CODEN: WJAPAC Impact Factor: 3.87 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 2, Issue 3. Page: 26-36 Research Article www.wjaps.com

FORMULATION AND CHARACTERIZATION OF ATORVASTATIN SOLID DISPERSIONS FOR IMPROVED BIOAVAILABILITY

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How to cite this Article Manju Singh, Richa Sharma and Vijay Kumar (2025). FORMULATION AND CHARACTERIZATION OF ATORVASTATIN SOLID DISPERSIONS FOR IMPROVED BIOAVAILABILITY. World Journal of Advance Pharmaceutical Sciences, 2(3), 26-36.

Article Info

Article Received: 04 July 2025,

Article Revised: 24 July 2025,

Article Accepted: 14 August 2025.

DOI: https://doi.org/10.5281/zenodo.17010503

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ABSTRACT

Solid dispersions (SDs) of atorvastatin (ATS) using PEO-PPO block copolymer resulted in the formation of an amorphous product with enhanced dissolution and bioavailability. Solubility enhancement was observed in the presence of selected carriers and it increased with the increase in concentration of carriers. The carrier and the active ingredient are dissolved in a suitable organic solvent is evaporated to an elevated temperature or under vaccum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule The accumulative solubility of atorvastatin (ATS) from PEO- PPO block copolymer (Poloxamer 188) was found to be superior from glyceryl monostearate and PEG 4000 carriers due to increased content which played major role in solubility enhancement thus improving dissolution rate of SD2 batch with maximum drug release (98.08 %) in 120 minutes. The optimized SDs were characterized by saturation solubility study, drug content, in vitro dissolution, fourier transform infra-red spectroscopy, scanning electron microscopy, and x-ray diffraction. Capsules containing optimized SDs were prepared and compared with marketed brand (LIPITOR®). Finally it can be concluded that optimized SDs of ATS ameliorate the solubility and dissolution of drug. Since the batch SD2 elicited superior results, it can be proposed as good candidate for systemic product development.

KEYWORDS: Atorvastatin, Solid dispersions, Poloxamer 188, Solubility enhancement, *In-vitro* dissolution.

INTRODUCTION

The therapeutic efficacy of oral pharmaceutical agents is often compromised due to their poor aqueous solubility, a prevalent challenge especially among the Biopharmaceutical Classification System (BCS) class II drugs. One such compound is Atorvastatin calcium, a widely prescribed antihyperlipidemic agent used in the management of hypercholesterolemia and prevention of cardiovascular diseases. Atorvastatin exhibits low oral bioavailability approximately 14% primarily due to its limited solubility in gastrointestinal fluids and significant first-pass metabolism.[1,2] Enhancing the solubility and

dissolution rate of Atorvastatin is, therefore, imperative for improving its bioavailability and therapeutic performance. Among the various approaches investigated for solubility enhancement, the preparation of solid dispersions has emerged as a promising and efficient technique. Solid dispersions involve dispersing the poorly soluble drug in an inert hydrophilic carrier matrix, typically in the amorphous or microcrystalline state, leading to increased surface area, wettability, and reduced particle size of the drug, which in turn facilitates improved dissolution.[3,4]

Solid dispersions can be classified based on the physical state of the drug and the method of preparation, such as eutectic mixtures, glass solutions, and amorphous precipitations in crystalline carriers. Hydrophilic carriers such as polyethylene glycols (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and other synthetic polymers are frequently employed due to their solubilizing capabilities and compatibility with a wide range of drugs. The method of preparation such as solvent evaporation, melt extrusion, spray drying, and fusion also plays a critical role in determining the physicochemical and functional properties of the final solid dispersion system. For this study, the solvent evaporation method was chosen owing to its simplicity, low processing temperature, and ability to produce a molecularly dispersed drug within the carrier matrix. By using this method, Atorvastatin was incorporated into different hydrophilic carriers to create solid dispersions aimed at enhancing its aqueous solubility and subsequent dissolution profile.[5,6]

The characterization of the prepared solid dispersions was critical to confirm the successful dispersion of Atorvastatin in the carrier matrix and to evaluate the changes in its physicochemical properties. Various analytical techniques, including differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM), were employed to assess the thermal behavior, drug-carrier interactions, crystalline to amorphous transformations, and surface morphology, respectively.[7,8] However, one of the most crucial analytical tools for evaluating the extent of drug release and solubility is ultraviolet-visible (UV-Vis) spectroscopy, which provides a rapid and non-destructive method for quantifying the concentration of the drug in dissolution and solubility studies. UV-Vis spectrophotometry is particularly advantageous due to its ease of operation, reproducibility, cost-effectiveness, and sensitivity for drugs like Atorvastatin, which exhibit characteristic absorbance in the UV region. In this study, Atorvastatin was detected at a specific wavelength of maximum absorbance (λmax) identified using a UV spectrophotometer, and the standard calibration curve was developed over a concentration range suitable for solubility studies.[9] The absorbance values were recorded, and linear regression analysis was conducted to determine the linearity, correlation coefficient (R^2), and other validation parameters, ensuring accuracy and reliability of the method.[10]

The UV analysis was not only instrumental in quantifying the amount of Atorvastatin solubilized from different solid dispersions but also in comparing the solubility enhancement relative to the pure drug and physical mixtures. The UV method also facilitated real-time monitoring of dissolution studies, which were conducted in simulated gastric and intestinal fluids to mimic physiological conditions.[11–14] The use of UV spectroscopy further enabled detection of subtle differences in release profiles across various formulations, providing insights into the influence of carrier type, drug-to-polymer ratio, and preparation method on drug release behavior. Additionally, the spectral analysis helped to confirm the absence of degradation or interaction products, as no significant shift in λmax was observed, indicating chemical compatibility between Atorvastatin and the carriers used. Thus, UV spectroscopy played a dual role in both the development and validation of the formulation and in the post-formulation evaluation process, providing a comprehensive analytical foundation for the study.[15]

The present study holds particular significance in the realm of formulation sciences due to the persistent challenge associated with formulating poorly soluble drugs like Atorvastatin. By focusing on solid dispersion techniques with judicious selection of hydrophilic carriers and an optimized solvent evaporation method, this research aims to bridge the gap between poor drug solubility and desired pharmacological outcomes.[12] Furthermore, the study incorporates detailed physicochemical characterization and robust analytical validation, thereby ensuring that the improvements in solubility and dissolution translate into potential bioavailability enhancement.[16] The novelty of this investigation lies in its systematic evaluation of multiple formulation variables, including the type and ratio of carrier polymers, which are often overlooked in conventional formulations. Additionally, the combination of solvent evaporation with precise analytical quantification using UV-Vis spectroscopy offers a reproducible and scalable pathway for pharmaceutical development. This approach may serve as a model platform for other BCS class II drugs facing similar biopharmaceutical limitations.[17]

The study is also distinctive in its comprehensive approach, integrating formulation science with analytical chemistry and material characterization. By doing so, it not only advances our understanding of solid dispersion mechanisms but also provides a viable alternative to conventional dosage forms of Atorvastatin. Given the increasing prevalence of hyperlipidemia and the need for patient-centric formulations with enhanced bioavailability, such research initiatives carry profound implications for both clinical practice and

pharmaceutical innovation.[18] Moreover, this work can significantly contribute to future formulation design by setting a precedent for the integration of solubility enhancement strategies with advanced analytical techniques. In conclusion, the preparation, characterization, and evaluation of solid dispersions containing Atorvastatin, as presented in this study, reflect a meaningful stride toward overcoming solubility-related challenges and optimizing oral drug delivery systems for maximum therapeutic efficacy.

MATERIALS AND METHODS

Materials

Atorvastatin USP was procured as a gift sample from MARS Healthcare Pvt. Ltd., Delhi, India, Poloxamer 188, Polyethyleneglycol 4000, Glyceryl monostearate, Glyceryl monostearate, Potassium bromide, purchased from General Import Co.(INDIA) Pvt. Ltd. Mumbai, Ethanol purchased from Ra Chem Enterprises Pvt. Ltd. Delhi, Methanol purchased from Fisher Scientific India Pvt. Ltd, obtained from HR institute of pharmacy, Utter Pradesh, Sodium Hydroxide, Potassium Dihydrogen orthophosphate, Concentrated Hydrochloric acid and Disodium hydrogen orthophosphate purchased from General Import Co.(INDIA) Pvt. Ltd. Mumbai.

Melting point determination

A small quantity of atorvastatin was filled in the capillary tube sealed at one end and kept it in melting point apparatus. The melting point was recorded and compared with literature value.[19]

UV spectrophotometric studies

10 mg of atorvastatin was dissolved in 100 ml of phosphate buffer pH 6.8 and from this 3 ml solution was pipetted out into a 10 ml volumetric flask. The volume was made up to 10 ml with distilled water (30 µg/ml). This solution was scanned in the range of 200 – 400nm in basic spectrum mode. λmax was recorded and compared with literature value.[11]

Preparation of calibration curve

Stock solution was prepared by accurately weighing 10 mg of atorvastatin and dissolved in phosphate buffer of (pH 6.8) in a 100 ml volumetric flask. From the stock solution 0.3, 0.6, 0.9, 1.2 and 1.5 ml was pipetted out and transferred to 10 ml volumetric flasks. The volume was then made up to 10 ml with respective media to prepare the final concentrations from (3–15) µg/ml.[20]

Saturation solubility study of pure drug

Excess amount of drug (20 mg) was added to three different 25 ml conical flasks, each containing 10 ml of distilled water (pH 5.86), 0.1 N HCl (pH 1.25), and 0.2 M phosphate buffer (pH 6.8). Flasks were placed in a mechanical shaker at 37 ± 5 ℃ for 72 hours. At the end of 72 hrs samples were filtered through the whatman filter paper. One ml of filtered samples were suitably diluted and analyzed at 247nm.[21]

Solubility study of pure drug with different concentration of carriers

Excess amount of drug (20 mg) was added to four different 25 ml conical flasks containing varying strength of poloxamer 188, glyceryl monostearate, PEG 4000 (0.25%, 0.5%, 0.75%, 1%) and 10 ml of distilled water (pH 5.86). Then flasks were placed in a mechanical shaker at 37 ± 5℃ for 72 hours. At the end of 72 hrs. Samples were filtered through the whatman filter paper. One ml of filtered samples were suitably diluted and analyzed at 247nm. Similar procedure was followed for glyceryl monostearate and PEG 4000.[22]

Preparation of solid dispersions

Physical Mixture

The physical mixtures of drug and carrier in 1:2, 1:4 and 1:6 molar ratio was obtained by mixing individual components that had previously been sifted (75-150µm) together with a spatula.[23]

Solvent evaporation method

The carrier and the active ingredient are dissolved in a suitable organic solvent is evaporated to a elevated temperature or under vaccum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. The solvent based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule and followed by removal of solvent by evaporation resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal formulation and dissolution properties. First of all 500 mg drugs were weighed and taken in vials and then polymers were added to it after proper weighing. Then the drug-polymer powders are mixed well physically and to these drug-polymer physical mixtures, solvent was added. Methanol was used as solvent for all the drugs except spironolactone; where acetone was used instead of methanol, as solubility of this drug in methanol was not up to mark. Solvent was added starting from a minimum amount and each time 0.5 ml of solvent was added to the existing content; i.e. 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml and so on if necessary. After adding each fraction of the solvent sonication was performed in sonicator to avoid excess addition of solvent. Solvent was being added until uniform and clear dispersion was achieved. As the boiling point of the solvent is low, it was easily evaporated by keeping the vials below dryer. After evaporation of the solvent vials were kept in desiccator for 48 hours. Finally formulations were withdrawn from vial, crushed in mortar and pestle and passed through 30 micron sieve. The samples were then ready for dissolution testing.[24]

Determination of Drug Content

10 mg of each solid dispersions were accurately weighed and dissolved in 10 ml of volumetric flask with

phosphate buffer (pH 6.8). One ml of sample was diluted with phosphate buffer (pH 6.8) up to 10 ml and assayed spectrophotometrically for atorvastatin at 247 nm using calibration curve based on standard solutions in phosphate buffer (pH 6.8). Results are expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in solid dispersions vs initially added amount). The studies were conducted in triplicate.[20]

***In Vitro* drug release**

In vitro dissolution of solid dispersions was performed using USP Type Apparatus II in 900 ml of phosphate buffer (pH 6.8) at an agitation rate of 75 rpm. The temperature of medium was maintained at 37 ± 0.5oC. 10 mg of drug or its equivalent weight of the prepared solid system was taken and analyzed for dissolution. A 5.0 ml sample was withdrawn at specific time points over a 2 hour period and equal volume of fresh dissolution medium was used to maintain a constant volume. Similarly in-vitro dissolution of the physical mixtures corresponding to the optimized formulations from each group was also carried out.[20]

Evaluation of solid dispersions

Micromeritic Studies

Bulk Density

Both loose (poured) bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of sample (5 gm) from each formulation was transferred in to a 25 c.c measuring cylinder. The initial volume of packing was recorded. The measuring cylinder was then tapped 100 times and the tapped volume of packing was recorded. LBD and TBD was calculated by the following formulas.[15]

$$LBD\ (Loose\ bulk\ density) = \frac{Weight\ of\ solid\ dispersions}{Volume\ of\ packing}$$

$$TBD\ (Tapped\ bulk\ density) = \frac{Weight\ of\ solid\ dispersions}{Volume\ of\ packing}$$

Angle of Repose (θ)

The frictional forces in solid dispersions can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Angle of repose (θ) of different formulations was determined by a fixed funnel method. The solid dispersions were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap formed by using the following equations.[15]

$\tan \theta = h/r$

$\theta = \tan\text{-}1\ (h/r)$

Where θ = Angle of repose

h = height of pile,

r = radius of pile

Compressibility index

It is indirect method of measuring powder flow, cohesiveness and particle size. The percentage compressibility of granules is direct measure of the potential bridge strength and was determined by using the following formula.[15]

$$Carr's\ compressibility\ index\ (\%) = \frac{(TBD - LBD)}{TBD} \times 100$$

Hausners Ratio

Hausners ratio (packing factor) is related to interparticle friction and used to predict the flow properties. Husners ratio was calculated as the ratio of bulk density after tapping to bulk density before tapping.[15]

$$Hausners\ ratio = \frac{TBD}{LBD}$$

CHARACTERIZATION OF SOLID DISPERSION SYSTEMS

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra were obtained using a shimadzu FTIR-8400 spectrometer (Shimadzu, Japan). The sample of pure drug, physical mixture, carrier and SD2 were previously ground and mixed thoroughly with KBr, an infrared transparent matrix. The KBr disks were prepared by compressing the powder. The 4 scans were executed at a resolution of 1cm-1 (from 4000- 400 cm-1).[15]

Scanning Electron Microscopy (SEM)

The surface morphology of pure drug, physical mixture, carrier and SD2, B were examined by Scanning Electron Microscope. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 15 Kv. 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.[11,12]

RESULTS AND DISCUSSION

Drug Identification Tests

The results of various identification tests carried out for atorvastatin are summarized in Table 1. All these tests confirm the identity and purity of atorvastatin and comparison of the experimental values with the literature values authenticated the study (U.S.P, 2004).

Table 1: Comparative values of respective parameters used to identify the drug.

Methods	Experimental value	Literature value
Melting point determination UV Spectrophotometric study Phosphate buffer pH 6.8	159 - 160^{0}C 247 nm	159.2-160.7^{0}C 248 nm

Calibration Curve

Calibration curve of atorvastatin in a concentration range from 3 – 15 mcg/ml was prepared in phosphate buffer pH 6.8.[15] The absorbance values of the respective concentrations are presented in Table 2 and the calibration curve is presented in Figure 1.

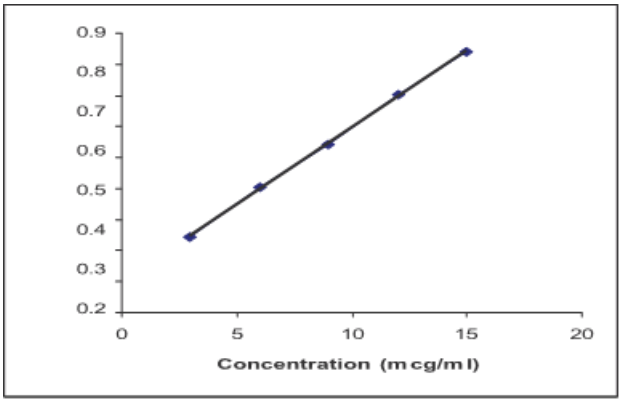

Figure 1: Calibration curve of atorvastatin in phosphate buffer pH 6.8.

Table 2: Calibration curve data of atorvastatin in phosphate buffer pH 6.8.

S. No.	Concentration (mcg /ml)	Absorbance* ± S.D	± C.V.
1	3	0.245 ± 0.002	0.816
2	6	0.402 ± 0.002	0.497
3	9	0.544 ± 0.003	0.551
4	12	0.703 ± 0.006	0.853
5	15	0.842 ± 0.008	0.95

* All values are expressed as mean ± S.D., n =5

Saturation Solubility Study

Saturation Solubility Study of Atorvastatin

Measurement of the concentration of drug in the test solutions was determined using spectrophotometer at 247 nm and the data is presented in Table 3. The saturation solubility studies indicated that the drug was practically insoluble in water (less than 100µg/ml) and with increase in pH the solubility of the drug increased. Atorvastatin is weakly acidic drug hence showed low solubility in acidic pH however the solubility of drug increased as the pH increased due to ionization of the drug at higher pH and highest value observed at pH 6.8 was used for analytical purpose.[5]

Table 3: Saturation solubility study of atorvastatin at 37±0.50C.

S. No	Media	Solubility*± S.D (mg/ml)
1	Phosphate buffer, pH 6.8	0.191 ± 0.002
2	0.1 N HCl, pH 1.25	0.100 ± .005
3	Distilled water, pH 5.86	0.128 ± 0.003

Saturation solubility study of atorvastatin with different concentration of carriers

The results of saturation solubility studies of atorvastatin in the presence of Poloxamer 188, Glyceryl monostearate, PEG 4000 in distilled water at 370C are shown in Table 3.5. Solubility enhancement was observed in the presence of selected carriers and it increased with the increase in concentration of carriers. Solubility enhancement was found to be in the order Poloxamer 188>Glyceryl monostearate>PEG 4000. The superior increment of solubility might due to increased oxyethylene content which played major role in solubility enhancement and a sharp increase at 0.75% w/v may be due to formation of micelles. Hence, the results showed that among all the three carriers, atorvastatin displayed maximum solubility with Poloxamer 188.[25]

Table 4: Saturation solubility study of atorvastatin in the presence of different concentration of carriers at 37±0.50c.

S. No	Concentration (%w/w)	Poloxamer 188	Glyceryl Monostearate	PEG 4000
1	0	0.132±0.003	0.123±0.003	0.00±0.003
2	0.25	0.159±0.003	0.169±0.004	0.002±0.003
3	0.5	0.192±0.002	0.171±0.005	0.024±0.002
4	0.75	0.197±0.004	0.187± 0.002	0.046± 0.001
5	1	0.244±0.005	0.209± 0.001	0.069± 0.002

All values are expressed as mean ± S.D., n = 5

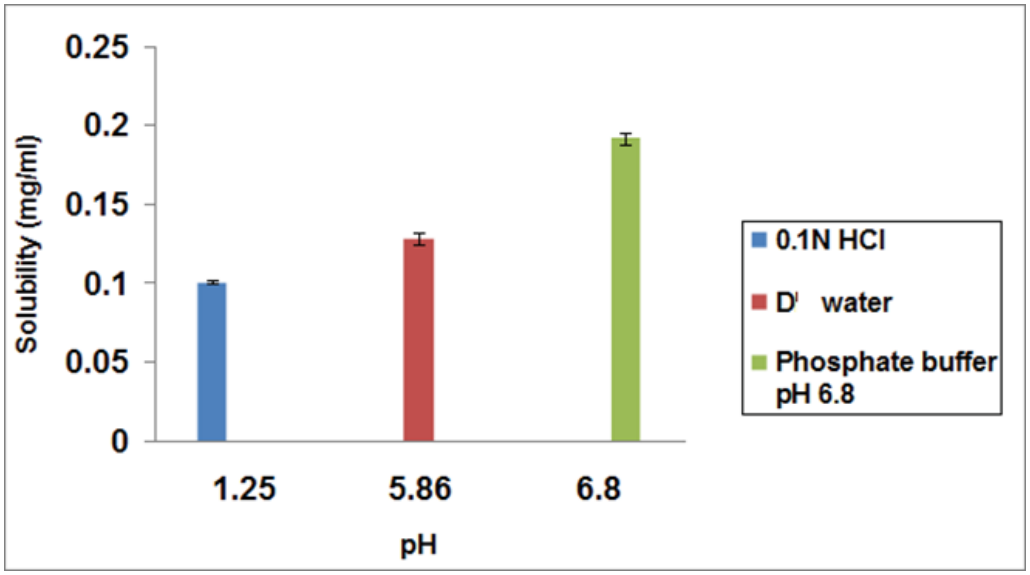

Figure 2: Saturation solubility of atorvastatin in different media.

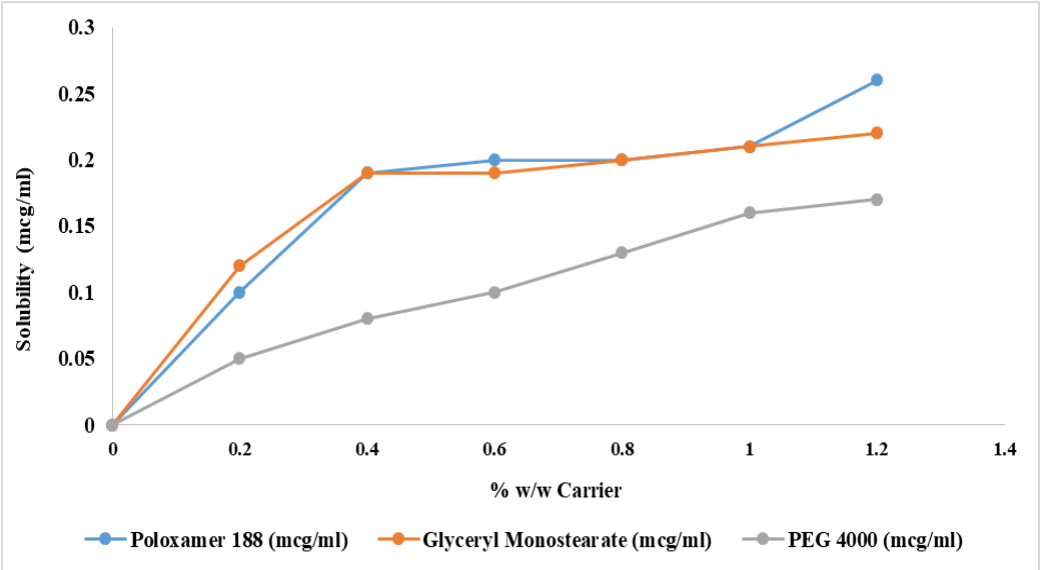

Figure 3: Saturation solubility of atorvastatin with different carriers.

Selection of Carrier

The results of solubility studies showed that among all the three carriers, Poloxamer 188 was most effective of all the examined carriers in improving atorvastatin solubility. Thus Poloxamer 188 was selected for further studies.

Determination of Drug Content

The actual drug content in each solid dispersions (SD) and physical mixture (PM) was determined. The results showed that SDs prepared from solvent evaporation method, its PM showed good agreement b/w theoretical and actual drug content.

Table 5: Determination of % drug content in different batches and its physical mixture.

S. NO.	Batch Code	% Drug content± SD*
1	SD1	95.40±0.43
2	SD2	96.32±0.58
3	SD3	95.34±0.58
4	SD4	93.16±0.95
5	SD5	90.91±0.20
6	PM1	93.37±0.32
7	PM2	92.51±0.21
8	PM3	95.45±0.11

* All values are expressed as mean ± S.D., n =8

***In Vitro* Drug Release**

The dissolution rate of atorvastatin in the form of powder, PMs, SDs was examined in phosphate buffer (pH 6.8). The dissolution of pure atorvastatin was extremely low, with only 21.04 % of drug release during 120 min of dissolution run in phosphate buffer (pH 6.8), which might be attributed to floating of the drug on the surface of dissolution medium. The relevant dissolution data are presented in Table 6. Solid dispersions of atorvastatin showed enhancement of drug dissolution due to the conversion of atorvastatin into a less crystalline and/or amorphous form. The improved dissolution rate was observed in all the prepared system and maximum release was seen in SD2 batch (98.08% in 120 min) prepared by solid evaporation method.[26]

Table 6: Comparative cumulative % drug release profiles of pure drug, SDs and its physical mixtures (PM) in phosphate buffer pH 6.8.

S. NO.	Time (min)	Pure drug (mg)	SD1	SD2	SD3	SD4	SD5
1.	0	0	0	0	0	0	0
2.	5	2.98±0.12	10.85±0.25	19.08±0.49	32.44±0.49	29.52±0.42	27.66±0.62
3.	10	4.95±0.11	26.91±0.30	41.72±0.50	52.32±0.71	51.69±0.20	51.08±0.68
4.	20	7.57±0.08	53.03±0.35	68.59±0.25	61.56±0.60	59.91±0.35	59.24±0.52
5.	30	13.12±0.09	57.21±0.41	90.58±0.14	85.39±0.62	84.14±0.52	83.78±0.60
6.	45	16.19±0.13	71.02±0.32	91.69±0.50	87.31±0.60	85.81±0.62	84.46±0.54
7.	60	17.68±0.12	89.13±0.30	92.34±0.56	88.22±0.70	89.35±0.40	88.72±0.64
8.	75	19.01±0.10	92.34±0.60	93.16±0.12	92.22±0.22	92.06±0.40	91.98±0.28
9.	90	19.89±0.12	94.16±0.42	986.34±0.54	95.56±0.59	95.43±0.52	95.02±0.22
10.	120	20.78±0.06	95.88±00.59	**98.08±0.09**	97.52±0.38	96.65±0.42	96.42±0.32

Table 6: Continued.

S. No.	Time (min)	PM1	PM2	PM3
1.	0	0	0	0
2.	5	7.08±0.59	9.68±0.44	11.25±0.65
3.	10	13.92±0.42	14.01±0.52	14.07±0.82
4.	20	18.98±0.32	19.66±0.84	19.58±0.88
5.	30	21.34±0.68	22.48±0.60	22.32±0.94
6.	45	28.28±0.59	29.72±0.60	29.39±0.80
7.	60	33.16±0.46	35.25±0.92	34.23±0.92
8.	75	34.44±0.78	38.09±0.56	39.24±0.56
9.	90	42.32±0.79	44.49±0.92	46.32±0.54
10.	120	46.63±0.92	52.12±0.96	51.71±0.56

* All values are expressed as mean ± S.D., n =3

Table 7: Batch percentage yield.

S. No.	Batch code	% Yield
1	SD1	91.6
2	SD2	97.5
3	SD3	94.1
4	SD4	82.5
5	SD5	86.5

* All values are expressed as t90% ± S.D., n =3

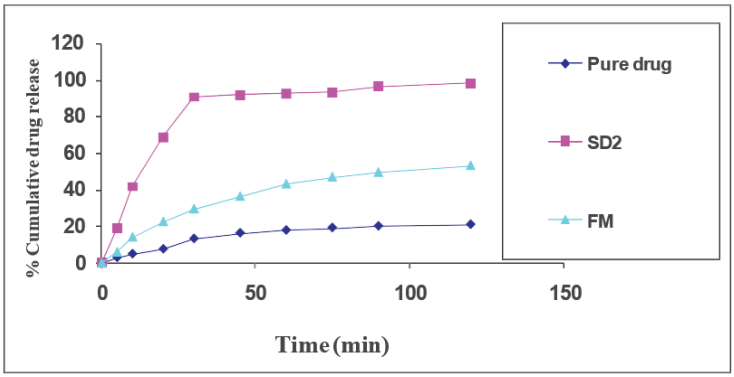

Figure 4: Comparative dissolution profile of % cumulative drug released of pure drug and different batches in phosphate buffer (pH 6.8)

Compare to Marketed Formulation

The dissolution rate profiles of atorvastatin release from marketed brand (FM) and batch (SD2) were represented in figure 5 and data were reported in Table 8. Release rates from the formulation (SD2) were evidently higher than the dissolution rate of drug from marketed brand (LIPITOR®). The value showed superiority of formulation (SD2) over that of marketed formulation.

Table 8: Comparative % drug release profiles of best developed batch SD2 and marketed brand of Atorvastatin (LIPITOR®)

Time (min)	Percentage (%) drug release	
	F_M	SD2
0	0	0
5	5.96±0.88	19.08±0.49
10	14.15±0.20	41.72±0.50
20	22.42±0.28	68.59±0.25
30	29.38±0.14	90.58±0.14
45	36.20±0.08	91.69±0.50
60	42.82±0.10	92.34±0.56
75	46.70±0.12	93.16±0.12
90	49.19±0.14	96.34±0.54
120	52.86±0.16	98.08±0.09

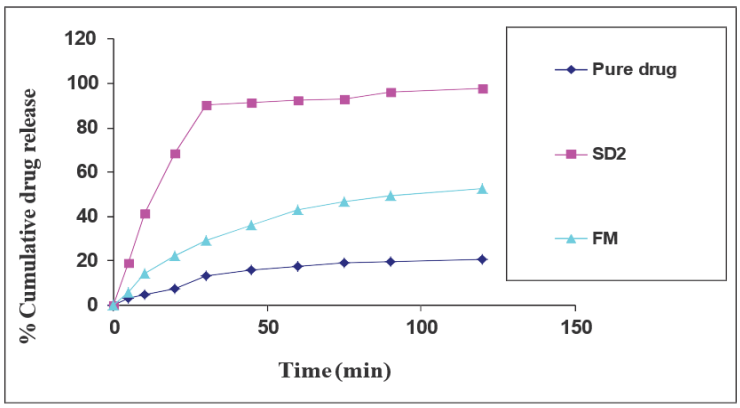

Figure 5: Comparative dissolution profile of % cumulative drug released of pure drug, SD2 and FM marketed formulation in phosphate buffer (pH 6.8)

Evaluation of Solid Dispersions

Micromeritic studies

Bulk Density

The LBD and TBD values for all sample of pure drug, physical mixture, carrier and SD2 was determined. LBD and TBD (g/cc) ranged from 0.416±0.03 to 0.500±0.07 and 0.540±0.05 to 0.595±0.06, respectively. The result indicated that SD2 exhibited excellent flow properties as compared to carrier which shows good flow properties, physical mixture shows fair and pure drug shows poor flow property.

Angle of Repose

Values obtained for angle of repose for all samples of pure drug, physical mixture, carrier and formulation SD2 was found to be in the range of 18±0.910 to 41.66±0.470.

SD2 exhibited excellent flow properties having angle of repose 18 ±0.910 (< 25) and pure drug had poor flow properties with angle of repose (41.66±0.460). Angle of repose was carried out in triplicate and average value was reported.

Compressibility Index

Carr's Compressibility index ranged from 8% to 28% as shown in Table No 3.12 for all samples of pure drug, physical mixture, carrier and SD2. The result demonstrated that SD2 displayed excellent flow properties. Pure drug had Carr's Compressibility index 28.46% which indicates poor flow property.

Hausners Ratio

Hausners ratio for all for all sample of pure drug, physical mixture, carrier and SD2 was in the range of 1.08 to 1.39. Result showed enhancement of flow properties of SD2 as 1.08 (<1.25) whereas pure drug displayed poor flow properties 1.39 (>1.25).

Table 9: Micromeritic properties of physical mixture, carrier, SD2 in comparison with pure drug.

Formulation code	Poured density (g/cc)*	Tapped density (g/cc)*	Carr's index (%)	Hausner's ratio	Angle of repose*(θ)^{o}	Flow property
Pure drug	0.416 ± 0.03	0.581 ± 0.07	28.46	1.39	41.66 ± 0.04	Poor
Carrier	0.476 ± 0.04	0.568 ± 0.09	16.22	1.19	27.40 ± 0.05	Good
Physical mixture	0.430 ± 0.08	0.595 ± 0.06	27.73	1.38	37.69 ± 0.01	Fair
SD2	0.500 ± 0.07	0.54 ± 0.05	8	1.08	18 ± 0.09	Excellent

* All values are expressed as mean ± S.D., n =4

Characterization of Solid Dispersion Systems

Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR studied were done to detect the possible interactions between the ATS and carrier (Poloxamer 188) in the solid dispersions leading to amorphous state of atorvastatin. Shows the IR spectra of pure drug, pure carrier, physical mixture and SD2. The FTIR spectra of pure atorvastatin presented characteristic peak at 3552 cm-1 and 3749 cm-1 (O−H stretch vibration), 2960 cm-1 (C−H stretch vibration) and 1730 cm-1, 1164 cm-1 and 1066 cm-1 (stretch vibration of −C−O and −C=O carbonyl functional group). The spectrum of Poloxamer 188 showed important bands at 3634 cm-1 (O−H stretch vibration) that was attributed to the presence of water confirming the broad endotherm detected in experiments and 1282 cm-1 (−C−O stretch vibration). The FT-IR spectra of physical mixture (PM) seemed to be only a summation of drug and carrier. This result suggested that there were no interactions between drug and carrier in PM and atorvastatin maintained its crystallanity as observed in thermal analysis. If the drug and carrier interact, then the functional groups in the FT-IR spectra will show band shifts and broadening compared to the spectra of drug and carrier. In the formulation SD2 band shifts observed at 1714 cm-1, 3446 cm-1 and 3629 cm-1 and broadening observed at 1165 cm-1 and it was also confirmed that intermolecular hydrogen bonding via the −C=O group of atorvastatin and O−H group of Poloxamer 188 formed in solid dispersions of SD2 formulation. Thus, a combination of interaction and decreased mobility of atorvastatin during preparation of solid dispersions may be the cause for stable amorphous form of drug inside the carrier.[27]

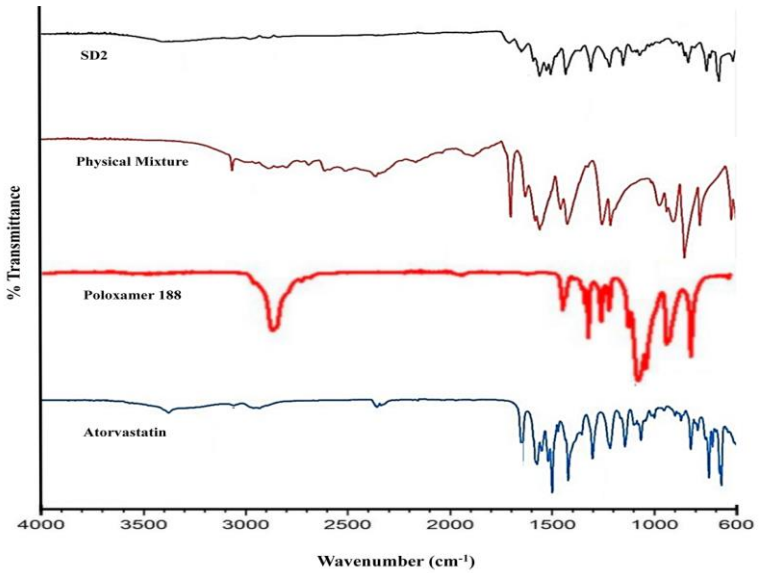

Figure 6: FTIR spectra of (a) Atorvastatin, (b) Poloxamer 188, (c) Physical mixture, (d) SD2.

Scanning Electron Microscopy (SEM)

SEM images of ATS, carrier (Poloxamer 188), its PM and solid dispersions of different batches SD2, were shown in. Pure drug consisted of a mixture of some large crystals (8 to 10 mm) with microparticles, which might have been generated due to micronization or any other size reduction process at the time of manufacturing. PM is seen as combined characteristics of drug and Poloxamer 188 unlike in SDs where drug crystals were not possible to distinguish from carrier. SDs formed at different inlet temperature revealed significant changes in particle shape and surface topography due to impact of solvent evaporation process. SD3 and SD4 appeared as irregular shaped agglomerates with presence of few microcrystals, suggesting possibility of residual crystallinity. Slight surface smoothness was observed in SD3, as compared to SD4, which could be attributed drug-carrier mixture. SD2 on the other hand looked like a smooth surface with very small particle size, suggesting presence of amorphous state. Thus corroborating XRD observation.[28]

Figure 7: SEM photomicrographs of Atorvastatin, Physical mixture and SD2.

CONCLUSION

Solid dispersions prepared from PEO-PPO block copolymer (Poloxamer 188) was effective in improving aqueous solubility and dissolution of poorly water soluble drug atorvastatin. The polymer was selected based on the results of the saturation solubility studies performed on three different groups of polymers namely Glyceryl monostreate, PEG 4000 and Poloxamer 188. The solid dispersions containing Poloxamer 188 (SD2) displayed enhanced dissolution compared to pure drug and marketed brand (LIPITOR®). Micromeritic studies viz Bulk density, Tapped density angle of repose and Carr's index when performed on the optimized batch displayed superior flow properties. Characterizations done by using FT-IR and SEM suggested the formation of an amorphous product. Therefore it can be concluded that optimized SDs of ATS enhanced the solubility and dissolution of drug.

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