a) existed in a crystalline mixture of smooth-surfaced particles (100-300 µm) with few smaller particles (20-40 µm), while Modafinil (Figure 4b) existed as small irregular particles (10-20 µm). On the contrary, physical mixture batch F27 (Figure 4c) consisted of more spherical particles of rather irregular surface. In the case of solid dispersion batch F9 (Figure 4d), the particles had a surface morphology similar to that of pure PEG 8000 which demonstrates the homogeneity of solid dispersion. The novel arrangements between particles of Modafinil and PEG 8000 might be responsible for the enhanced solubility of Modafinil in solid dispersion.

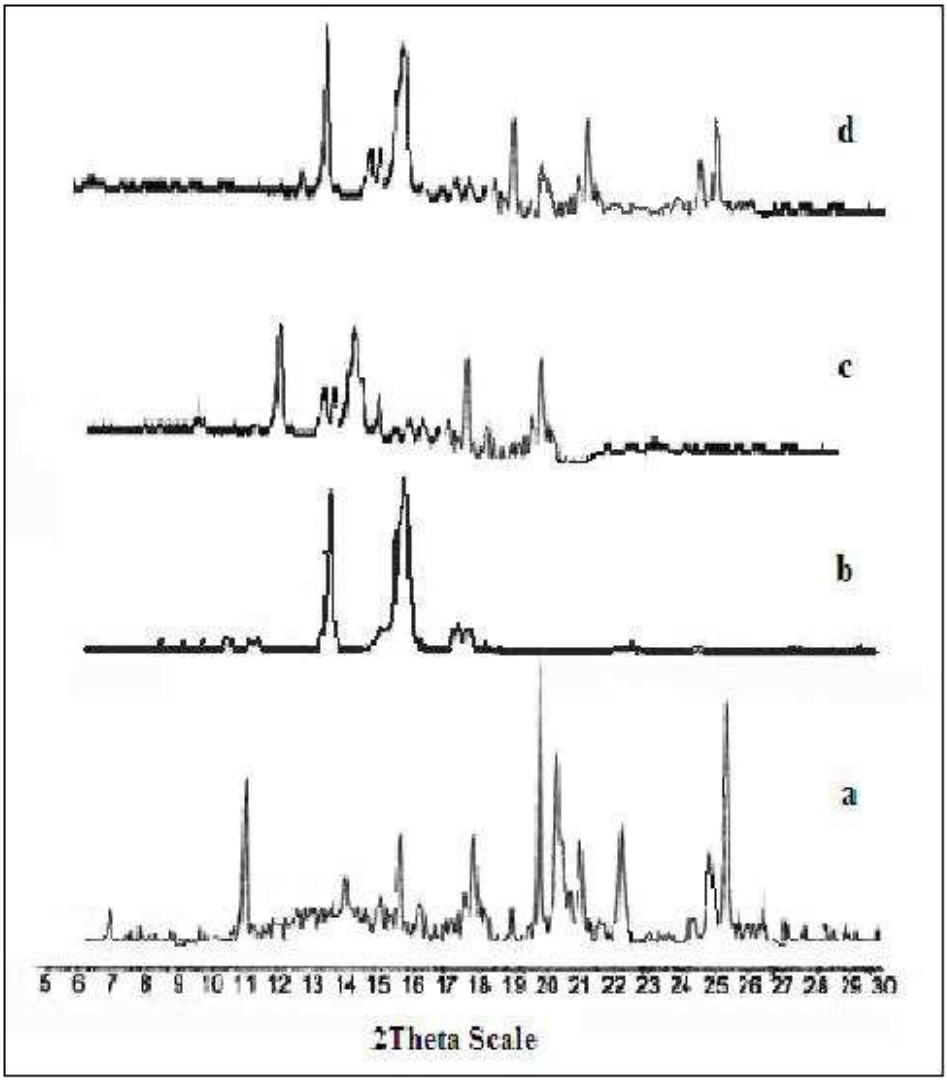

Figure 3. X-ray powder diffraction spectra of a) Modafinil, b) PEG 8000, c) SD batch F9 and d) PM batch F27

Batch F9 was formulated as tablet and extensively evaluated for *in-vitro* dissolution and stability study. Tablet containing batch F27 was prepared to understand the effect of simple mixing and tablet containing pure drug was prepared to understand magnitude of improvement in dissolution rate.

Table 4. Composition of tablet containing pure drug, solid dispersion and physical mixture

Tablet ingredients	Batch TF9	Batch TF27	Batch CT
Modafinil + PEG (100 mg + 400 mg)	500	500	100
Cross povidone (mg)	32	32	32
PVP K30 (mg)	40	40	40
Starch (mg)	80	80	80
MCC (mg)	124	124	124
Mg. Stearate (mg)	24	24	24
Total (mg)	800	800	800
Content uniformity	98.55	99.61	97.95

Batch TF9, TF27 and CT are coded for tablet of batch F9, batch F27 and conventional tablet respectively.

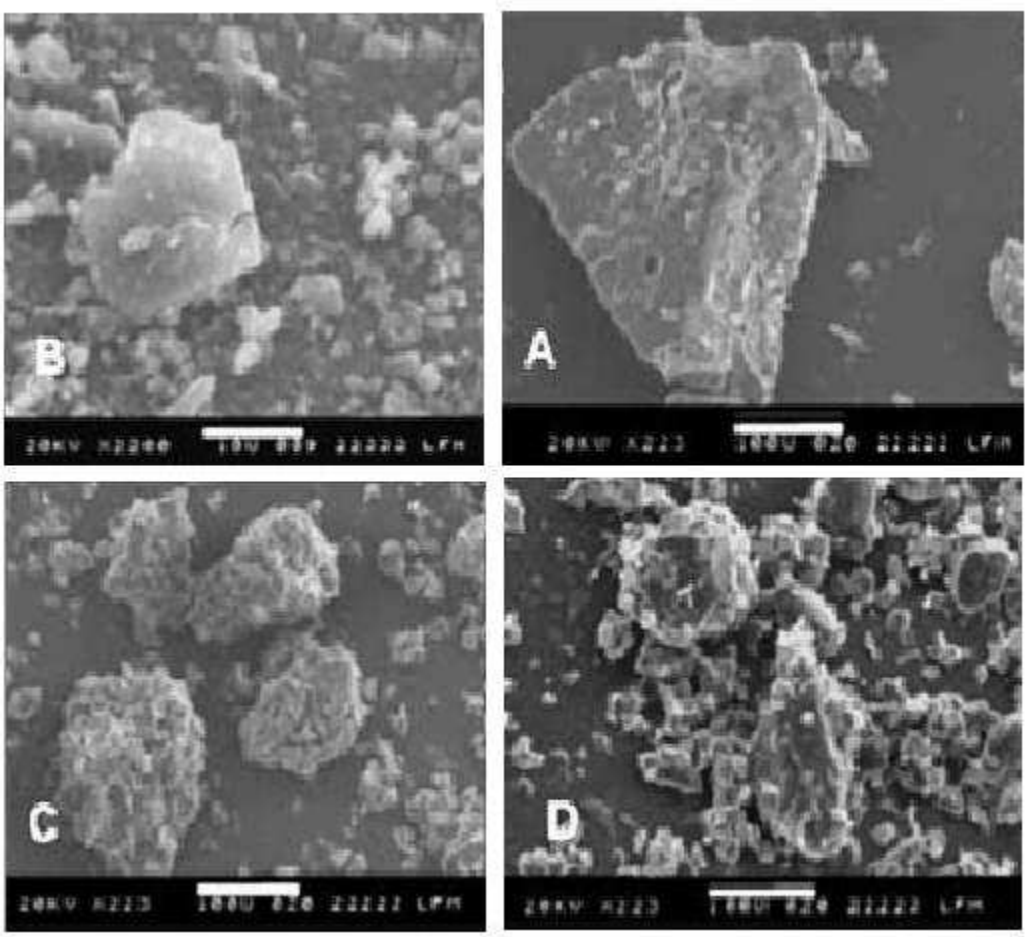

Figure 4. . Scanning electron microscopy images of a) PEG 8000, b) Modafinil, c) batch F27 and d) batch F9

All the three tablet batches were characterised for *in-vitro* drug dissolution and six months stability (Table 5). The solid dispersion F9 and physical mixture F27 were also studied for six months stability by taking melting point and saturation solubility as evaluation parameters (Table 5).

Table 5. Stability data for six months

Batches	Melting point (°C)		Saturation solubility (mg/ml)		Cumulative percentage drug release after 1 hour	
	0 m	6 m	0 m	6 m	0 m	6 m
F9/TF9[a, b]	119	131	2.58	1.86	92.79	67.04
F27/TF27[a, b]	162	164	0.62	0.60	57.93	51.24
drug/CT[a, b]	166	165	0.06	0.06	46.34	43.55

Values shown above are average of three determinations
[a]melting point and saturation solubility data is that of batch F9, F27 and pure drug;
[b]Cumulative percentage drug release after 1 hour data is of batch TF9, TF27 and CT.

It was observed that, melting point of solid dispersion (batch F9) was increased by 9.2 % as compared to 1.2 % and 0.6 % in physical mixture (batch F27) and conventional tablet (batch CT) respectively, suggested stability problem in solid dispersion. Saturation solubility was decreased by 27.9 % in batch F9 as compared to 3.2 % and almost nil in batch F27 and batch CT respectively. Similarly cumulative percent drug release was decreased by 27.8 % in batch F9 as compared to 11.7 % and 6.0 % in batch F27 and batch CT respectively. This data strongly suggested 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 4000, PEG 6000 and PEG 8000) by melting and solvent evaporation method resulted in increased saturation solubility of Modafinil. As demonstrated by characterization of solid dispersion by FTIR, DSC, XRPD and SEM study, a decreased crystallinity of Modafinil as well as modification in surface morphology of Modafinil due to coating of hydrophilic carrier (PEG) can explain

the enhanced solubility and improved dissolution rate. This study conclusively demonstrated that solid dispersion can be utilized successfully to improve dissolution profile of poorly water soluble drug after stabilizing the solid dispersions with suitable method.

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