

FORMULATION AND EVALUATION OF SOLID DISPERSION OF ATORVATSTATIN WITH VARIOUS CARRIERS

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ABSTRACT

Hyperlipidemia or hyperlipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol and its more common in elderly patients. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase. However its absolute bioavailability is 14%. To increase the solubility of drug solid dispersion was prepared. Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with mannitol, PEG 4000 and PVP-K30. These solid dispersions were analysed for the solubility and invitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. Further FTIR, DSC, SEM studies were carried out. Solid dispersion prepared with PEG 4000 shows the presence of amorphous form confirmed by the characterization study. The study also shows that the dissolution rate of Atorvastatin can be enhanced to considerable extent by solid dispersion technique with PEG.

Keywords: Atorvastatin, Solid dispersion, PEG 4000, PVP-K30 and Mannitol.

INTRODUCTION

Hyperlipidemia or hyperlipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol. An individual's specific biochemical and metabolic profile can often work against even the healthiest lifestyle. For these "biochemically challenged" patients, lipid-lowering agents such as the statins have literally provided a new lease on life. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase. Atorvastatin reduces total cholesterol, LDL-cholesterol in patients with homozygous and heterozygous familial hypercholesterolemia, non familial hypercholesterolemia and mixed dyslipidemia. It also reduces the VLDL-cholesterol and triglyceride. Atorvastatin calcium is a synthetic lipid lowering agent, which competitively inhibits 3-hydroxy-3methyl-glutaryl CoA^{1,2,3}

Statins are the most commonly prescribed lipid-lowering agents because they are effective, well tolerated and easy to administer. They are generally effective, are supported by favorable outcome studies and have relatively few adverse effects. The six statins currently available are atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol),

lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor).⁴

There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation, complexation with cyclodextrins. Cyclodextrins (CD's) as they are known today, were called cellulose when first described by Villiers in 1891. Soon after, Schardinger identified the three naturally occurring cyclodextrins--alpha, beta, and gamma. These new compounds were referred to as Schardinger sugars. For 25 years between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrating that these sugars formed stable aqueous complexes with many other chemicals. By the mid 1970's, each of the natural cyclodextrins had been structurally and chemically characterized and many more complexes had been studied. Briefly, the natural cyclodextrins are produced from starch by the action of cyclodextrin glycosyltransferase (CGTase), an enzyme produced by several organisms, Bacillus macerans being the earliest source. Structurally, cyclodextrins consist of 6, 7, or 8 (α , β , and γ respectively) D-glucopyranosyl units, connected by α -(1,4) glycosidic linkages. The most stable three dimensional molecular configuration for these non-reducing cyclic oligosaccharides takes the form of a toroid with the upper (larger) and lower (smaller) opening of the

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toroid presenting secondary and primary hydroxyl groups, respectively, to the solvent environment. The interior of the toroid is hydrophobic as a result of the electron rich environment provided in large part by the glycosidic oxygen atoms. It is the interplay of atomic (Van der Waals), thermodynamic (hydrogen bonding), and solvent (hydrophobic) forces that accounts for the stable complexes that may be formed with chemical substances.⁵

For the past one decade, there has been an enhanced demand for a more patient user friendly and complaint dosage forms. As a result, the demand for developing new technologies has been increasing many folds annually. Since the development cost of a new drug molecule is very high, efforts are now made by pharmaceutical companies to focus on development of new drug dosage forms for existing drugs with an improved bioavailability and increased therapeutic efficacy together with reduced dosing frequency to minimize side effects and to make more cost effective dosage form. Oral dosage forms have always been a popular route of administration due to ease of ingestion, pain avoidance, and versatility and most importantly the patient compliance.⁶

The physiology and psychology of the elderly are different from those of young people. Due to their decline in swallowing ability and because of their hand tremors, oral administration in elderly is a significant problem. Many patients find it difficult to swallow tablets and capsules and do not take medication as prescribed. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed, mentally ill, developmentally disabled, uncooperative patient, patient with reduced intake regime, active working patients who are busy or traveling specially who have no access to water. In some cases such as motion sickness, sudden episode of allergic attack or coughing, swallowing tablet may become difficult.

To fulfill these medical needs, pharmaceutical technologists have channelised their efforts to develop a novel oral dosage form known as Rapidly Dispersible Tablets, tables that disintegrate and dissolves rapidly in saliva without need of drinking water. The rapid Dispersible tablets dissolve usually in oral cavity within 15 seconds to 3 minutes. The faster the drug into solution, the quicker the absorption and onset of drug effect.^{7,8}

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting (fusion), solvent, or melting solvent method. Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs (Chiou and Riegelman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000). In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. The mechanisms for the enhancement of the dissolution rate of solid dispersions have been proposed by several investigators. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers.⁹

MATERIALS AND METHODS

Materials

Atorvastatin was obtained as a gift sample from DRL (Hyderabad, India). All other chemicals and reagents were of analytical grade.

Method of estimation of Atorvastatin¹⁰

A simple, fast, reproducible and precise method of estimation for Atorvastatin was carried based on the solubility of Atorvastatin in methanol. 10 µ/ml solution was scanned from 200-400 nm. The absorption maximum was found to be 246.5 nm. Beers range was found to be 2-26 µg/ml. Solubility measurements of Atorvastatin were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Atorvastatin was added to 25ml of aqueous solution of water soluble carriers like urea, Poloxamer-407, citric acid, mannitol, PVPK 30 and PEG-4000 in the various ratios such as 1:1, 1:3, 1:5 and 1:10 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Atorvastatin in UV 246.5 nm.

Preliminary solubility studies of Atorvastatin¹¹

Solubility measurements of Atorvastatin were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Atorvastatin was added to 25ml of aqueous solution of water soluble carriers like urea, Poloxamer-407, citric acid, mannitol, PVPK 30 and PEG-4000 in the various ratios such as 1:1, 1:3, 1:5 and 1:10 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Atorvastatin in UV 246.5 nm.

Preparation of solid dispersions of Atorvastatin^{12,13}

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Solid dispersions were prepared by hot melt method and solvent evaporation methods. In hot melt method, the insoluble drug is dispersed into a molten carrier and cooled immediately. In solvent evaporation method, both drug and the carrier were dissolved in a common volatile solvent, and the solvent was evaporated to get solid dispersions. Atorvastatin is practically water insoluble molecule. In order to improve its solubility in water solid dispersions were prepared.

Hot melt method^{12,13}

In hot melt method, the carriers such as PEG 4000 and mannitol were selected based on the preliminary solubility study. The drug to polymer ratio was kept 1:1, 1:3, 1:5 and 1:10. The carrier was first melted in the china dish at about 60 °C and the drug was dispersed in the molten mixture with constant stirring. The dispersion was poured and cooled immediately. The solid dispersions obtained from this method were tacky enough.

Solvent evaporation method^{12,13}

In solvent evaporation method, drug and the carrier were dissolved in methanol and the adsorbent like micro crystalline cellulose (MCC) were dispersed in the same medium with constant stirring. Solution was evaporated under low pressure to get the solid dispersion. In this

method PVP-K-30 was used as carriers and MCC was used as adsorbent. Drug: carrier: adsorbent ratio was kept 1:1:2 and 1:2:2.

Solubility studies of Atorvastatin solid dispersion¹³

Solubility measurements of Atorvastatin were performed according to a published method (Higuchi and Connors, 1965). Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Atorvastatin in UV 246.5 nm.

Evaluation of solid dispersion¹⁴

Solid dispersions obtained from the above methods were screened for their solubility. The solid dispersion showing good solubility were further studied for drug content, in vitro release studies, FTIR, DSC and SEM study.

Drug content

The amount of drug present in a 10 mg equivalent amount of solid dispersion was determined by, dissolving the powder mixture in 10 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 246.5 nm. Drug concentration was determined from standard graph.

In vitro release studies¹⁵

In vitro dissolution studies were performed for selected solid dispersion. The following conditions were maintained for the dissolution process:

Instrument: Electro lab- USP Dissolution test apparatus.

Apparatus: Paddle type.

Temperature: 37±0.1°C

RPM: 75

Dissolution medium: Distilled water.

Volume of medium: 500 ml.

Sampling intervals: Every 30 min up to 4 hour

Sample volume: 5 ml withdrawn and replaced with 5 ml of distilled water.

FTIR STUDIES¹⁶

Instrument used was Shimadzu FTIR-8700 spectrophotometer. In this study, potassium bromide disc method was employed. Pure drug, physical mixtures, and solid dispersion studied by IR. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded.

SEM (Scanning Electron microscope) studies¹⁷

The surface morphology of the layered sample was examined by using SEM. The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer (30Å) of gold by employing POLARON-E 3000 sputter coater. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

DSC (Differential Scanning calorimetry) studies^{16,17}

Differential scanning calorimetry was conducted using Mettler Toledo Star system, Metallurgy department, Indian Institute of Science, Bangalore, India. Sample were weighed (5.00-8.00 ± 0.5 mg) and placed in sealed aluminium pans. The coolant was liquid nitrogen. The samples were scanned at 10°C/ min from 20^o C to 300^o C.

DSC thermograms of pure Atorvastatin, physical mixtures and solid dispersions were recorded.

RESULTS AND DISCUSSION

Standard graph

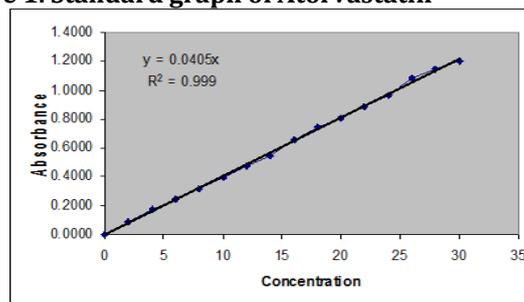
Atorvastatin was found to be soluble in organic solvents such as methanol. A simple reproducible method of estimation was carried out in methanol ranging from 2-26 mcg/ml solutions at 246.5nm (Table 1) against the blank the standard graph obtained was linear, with regression coefficient 0.999. (Figure 1) Atorvastatin is very slightly soluble in water and having poor bioavailability and coming under the category of class 2 of biopharmaceutical classification (BCS) system. In order to improve its bioavailability, solid dispersion and cyclodextrin complexes of the drug were prepared.

Table 1. Standard graph of Atorvastatin

S no	Conc. (mcg/ml)	Absorbance	± S.D.*
1	0	0.0000	0.00
2	2	0.0847	± 0.0613
3	4	0.1750	± 0.0140
4	6	0.2443	± 0.0176
5	8	0.3163	± 0.0146
6	10	0.3940	± 0.0166
7	12	0.4707	± 0.0150
8	14	0.5457	± 0.0255
9	16	0.6527	± 0.0350
10	18	0.7410	± 0.0125
11	20	0.8100	± 0.0234
12	22	0.8870	± 0.0276
13	24	0.9663	± 0.0235
14	26	1.0803	± 0.0155

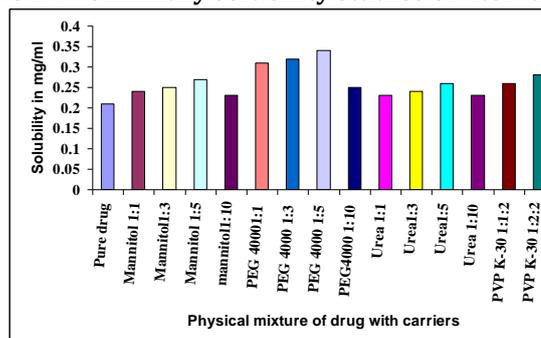
S.D.* = Average of three readings

Figure 1. Standard graph of Atorvastatin



In case of solid dispersions initially preliminary solubility analysis (Figure 2) were carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility found to be 0.21 mg/ml.

Figure 2. Preliminary solubility studies of Atorvastatin



(Table 2 and 3) From this physical mixtures of Mannitol, PEG 4000 in the ratio of 1:1, 1:3, 1:5 and PVP -K30 in the ratio of 1:1:2 and 1:2:2 selected for the preparation of the solid dispersion. Solid dispersions were prepared by both hot melt method and solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis were carried out this is

compared with physical mixtures of the same drug to carrier ratio. The formulation with PEG 4000 in the ratio of 1:5 (drug to carrier) which had increased the solubility almost 2 fold compared to that of pure drug.(Figure 3)

Solid dispersion produced by hot melt methods yield found are, in case of Mannitol dispersion 1:5, PEG 4000 1:5, PVP-K-30 1:2:2 (incase of solvent evaporation)ratio were found to be 89.1% 90.1%, 69% respectively. Drug content of the formulation found to be are in case of Mannitol dispersion 1:5, PEG 40001:5, are 85 and 94.5% respectively were as with PVP K-30 89.03%. Hence with these results PEG 4000 in the ratio of 1:5 selected as optimum formulation.

Table 2. Preliminary solubility studies of Atorvastatin

S no	Carrier (Drug: carrier)	Solubility mg/ml
1	Pure drug	0.21
2	Mannitol 1:1	0.24
3	Mannitol 1:3	0.25
4	Mannitol 1:5	0.27
5	Mannitol 1:10	0.23
6	PEG 4000 1:1	0.31
7	PEG 4000 1:3	0.32
8	PEG 4000 1:5	0.34
9	PEG 40001:10	0.25
10	Urea 1:1	0.23
11	Urea 1:3	0.24
12	Urea 1:5	0.26
13	Urea 1:10	0.23
13	PVP K-30 1:1:2	0.26
14	PVP K-30 1:2:2	0.28

Table 3. Solubility studies of Atorvastatin solid dispersion.

S no	Solid dispersions (Drug : carrier)	Solubility (mg/ml)
1	Mannitol 1:1	0.28
2	Mannitol 1:3	0.33
3	Mannitol 1:5	0.36
4	PVP K-30 1:1:2	0.33
5	PVP K 30 1:2:2	0.36
6	PEG 4000 1:1	0.33
7	PEG 4000 1:3	0.34
8	PEG 4000 1:5	0.39

Table 4. Dissolution Profile of Pure Drug

Time in Minutes	Absorbance	mcg/ml	mcg/10ml	mcg/500ml	Loss	Cumulative Loss	Cumulative Release	Cumulative Percent Release
30	0.004	0.0980	0.98	492.5			0.492	4.92
60	0.009	0.2216	2.216	1108	0.98	0.98	1.108	11.08
90	0.014	0.3448	3.448	1724	2.216	3.201	1.727	17.27
120	0.02	0.4926	4.926	2463	3.448	6.649	2.469	24.69
180	0.033	0.812	8.12	4060	4.926	11.57	4.071	40.71
240	0.045	1.108	11.08	5540	8.12	19.69	5.559	55.59

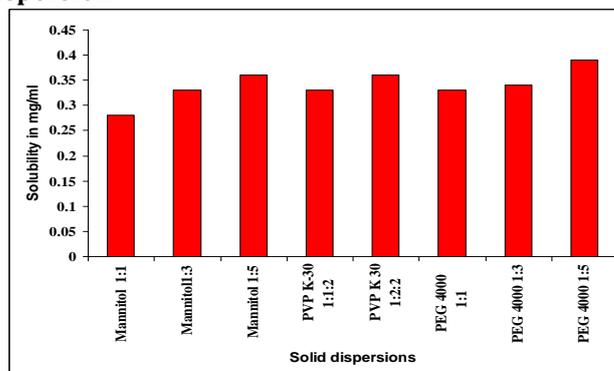
Table 5. Dissolution profile of solid dispersion PVP-K 30

Time in Minutes	Absorbance	mcg/ml	mcg/10ml	mcg/500ml	Loss	Cumulative Loss	Cumulative Release	Cumulative Percent Release
30	0.008	0.197	1.97	985			0.985	9.85
60	0.015	0.3692	3.692	1845	1.97	1.97	1.846	18.46
90	0.021	0.517	5.17	2585	3.692	8.86	2.593	25.93
120	0.028	0.6896	6.896	3448	5.17	14.03	3.462	34.62
180	0.04	0.9852	9.852	4926	6.896	20.92	4.946	49.46
240	0.053	1.305	13.05	6525	9.852	30.772	6.55	65.53

Table 6. Dissolution profile of solid dispersion of Mannitol 1:5

Time in Minutes	Absorbance	mcg/ml	mcg/10ml	mcg/500ml	Loss	Cumulative Loss	Cumulative Release	Cumulative Percent Release
30	0.009	0.221	2.21	1105			1.105	11.05
60	0.016	0.394	3.94	1970	2.21	2.21	1.972	19.72
90	0.025	0.615	6.15	3075	3.94	6.15	3.081	30.81
120	0.032	0.788	7.88	3940	6.15	12.2	3.952	39.52
180	0.043	1.059	10.59	5295	7.88	19.8	5.312	53.1
240	0.057	1.403	14.03	7015	10.59	31.3	7.046	70.46

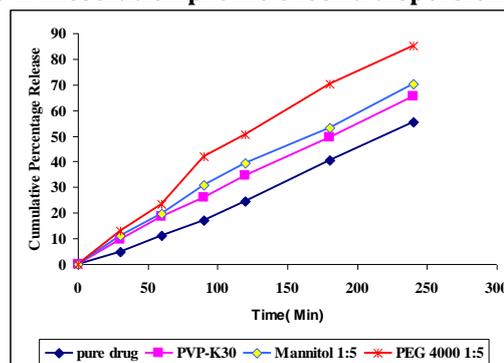
Figure 3. Solubility studies of Atorvastatin solid dispersion



Dissolution study

Dissolution profiles of the atorvastatin particles and solid dispersions shown in Figure 4.

Figure 4. Dissolution profile of solid dispersion



The rate of dissolution was found to be increased in all the solid dispersions as shown by time taken for 50% ($t_{50\%}$) of drug to be released. Solid dispersion prepared with PEG 4000 showed fastest release with $t_{50\%}$ of 116 minutes. While mannitol and PVP K-30 dispersions had $t_{50\%}$ of 144 and 188 minutes respectively. Where as pure drug had taken 228 minutes. Thus it was observed that solid dispersion of PEG 4000 in 1:5 drug to carrier ratio had maximum solubility of Atorvastatin with enhanced dissolution rate. (Table 4, 5, 6, 7, 8 and 9)

Table 7. Dissolutions profile of solid dispersion of peg 4000 1:5

Time in Minutes	Absorbance	mcg/ml	mcg/10ml	mcg/500ml	Loss	Cumulative Loss	Cumulative Release	Cumulative Percent Release
30	0.011	0.27	2.7	1350			1.35	13.5
60	0.019	0.467	4.67	2335	2.7	2.7	2.337	23.37
90	0.034	0.837	8.37	4185	4.67	7.37	4.192	41.92
120	0.041	1.009	10.09	5045	8.37	15.74	5.06	50.60
180	0.057	1.403	14.03	7015	10.09	25.83	7.04	70.40
240	0.069	1.699	16.99	8495	14.03	39.86	8.534	85.34

Table 8. Yield obtained in the solid dispersions

S no	Name of the solid dispersion(Drug:carrier)	Theoretical yield (gm)	Practical yield (gm)	Percentage yield (%)
1	Mannitol solid dispersion (1:5)	3	2.8	89.1
2	PVP K 30 (1:2:2)	0.25	0.17	69
3	PEG dispersion dispersion (1:5)	3	2.9	90.1

Table 9. Amount of drug present in the prepared Solid dispersions

S no	Name of the Solid dispersion.(Drug:carrier)	Amount of drug present in 10 mg Equivalent powder (mg)	Percentage of drug content (%)
1	Mannitol solid dispersion (1:5)	8.522	85.00
2	PVP K 30 (1:2:2)	8.903	89.03
3	PEG solid dispersion (1:5)	9.45	94.50

FTIR studies

The prominent peaks of atorvastatin was observed (Figure 5a) the region of 3365.84 cm⁻¹ due to the (-OH stretching), a peak at 3200.12 cm⁻¹ due to the N-H stretching and a peak at 1650 cm⁻¹ observed due to the carbonyl group. At the lower frequencies 1315.36 (C-N stretching), 1108 cm⁻¹ (C-O stretching) 1218 cm⁻¹ for (C-F stretching) observed. PEG 4000 shows the prominent peak at 3431.13 due to the (O-H stretching) (Figure 5b).

Physical mixture (Figure 5c) of the drug and PEG 4000 shows summation of the spectra of the drug and PEG 4000 equivalent to the addition of the spectrum of polymer and drug. This indicates that interaction has occurred with simple physical mixture of drug and polymer. In case of solid dispersion (Figure 5d) of the drug and PEG shows overlapping of O-H and N-H group and broadening of the peak was observed. At the same time peak has shifted toward the higher wavelength 3411.84 may be due to the presence of more number of O-H groups in PEG. However other peaks related to C-H, C-O, C-N, stretching, remain unchanged. This indicates that overall symmetry of the molecule might not be significantly changed (Table 10)

Table 10. Comparison of IR values of pure drug with solid dispersions

Functional groups	Wave number In cm ⁻¹		
	Range	Pure drug	Solid dispersion with PEG 4000
OH	3500-3300	3365.84	3441.84
N-H	3350-3180	3200.12	3440.8
C=O	1680-1630	1650	1652.88
Aliphatic C-H	3000-2800	2966	2887.24
		2923	
C=C	1600-1475	1475	1596.95
		1577	1529.45
			1467.73
C-N	1350-1000	1315.36	1344.29
C-O	1300-1000	1108	1280
		1218	
C-F	1400-1000	1157.21	1112.85

SEM studies

SEM study indicated (Figure 6a) that pure drug particles were irregular in shape, while the physical mixture of the drug and carrier shows that drug particle remains dispersed and physically adsorbed on the surface of the carrier particles. The solid dispersion of Atorvastatin of Atorvastatin and PEG 4000 showed a homogeneous dispersion indicating that the atorvastatin molecules were

dispersed uniformly in carrier matrices of solid dispersion prepared by melting method at 1:5 ratios, assuming amorphous solid dispersion state. (Figure 6b)

Figure 5. FTIR spectra of prue drug , physical mixture and solid dispersion.

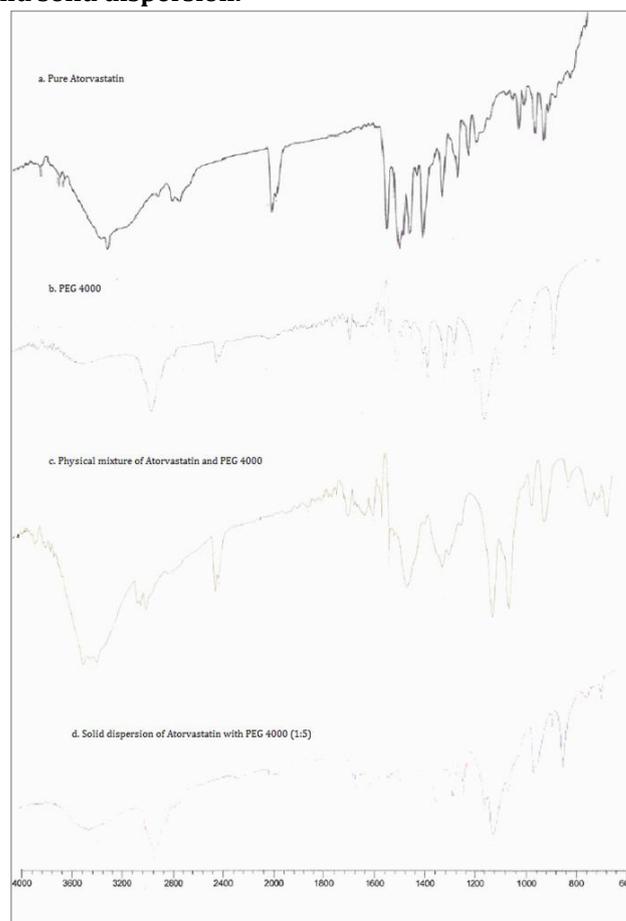
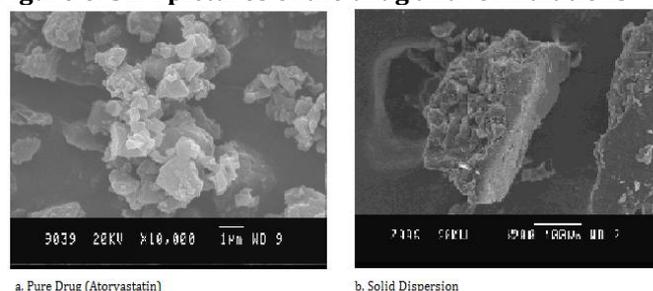


Figure 6. SEM pictures of the drug and formulations



DSC studies

DSC thermo gram of atorvastatin showing (Figure 7a) two endothermic peaks one of which at 151.48°C corresponding to the melting point of Atorvastatin and another at 63.81°C due to loss of water or dehydration. In case of physical mixture (Figure 7b) of Atorvastatin and PEG 4000 systems it has been seen that the persistence of the endothermic peak of atorvastatin as well as PEG 4000. However the drug peak has shifted toward slightly higher temperature with lower intensity. Similarly PEG 4000 (Figure 7c) shows a broad endothermic effect from 40-120°C having a peak at 66.26°C. Solid dispersion of Atorvastatin with drug shows (Figure 7d) no peaks related to atorvastatin, was seen. This indicates that Atorvastatin no longer present in the crystalline form, may have got converted into the amorphous form. It also suggests that atorvastatin appears to be soluble in the liquid phase of PEG 4000.

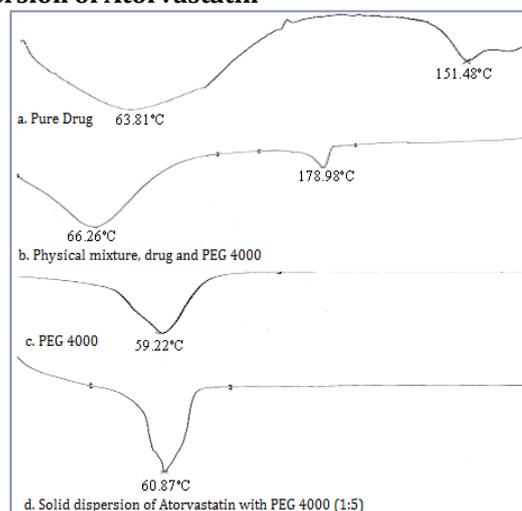
CONCLUSION

Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with mannitol, PEG 4000 and PVP-K30. These solid dispersions were analysed for the solubility and Invitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. In present study solid dispersion prepared with PEG 4000 shows the presence of amorphous form confirmed by the characterization study.

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Figure 7. DSC curve of single components and solid dispersion of Atorvastatin



The study also shows that dissolution rate of Atorvastatin can be enhanced to considerable extent by solid dispersion technique with PEG.

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