Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (8):180-191
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Enhancement of solubility and dissolution of atorvastatin by solid dispersion technique with novel carriers

A. Thirupathaiah*[1,2] and R. Shyam Sunder[3]

[1]*Dept of Pharmaceutical Sciences, OUCT, Osmania University, Hyderabad-500007, Telangana, India*
[2]*Faculty, Dept of Chemistry and Pharmaceutical Sciences, University college of science and Informatics, Mahatma Gandhi University, Nalgonda- 508 254, Telangana, India*
[3]*Faculty of Pharmacy, Osmania University, Hyderabad-500007, Telangana, India*

ABSTRACT

Atorvastatin calcium (ATC) is a selective competitive inhibitor of HMG CoA reductase. However its absolute bioavailability is 14%, to increase the solubility and dissolution of hydrophobic drug (ATC) and to enhance the bioavailability 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 Soluplus, Kolliwax GMS II, Kolliphor P188, Kleptose HPB and PVPK-30 in proportions 1:1 and 1:3 besides SLS as surfactant (0 or 2%) to improving its aqueous solubility and rate of dissolution by solvent evaporation technique. All the formulations showed marked improvement in the solubility behavior and improved drug release. From all the formulations we demonstrated that Kolliwax GMS increases the aqueous solubility of Atorvastatin calcium and hence SD20 was found to be optimized formulation. The optimized formulation SD20 was characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) to ascertain if there were any physicochemical interactions between drug and carrier that could affect dissolution and the change in the nature of the compound. The results obtained showed that the aqueous solubility and rate of dissolution was significantly improved when formulated in solid dispersion as compare to pure drug.

Keywords: Atorvastatin calcium, solid dispersions, Kolliwax GMS II, aqueous solubility

---

INTRODUCTION

There were several ways where bioavailability of the drug can be enhanced, all methods are 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 [1]**.** The enhancement of the bioavailability of poorly water soluble drugs is one of the greatest challenges of drug development. Amongst them is the dispersion of the drug into an inert, hydrophilic polymer matrix. There is general consensus in the pharmaceutical industry that poorly water-soluble drug candidates are becoming more prevalent [2]**.**

Solubility of active pharmaceutical ingredients has also been a concern for formulators, since inadequate aqueous solubility may hamper development of product and limit bioavailability of oral products. Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across the biological membrane; the main pathway for drug absorption is a product of permeability and solubility. Various method have been

reported for solubility and dissolution rate enhancement of BCS class II drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellar solubilization and hydrotropy [3,4].

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability [5]. Solid dispersion was first characterized by Sekiguchi and Obi [6], they noted that the formulation of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water soluble drugs. In the late sixties, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline ones [7].

Several methods are used in solid dispersion preparations, such as hot melt extrusion, supercritical fluid method and solvent evaporation method. The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [8, 9, 10]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [11].

Atorvastatin is a white crystalline powder, molecular formula: $(C_{33}H_{34}FN_2O_5)_2$ $Ca.3H_2O$, molecular weight: 1209.12, bioavalability-12%, and half life: 14h. It is a selective competitive HMG-COA reductase inhibitor drug that lowers the level of cholesterol in the blood and triglyserides in patients with hypercholesterolemia [12]. It belongs to a class of drugs referred to as statins, which includes lovastatin (Mevacor), simvastatin, (Zocor), fluvastatin (Lescol), and pravastatin (Pravachol) and rosuvastatin (Crestor). All statins, including Atorvastatin, prevent the production of cholesterol in the liver by blocking HMG-CoA reductase, an enzyme that makes cholesterol. Statins reduce total cholesterol as well as LDL cholesterol in blood. LDL cholesterol is believed to be the "bad" cholesterol that is primarily responsible for the development of coronary artery disease. Reducing LDL cholesterol levels retards progression and may even reverse coronary artery disease. Atorvastatin also raises the concentrations of HDL ("good") cholesterol that protects against coronary artery disease and reduces the concentration of triglycerides in the blood. (High blood concentrations of triglycerides also have been associated with coronary artery disease.) The FDA approved Atorvastatin in December 1996 [13, 14, 15]**.**

MATERIALS AND METHODS

Materials:
Atorvastatin calcium pure drug was generous gift from Aurobindo Pharma Ltd, Hyderabad, India. Kleptose HPB, Kolliphor P188 and Mannitol were obtained from BASF, Mumbai. Kolliwax GMS, PEG 6000, PEG 4000 were obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. Soluplus were gifted from BASF, Germany. Urea and PVP K-30 and were gifted from Dow Chemicals, USA. All other chemicals used were of analytical grade.

Preliminary solubility studies of Atorvastatin [16]
Solubility measurements of Atorvastatin calcium 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, PEG6000, Soluplus, KolliwaxGMS II, Kolliphor P188, Kleptose HPB, Mannitol, PVPK-30 and PEG4000 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 244nm.

Preparation of Atorvastatin solid dispersion by the solvent evaporation method [17, 18]
The calculated amount of Atorvastatin and the employed polymers (Soluplus, KolliwaxGMS II, Kolliphor P188, Kleptose HPB and PVPK-30) in different drug-polymer ratios (1:1 and 1:3) besides SLS as surfactant (0 or 2%) (Shown in **table 1**) are weighed and mixed together in a porcelain dish. Twenty different formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of methanol as a common solvent. Then the solvent was evaporated in oven at temperature 50ºC till complete evaporation. The solid dispersions prepared were pulverized in a mortar and sieved, the fraction of the powder that passed through 45µm stored in a desicator and used for further investigations.

Table 1: Formulation table for the Atorvastatin solid dispersions

S. No	Ingredients (Units)	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9	SD10
1	Atorvastatin (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
2	PVP K30 (gm)	0.2	0.2	0.6	0.6	-	-	-	-	-	-
3	Soluplus (gm)	-	-	-		0.2	0.2	0.6	0.6	-	-
4	Kolliphor P 188 (gm)	-	-	-	-					0.2	0.2
6	Kleptose HPB (gm)	-	-	-	-	-	-	-	-	-	
7	Kolliwax GMS II (gm)	-	-	-	-	-	-	-	-	-	-
8	SLS (gm)	0%	2%	0%	2%	0%	2%	0%	2%	0%	2%
9	Methanol (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 2: Formulation table for the Atorvastatin solid dispersions

S. No	Ingredients (Units)	SD11	SD12	SD13	SD14	SD15	SD16	SD17	SD18	SD19	SD20
1	Atorvastatin (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
2	PVP K30 (gm)	-	-	-	-	-					
3	Soluplus (gm)	-	-	-	-	-					
4	Kolliphor P 188 (gm)	0.6	0.6	-	-	-					
6	Kleptose HPB (gm)			0.2	0.2	0.6	0.6				
7	Kolliwax GMS II (gm)	-	-					0.2	0.2	0.6	0.6
8	SLS (gm)	0%	2%	0%	2%	0%	2%	0%	2%	0%	2%
9	Methanol (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Solubility studies of Atorvastatin solid dispersion by solvent evaporation method:
Solubility measurements of Atorvastatin were performed according to a published method [17]**.** Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Atorvastatin in UV 244nm.

Evaluation of Atorvastatin solid dispersions
Solid dispersions obtained from the above method were tested for their Physical appearance, % Practical yield, Drug content, FTIR, DSC, SEM study and in-vitro release studies.

Physical appearance
It includes the visual inspection of solid dispersion.

Percentage Practical Yield
Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation [19].

$$\% \text{ Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer + Surfactant)}} \times 100$$

Drug content
Solid dispersions equivalent to 20 mg of Atorvastatin were weighed accurately and dissolved in 100 ml of methanol. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 244 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation as follows [20].

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* Dissolution study of solid dispersion**
The dissolution rate of Atorvastatin calcium as such and from solid dispersions prepared was studied respectively in 900 ml of phosphate buffer pH 6.8 using USP type II (paddle type) dissolution test apparatus with a paddle stirrer at 75 rpm. A temperature 37±5^{o}C was maintained throughout the study. Drug or solid dispersion equivalent to 20 mg of Atorvastatin calcium was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter

(0.45µ) at different intervals of time, suitably diluted and assayed at 244 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid [21].

FTIR studies [22]
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) studies [23]
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.

Stability studies:
Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75%±5%RH and temperature of 40 ^{0}C±2^{0}C for stability studies. Samples were removed after 1, 2, 4 and 6 months, evaluated for % drug content and in vitro dissolution study and compared with those SD tested immediately after preparation [17].

Preliminary solubility studies of Atorvastatin:
In case of solid dispersions initially preliminary solubility analysis was carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility was found to be 2.09µg/ml (**Table 2**). From this study, drug and Kolliwax GMS in the ratio of 1:1 shown highest drug solubility i.e. 15.17 µg/ml, almost 8 fold increased compared to that of pure drug. For all the water soluble carriers used in preliminary solubility studies, PEG 6000,PEG 4000,Mannitol and Urea shown low solubility when compared with other carriers and did not included in the preparation of Atorvastatin solid dispersions. The graphical representation of solubility studies of Atorvastatin physical mixtures was shown in **Figure 1**.

Table 3: Preliminary solubility studies of Atorvastatin in different polymers

Physical Mixture	Solubility (µg/ml)
Pure Drug	2.09±0.04
Drug + Mannitol	2.52±0.13
Drug + Soluplus	9.27±0.003
Drug + Kolliwax GMS II	15.17±0.02
Drug + Kolliphor P188	8.32±0.01
Drug + PEG 6000	3.99±0.04
Drug + Urea	3.41±0.05
Drug + PEG 4000	3.45±0.07
Drug + PVP K 30	4.02±0.11
Drug + Kleptose HPB	5.15±0.13

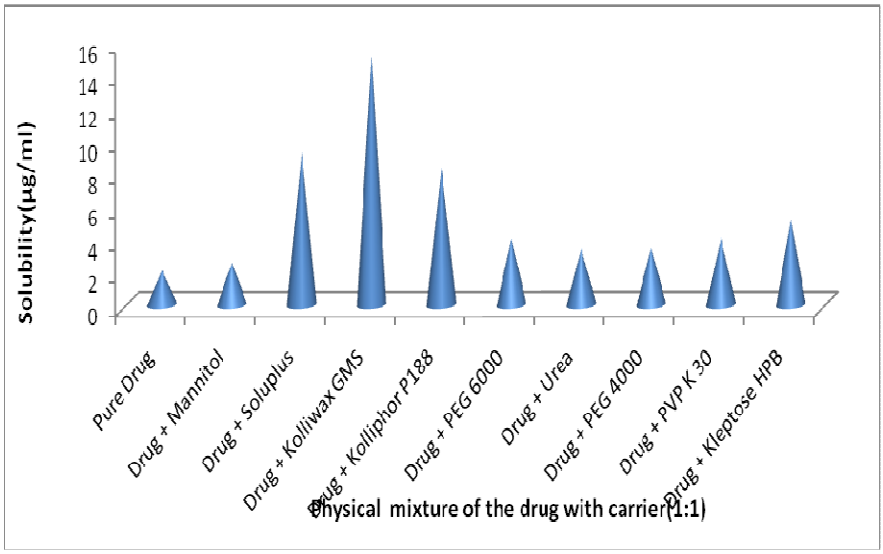

Figure 1: Solubility studies of Atorvastatin physical mixture

Preparation of Atorvastatin solid dispersions

Solid dispersions of Atorvastatin were prepared by using Kolliphor P188, Kolliwax GMS, PVP K 30,Kleptose HPB,and Soluplus in two different drug-polymer ratios (1:1 and 1:3) besides SLS as surfactant (0 or 2%) are weighed and mixed together in a porcelain dish. Twenty different formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of Methanol as a common solvent. Then the solvent was evaporated in oven at temperature 50ºC till complete evaporation. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a 45µm sieve before packing in an airtight container, stored in a desiccator and used for further investigations. In the present investigation 20 formulations were prepared and their complete composition was shown in **Table 1.** All the solid dispersions prepared were found to be fine and free flowing powers.

Figure 2: Atorvastatin Solid dispersions

Evaluation parameters:

Solubility studies of Atorvastatin solid dispersions:

Different formulations of Atorvastatin solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (SD20) with Kolliwax GMS in the ratio of 1:3 and with SLS shown highest solubility i.e.20.05±0.02µg/ml, almost 10 fold

compared to that of the pure drug (Pure drug solubility is 2.09±0.04µg/m**l**). The results are tabulated in **Table 4** and graphical representation was shown in **Figure 3**.

Table 4: Solubility studies of Atorvastatin solid dispersions prepared by solvent evaporation method

S. No.	Formulation code	Solubility (µg /ml)*
1	Pure drug (Atorvastatin)	2.09±0.04
2	SD1	4.99±0.07
3	SD2	5.67±0.13
4	SD3	6.98±0.22
5	SD4	7.77±0.08
6	SD5	10.21±0.02
7	SD6	11.22±0.03
8	SD7	13.01±0.02
9	SD8	14.33±0.04
10	SD9	8.37±0.03
11	SD10	9.16±0.04
12	SD11	10.86±0.01
13	SD12	11.55±0.03
14	SD13	6.26±0.04
15	SD14	8.16±0.03
16	SD15	9.76±0.04
17	SD16	12.56±0.07
18	SD17	15.26±0.02
19	SD18	17.56±0.03
20	SD19	18.42±0.02
21	SD20	20.05±0.02

**Mean±SD, n=5*

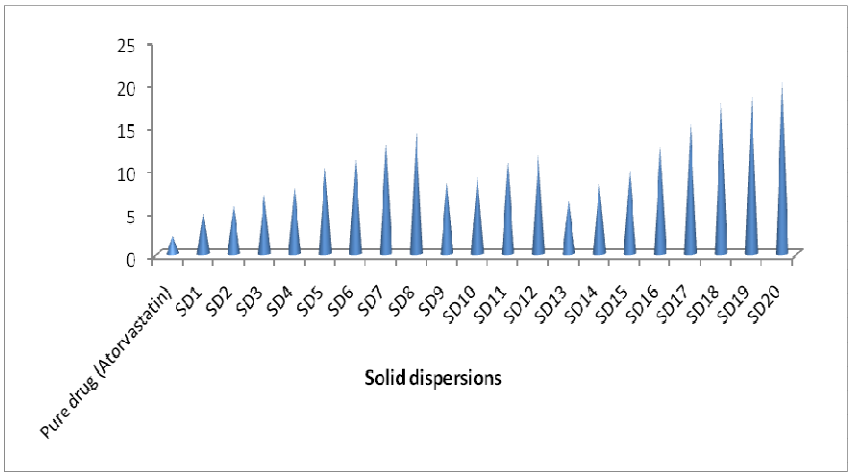

Figure 3: Solubility studies of Atorvastatin solid dispersion

% Practical yield and drug content:

The results of % practical yield for all formulations of solid dispersions found to be 84.88% - 99.13%. The results of % practical yield studies are shown in **Table 5**. Maximum yield was found to be 99.13% in formulation SD20. Actual drug content of all 20 formulations are shown in **Table 5**. The drug content of the prepared solid dispersions was found to be in the range of 87.62 – 99.03%. Maximum % drug content i.e. 99.03% was found in the formulation SD20.

Table 5: % Practical yield and drug content for Atorvastatin solid dispersions

S. No	Formulation	% Practical Yield	% Drug content
1	SD1	95.21	91.47
2	SD2	92.46	94.77
3	SD3	93.68	87.62
4	SD4	84.88	90.33
5	SD5	96.55	92.47
6	SD6	91.68	94.92
7	SD7	91.98	93.50
8	SD8	96.22	94.52
9	SD9	91.87	91.53
10	SD10	94.26	92.56
11	SD11	91.99	94.57
12	SD12	96.12	91.64
13	SD13	91.87	92.43
14	SD14	93.27	89.37
15	SD15	94.26	92.52
16	SD16	94.88	95.08
17	SD17	89.23	91.01
18	SD18	85.23	90.99
19	SD19	86.33	93.88
20	SD20	99.13	99.03

In vitro dissolution studies

The drug release data obtained for formulations SD1-SD20 are tabulated in **Table 6, 7 & 8**. It shows the cumulative percent drug released as a function of time for all formulations. The cumulative percent drug released after 90 min was shown in table.

In vitro studies reveal that there is marked increase in the dissolution rate of Atorvastatin from all the solid dispersions when compared to pure Atorvastatin itself. From the in vitro drug release profile, it can be seen that formulation SD20 containing Kolliwax GMS II (1:3 ratio of drug: Kolliwax GMS II with surfactant) shows higher dissolution rate i.e. 99.0±1.4% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier.The graphical representation of solid dispersions of SD1-SD8, SD9-SD14& SD15-SD20 with pure drug was depicted in **Figures 4, 5 & 6**.

Table 6: In vitro dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD1-SD8)

Time (Min)	Cumulative % drug release								
	Pure drug	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
0	0	0	0	0	0	0	0	0	0
5	2.35 ±0.43	23.5±1.3	25.5±1.3	27.5±1.3	29.5±1.3	26.6±2.9	25.2±3.7	26.6±2.9	23.6±2.9
10	4.18±0.12	33.0±2.4	35.0±2.4	37.0±2.4	39.0±2.4	36.7±3.9	32.6±1.9	41.7±3.9	33.7±3.9
20	6.10±0.36	39.5±3.3	41.5±3.3	45.5±3.3	48.5±3.3	58.8±2.0	44.6±2.5	53.8±2.0	48.8±2.0
30	11.90± 0.73	43.1±2.6	49.1±2.6	51.1±2.6	53.1±2.6	63.4±1.4	56.8±0.55	65.4±1.4	63.4±1.35
45	16.09±0.40	56.0±0.4	58.0±2.2	61.0±2.12	65.0±2.01	77.7±0.8	68.5±0.13	73.7±3.7	72.7±3.6
60	20.93 0.80	61.2±0.03	65.2±0.25	68.2±1.2	69.2±4.3	84.4±2.2	79.9±2.5	83.5±2.9	84.4±2.2
90	24.95±0.64	71.8±1.12	73.8±1.01	75.8±1.22	79.8±1.22	82.6±1.7	85.1±3.8	86.6±1.7	85.6±1.7

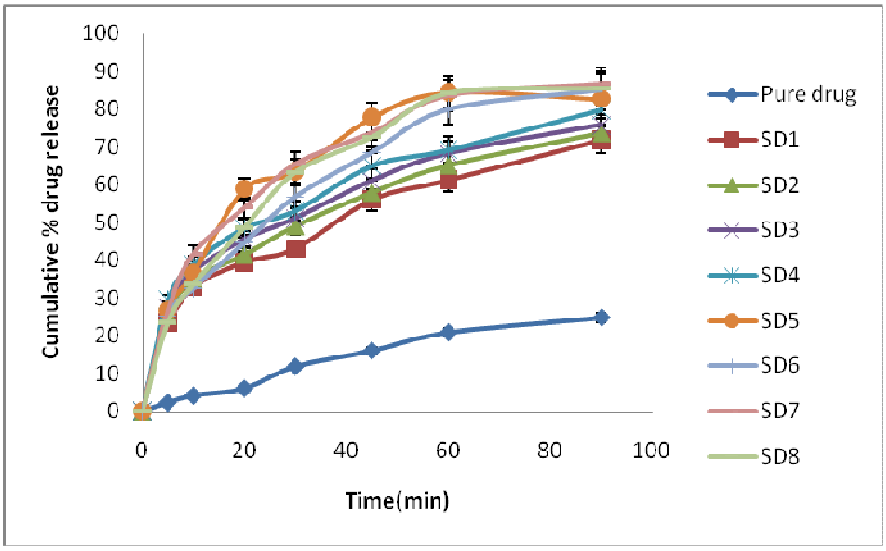

Figure 4: In vitro dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD1-SD8)

Table 7: *In vitro* dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD9-SD14)

Time in Min	Cumulative % drug release					
	SD9	SD10	SD11	SD12	SD13	SD14
0	0	0	0	0	0	0
5	20.6±2.9	22.6±2.9	26.8±2.0	30.3±2.5	23.3±3.4	26.4±2.9
10	31.7±3.9	32.7±3.9	30.3±2.9	36.9±1.5	31.2±1.4	33.8±2.3
20	50.8±2.0	44.8±2.0	46.5±3.3	48.5±2.7	43.3±2.3	39.5±1.6
30	61.4±1.4	58.4±1.4	55.5±3.8	58.2±2.6	59.1±2.9	45.8±1.8
45	70.7±3.8	69.7±3.8	65.5±1.9	68.5±2.2	63.2±1.4	59.5±1.7
60	81.4±2.2	78.4±2.2	72.9±3.3	79.3±2.9	77.5±3.6	69.9±1.8
90	84.6±1.7	87.6±1.7	89.4±3.1	92.5±2.8	82.8±3.3	84.2±1.2

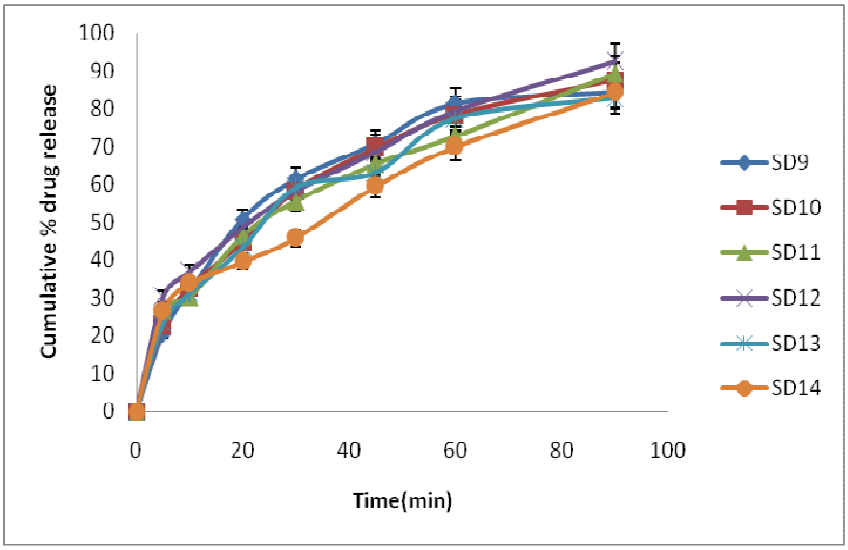

Figure 5: In vitro dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD9-SD14)

Table 8: In vitro dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD15-SD20)

Time in Min	Cumulative % drug release					
	SD15	SD16	SD17	SD18	SD19	SD20
0	0	0	0	0	0	0
5	25.5±1.3	21.5±1.3	26.6±2.9	23.4±2.9	21.5±1.3	40.1±2.3
10	31.0±2.4	31.0±2.4	36.7±3.9	28.8±2.3	31.0±2.4	59.2±2.8
20	35.5±3.3	32.5±3.3	58.8±2.0	31.5±1.6	32.5±3.3	68.5±2.2
30	39.1±2.6	41.1±2.6	63.4±1.4	32.8±1.8	33.1±2.6	77.2±2.3
45	46.0±2.4	45.0±2.4	77.7±3.8	37.5±1.7	36.0±2.4	89.4±3.0
60	66.2±4.3	68.2±1.5	84.4±2.2	41.9±1.8	41.2±4.3	96.6±1.6
90	87.8±2.1	91.8±3.4	90.6±1.7	91.2±1.2	94.8±3.4	99.0±1.4

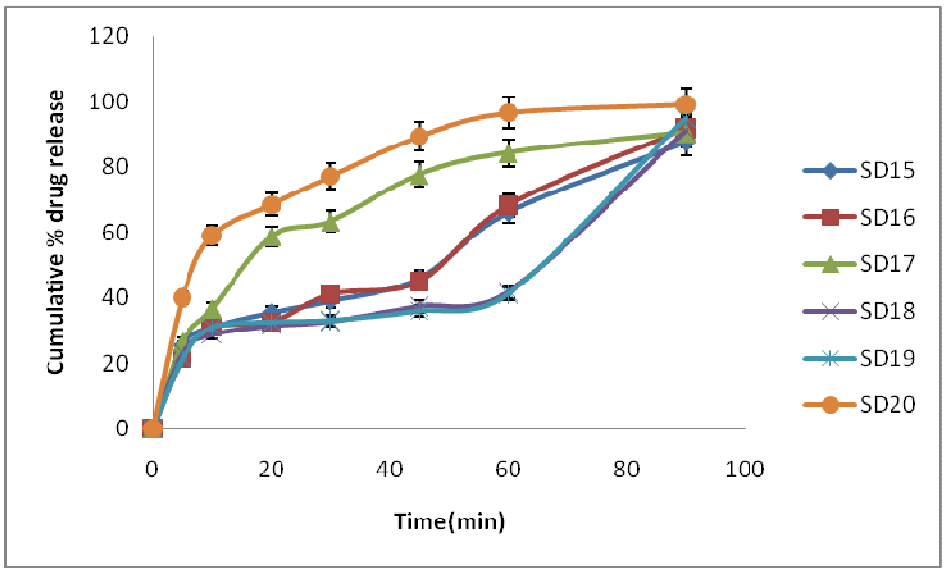

Figure 6: In vitro dissolution profile of pure drug and different formulations of Atorvastatin solid dispersions (SD15-SD20)

Stability studies:

Optimized formulation (SD20) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months at Accelerated stability conditions according to ICH guidelines. To evaluate the physical state of the drug, the systems were evaluated for drug content, In vitro drug release profile and characterized by XRD after storage for 6 months. The systems were stable during a 6-month period. From these results it was concluded that, optimized formulation (SD20) is stable and retained their original properties with minor differences which depicted in **Table 9.**

Table 9: Evaluation parameters of optimized formulation (SD20) stored at 40 ±2^{0}c /75 ±5%rh

Retest time for optimized formulation	% Drug content	*In-vitro* drug release (%)
0 days	99.03	99.21
30 days	97.29	98.45
60 days	96.75	97.51
120 days	95.05	96.35
180 days	94.52	96.05

FTIR studies:

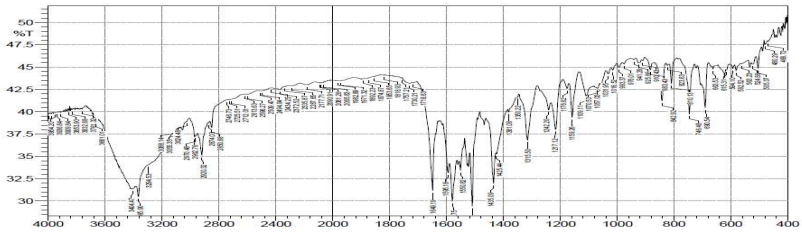

Figure 7: FTIR Spectrum of Atorvastatin pure drug

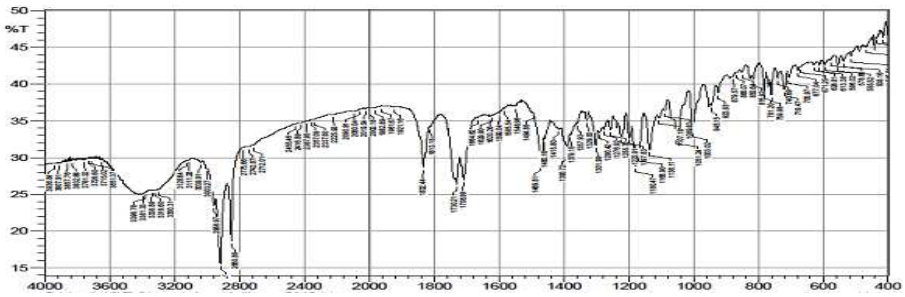

Figure 8: FTIR Spectrum of Kolliwax GMS II

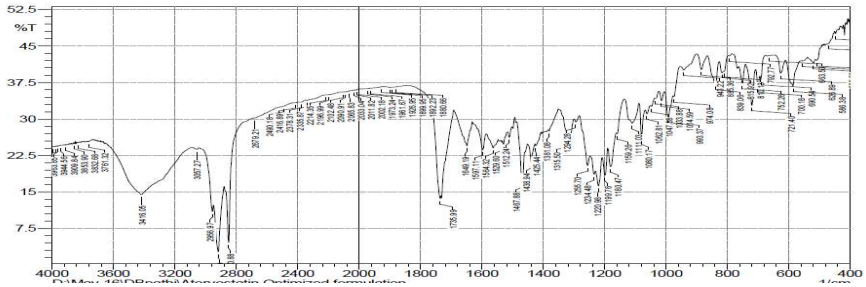

Figure 9: FTIR Spectrum of Atorvastatin optimized formulation (SD20)

The FTIR spectra of pure atorvastatin calcium showed characteristic peaks at 2955.15 cm $^{-1}$ 310 (C-N-stretching), 3059.15 cm $^{-1}$(C-H-stretching), 1313.56 cm $^{-1}$ (C-HO-stretching alcoholic group), 1564.97 cm $^{-1}$ (C=O-stretching amidic group), 3403.27 cm $^{-1}$ (N-H-stretching), 1656.97 cm $^{-1}$ (C=C-bending), 751.62 cm $^{-1}$ 696.95 cm $^{-1}$ (C-F-stretching), 1104.39 cm $^{-1}$ (O-H-bending). It might be the possibility of intermolecular hydrogen bonding between adjacent atorvastatin calcium molecules. The spectrum of pure atorvastatin calcium was equivalent to the spectra obtained by the optimized formulation (SD20) (**Figures 7, 8 and 9).**

X-Ray Diffraction patterns:

The Atorvastatin calcium solid dispersions were analyzed in Bruker D8 advanced PXRD instrument to find out whether the solid dispersions of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Atorvastatin indicates that Atorvastatin was present as a crystalline material (**Figure10**). On the other hand, the spectrum of optimized formulation SD20 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (**Figure 11**). The enhancement in the dissolution rate of the drug from the drug-Kolliwax GMS II solid dispersion is ascribed to the marked reduction in the crystallinity of the drug.

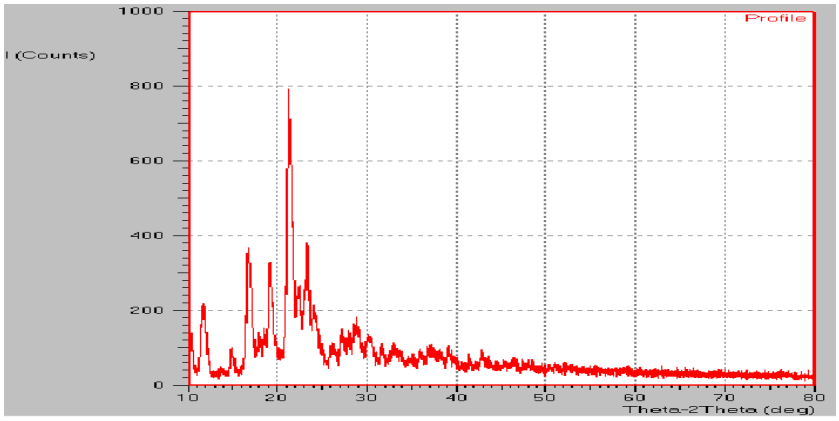

Figure 10: X-Ray powder diffractogram of Atorvastatin pure drug

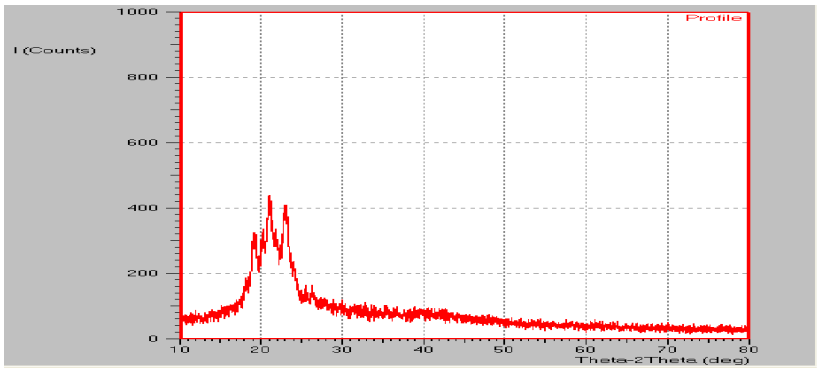

Figure 11: X-Ray powder diffractogram of Atorvastatin optimized formulation (SD20)

SEM Studies:

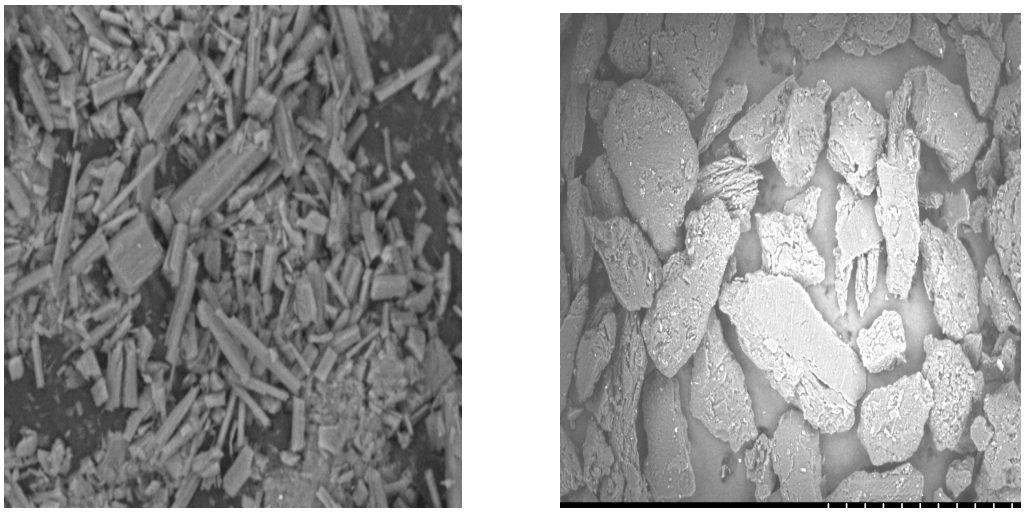

Figure 12: Pure drug of Atorvastatin and Atorvastatin optimized formulation (SD20)

SEM photographs for pure drug and optimized formulation SD 20 are shown in **Figures 12** the drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be

incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

CONCLUSION

In the present study it was clearly demonstrated that solid dispersion formulation can be effectively produced by processing via solvent evaporation method with enhanced solubility and dissolution rate. Novel polymer–surfactant combinations were optimized and stable SD systems were developed successfully. Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with Soluplus, Kolliwax GMS II, Kolliphor P188, Kleptose HPB and PVPK-30.Utilization of Kolliwax GMS along with suitable surfactants offers excellent possibilities to develop stable amorphous solid dispersion.

Drug content analysis and in vitro dissolution study of Kolliwax GMS is most preferably used for solubility and dissolution enhancement than other polymers. FT-IR studies shows there was no degradation of drug. The solubility and dissolution studies showed there is a possibility of improved solubility of ATC through solid dispersion with Kolliwax GMS.

Analysis of X-ray diffraction showed that Atorvastatin existed in the amorphous form within the solid dispersion formulation fabricated using the solvent evaporation process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Atorvastatin to an amorphous form. Finally it could be concluded that solid dispersion of Atorvastatin using novel carriers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

REFERENCES

[1] B D Shewale; N P Sapkal; N Al Raut; *Indian J Pharm Sci*, ***2008***; 70(2): 255–257
[2] V. Monika Sharma; G Rajeev Garg; D. Gupta; J Pharm Sci Innov, **2013**; 2(4): 73-81
[3] C. Ravindran; *Der Pharmacia Sinica*, **2011**; 2 (4): 218-240.
[4] Y. Thorat; Gonjari I; Hosmani A; *Inter j of pharma sciences and res*, **2011**; 2(10): 2501-2513.
[5] QMD Craig; *Int J Pharm*, **2005**; 231: 131–144.
[6] K Sekiguchi; N Obi; *Chem. Pharm. Bull*, **1961**; 9: 866-72.
[7] T Vilhelmsen; H Eliasen; T Schæfer; *Int. J. Pharm*, **2005**; 303:132–142
[8] S Hasegawa; T Hamaura; N Furuyama; A Kusai; E Yonemochi; K Terada; *Int. J. Pharm*, **2005**; 302: 103–112.
[9] GR Lloyd; DQ Craig; A Smith; *Eur. J. Pharm. Biopharm*, **1999**; 48: 59 65
[10] E Rodier; H Lochard; M Sauceau; JJ Letourneau; B Freiss; J Fages; *Eur. J. Pharm. Sci*, **2005**; 26: 184–193.
[11] DH Won; MS Kim; S Lee; JS Park; SJ Hwang; *Int. J. Pharm*, **2005**; 301:199–208.
[12] TripathiKD. Essentials of medical pharmacology.6th ed, Jaypee Brothers Medical Publications. New delhi : (IND) **2008**:460-62.
[13] Indian Pharmacopoeia, 5th Ed., Ghaziabad; the Indian Pharmacopoeia Commission: **2007**; 2: 131-134.
[14] K. R Bobe; C R Subrahmanya; Sarasija Suresh; D T Gaikwad; M D Patil; T S Khade; Bm Gavitre; V S Kulkarni; U T Gaikwad; *Inter J Of Comprehensive Pharmacy*, **2011**;1(2): 1-6.
[15] R Kishor; Rajmalle, Mohmed Zameerruddin Jadhav; S.B Kadam; V.S Bharkad; V.B., *World J of Pharmacy and Pharma Sci*, **2014**; 3(06): 534-544.
[16] C.V.S. Subrahmanyam; Textbook of Physical Pharmaceutics, 2nd Ed., Vallabh Prakashan, **2009**, 215-227
[17] T Higuchi; Connors K; *Adv Anal Chem Instrum*, **1965**; 4:117-212.
[18] K Dhirendra; S Lewis; N Udupa; *Pak. J. Pharm. Sci*, **2009**; 22(2): 234-246.
[19] K Lakshmi; M. Pranav kumar reddy; Rajesh kaza; *Inter J of Innovative Pharma Research*, **2012**; 3(4): 247-251.
[20] Shingala ketan; Chetan singh chauhan; Deepak dumaniya; *Journal of Pharma sci and Bio sci Res*, **2013**; 3 (2):77-90.
[21] H Valizadeh; A Nokhodchi; N Qarakhani; *Drug Dev Ind Pharm*, **2004**; 30(3):303-17.
[22] M Yang; P Wang; CY Huang; *Int J Pharm*, **2010**; 395(1-2):53-61.
[23] Breitenbach; *J. Eur J Pharm Biopharm*, **2002**; 54: 107–117.