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Original Article

Formulation Development and Evaluation of Atorvastatin Soy Lecithin Solid Dispersion: A Promising Approach for Solubility Enhancement

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ABSTRACT

Background: Hyperlipidaemia remains a significant contributor to cardiovascular disorders, with statins being the primary therapeutic agents for its management. However, the clinical efficacy of these drugs, particularly atorvastatin, a statin with an extended plasma half-life of 18-24 hr is hindered by poor aqueous solubility, which limits bioavailability. This study aimed to address this limitation by enhancing the solubility and dissolution profile of atorvastatin through advanced formulation strategies. **Materials and Methods:** A solid dispersion approach utilizing phospholipids as a matrix-forming agent was employed to improve drug solubility. The dispersion was synthesized via solvent evaporation, with methanol-ethanol (1:1) selected as the optimal solvent system based on preliminary solubility assessments. Adsorbents and disintegrants were integrated to optimize flowability and dissolution kinetics. The impact of varying phospholipid-to-drug ratios on performance was systematically evaluated. **Results:** The formulation with a 2:3 drug-to-phospholipid ratio demonstrated superior outcomes, achieving a solubility of 614±24 µg/mL and 91.2±2.27% dissolution within 90 min. Advanced analytical techniques, including Differential Scanning Calorimetry (DSC) and powder X-ray Diffraction (XRD), confirmed the amorphous dispersion of atorvastatin within the phospholipid matrix. Subsequently, an orodispersible tablet was developed using the optimized dispersion, exhibiting favorable pharmaceutical attributes. **Conclusion:** The integration of phospholipids in solid dispersion systems presents a viable strategy to overcome solubility challenges associated with atorvastatin, offering a scalable and effective solution for enhancing its therapeutic potential.

Keywords: Solid dispersion, Atorvastatin, Soy Lecithin, Solubility Enhancement, Orodispersible Tablets.

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INTRODUCTION

Hyperlipidaemia increases the risk of cardiovascular diseases, namely atherosclerosis, myocardial infarction, and coronary artery disease.[1] Elevated levels of total cholesterol, triglycerides, plasma lipoproteins like Very Low-Density Lipoprotein (VLDL) and Low-Density Lipoprotein (LDL), and reduced levels of High-Density Lipoprotein (HDL) are all considered indicators of this condition.[2,3] Atorvastatin (ATS), a lipid-lowering agent, inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA). Since it is a crucial enzyme for converting HMG CoA to mevalonate, HMG CoA reductase inhibition abolishes cholesterol synthesis.[4] Therefore, it can be used as primary prevention for cardiovascular diseases. Chemically, ATS is (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1-H-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid. Its crystalline nature is primarily responsible for its limited aqueous solubility (0.1 mg/mL) and low oral bioavailability (12%). As it is a BCS class II drug, dissolution is the rate-limiting step in the absorption process. Thus, the bioavailability can be improved by simply increasing the solubility of the drug.[5]

Several techniques like co-crystallization, micronation, nanonization, lipid-based formulations, salt formation, prodrug, complexation, and solid dispersion have been used for solubility enhancement of poorly soluble drugs. Solid dispersion is one effective strategy in this direction. A hydrophobic drug dispersed in the fine crystalline, amorphous, or solubilized state in a hydrophilic matrix has been referred to as "solid dispersion." Various methods are used to prepare solid dispersion, including solvent evaporation, hot melt extrusion, and spray drying.[6] In this investigation, we used the solvent evaporation method for the preparation of solid dispersion. The drug and carrier are

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dissolved in a volatile solvent as part of the solvent evaporation process, which evaporates to give solid dispersion.[7] Since organic solvent evaporation occurs at low temperatures, this approach can prevent the thermal degradation of drugs or carriers.[8]

The solubility of ATS has been improved by solid dispersion using various carriers like locust bean gum,[9] skimmed milk,[5] polymers such as poloxamer 188,[10] PEG 4000,[11] PEG 4000 or PEG 10000 with surfactant poloxamer 188,[12] Hydroxypropyl Methylcellulose (HPMC) with Sodium Lauryl Sulfate (SLS),[6] PEG 6000,[13] and Kollicoat IR or PVP K30 with PEG 6000.[14] It has been suggested that drug molecules dispersed in polymeric carriers increase the drug dissolution rate. Polymer-based solid dispersion tends to absorb atmospheric moisture, affecting the solubilization potential due to the recrystallization of the drug in solid dispersion during storage.[15] Hence, third-generation solid dispersions containing polymer-carriers and surfactants have been prepared to prevent the conversion of an amorphous form of the drug in solid dispersion to a crystalline state.[6] Compared to polymers, phospholipids have the advantage that their minimum amount is sufficient to be effective.[16] Therefore, phospholipids as carriers in solid dispersion are promising due to their amphiphilic properties, facilitating the dispersion of hydrophobic drugs in aqueous media.[17]

Several experiments have been conducted to include phospholipid as a matrix for preparation solid dispersion. Hussain *et al.*, formulated ibuprofen solid dispersion using dimyristoyl phosphatidyl glycerol,[16] Taksande *et al.*, prepared solid dispersion of lamotrigine using soy lecithin,[18] Sosada *et al.*, developed solid dispersion of ibuprofen using rapeseed phospholipid matrix,[19] Fong *et al.*, formulated celecoxib solid dispersion in phospholipid matrix by freeze-drying method to study whether the increase in celecoxib solubility subsequently increases the permeability across intestinal barrier,[20] Jacobsen *et al.*, prepared and compared solid dispersion containing two types of phospholipids monoacyl and diacyl phosphatidylcholine based on permeation of celecoxib.[21] Yeo *et al.*, reported a study of solid dispersion in a phospholipid matrix containing adsorbent and disintegrant or hydrophilic polymer.[15] Similarly, Jo *et al.*, fabricated celecoxib solid dispersion in a phospholipid matrix, adsorbent material, and hydrophilic material like disintegrants or diluents.[17] ATS has yet to be explored to enhance its solubility by preparing solid dispersion in a phospholipid matrix.

Phospholipid-based formulation leaves behind its lipidic texture. To overcome it, mesoporous adsorbent material was employed. Adsorbent carrier masks the sticky texture and thereby aid to make free-flowing powder.[15-17] However, phospholipid-based matrices are strongly adsorbed into the pores, making the desorption difficult. Therefore, hydrophilic materials like disintegrants, diluents, or hydrophilic polymers can be used in formulation to enhance the hydration process.[17,22,23] Since a film of the drug in a phospholipid matrix is deposited on adsorbent material, this type of solid dispersion is called pro-liposome,[20-21,24] which, upon hydration, forms liposome. This drug-incorporated bilayer structure reaches the site of absorption, enhancing the bioavailability of the drug.[16]

The present investigation was carried out to enhance the solubility and dissolution of ATS using a solid dispersion technique. A solvent evaporation technique prepared a solid dispersion containing a drug, a phospholipid carrier, and an adsorbent material.

MATERIALS AND METHODS

ATS was procured from Mylan Lab Ltd., Soy lecithin was obtained from Himedia Lab, Mumbai. Aluminum magnesium metasilicate and croscarmellose were purchased from Tomito Pharmaceuticals Pvt. Ltd., and Akhil Healthcare Mumbai. Methanol and ethanol were obtained from Merk. All the reagents used in experiments were of analytical grade.

Preparation of solid phospholipid dispersion and physical mixture

Solid dispersions were fabricated using the solvent evaporation methodology. Preliminary trials evaluated solvent systems including methanol, ethanol, and chloroform-to identify the optimal medium for maximizing drug solubility (Table 1). The solvent system demonstrating superior solubility was selected for subsequent formulation of solid dispersions (Table 1). Briefly, Atorvastatin (ATS) and soy lecithin (phospholipid carrier) were dissolved in the chosen solvent and subjected to ultrasonication for 30 min. Precise quantities of an adsorbent (aluminum magnesium metasilicate) and a disintegrant (croscarmellose sodium) were then incorporated into the solution, followed by thorough homogenization. The mixture was heated to 600°C under continuous magnetic stirring to evaporate the solvent. Resulting solid dispersions were stored in a desiccator for 24 hr to ensure complete drying. A Physical Mixture (PM) was prepared by grinding ATS, phospholipid, adsorbent, and disintegrant in identical proportions. Both the dried solid dispersion and PM were sieved through a 100-mesh sieve and retained in a desiccator for further analysis. Various phospholipid-to-drug ratios were tested, and the batch exhibiting optimal solubility and drug release was selected for advanced characterization via Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Fourier-Transform Infrared Spectroscopy (FTIR).

UV-spectrometric analysis of pure ATS

To determine absorption maxima (λ_{max}), drug solutions of 2 µg/mL concentration were prepared separately in solvents such as methanol, water, and phosphate buffer and scanned between the UV range of 200-400 nm. The 2-20 µg/mL drug solutions in each solvent were analyzed at their respective λ_{max}.[18,25,26]

Saturation solubility

Saturation solubility of ATS, physical mixture, and ATS solid dispersions were performed by adding an excess quantity of solute in 20 mL distilled water in a screw cap volumetric flask. The solution was stirred in a shaker incubator at 37±0.5°C at 30 rpm for 48 hr. Once equilibrium was achieved, the aliquot was withdrawn and filtered through Whatman filter paper of 0.45 µg, and the filtrate was analyzed by UV-spectrophotometer (Jasco, Inc.) at 240 nm.[18]

Drug content

Drug content quantification involved dissolving 10 mg of solid dispersion formulations or physical mixtures in 10 mL methanol, followed by sonication for 30 min. The resulting solution was subsequently filtered, and an aliquot (1 mL) of the filtrate was diluted tenfold with methanol. Drug concentration was determined via UV-vis spectrophotometric analysis at a wavelength of 246 nm.

$$\% \text{ Drug Content } = \frac{\text{Practical}}{\text{Theoretical}} \times 100$$

In vitro dissolution studies

Dissolution testing was conducted using a USP Type I (basket) dissolution apparatus (Universal Lab). A sample equivalent to 50 mg of Atorvastatin (ATS) was introduced into 900 mL of pH 6.8 phosphate buffer maintained at 37±0.5°C. The basket was rotated at 100 revolutions per minute (rpm) to ensure uniform mixing. At predefined time points, 10 mL aliquots were collected from the dissolution medium, and an equal volume of freshly pre-warmed buffer was replenished to sustain sink conditions throughout the study. The aliquots were filtered and analyzed using a UV-visible spectrophotometer (Jasco, Inc.) at 242.6 nm. Each formulation was tested for its dissolution capacity in triplicate ($n = 3$).[11-12,18] For dissolution profile comparison, Dissolution Efficiency (DE) was calculated using following equation:

$$D.E. = \frac{\int_0^t y \times dt}{y^{100} \times t} \times 100$$

Where, y is percent of drug dissolved at time t. Area Under Curve (AUC) in numerator was calculated by trapezoidal rule.[11,12,18]

Fourier Transform Infrared Spectroscopy (FT-IR)

Fourier-Transform Infrared (FTIR) spectroscopy was performed using a Bruker Alpha spectrophotometer configured with an Attenuated Total Reflectance (ATR) module. Spectral data were acquired across a 4000-500 cm^{-1} range during analysis. Key alterations in peak characteristics such as emergence, broadening, or elimination-observed in physical mixtures and solid dispersions were contrasted against the distinct peaks of the pure compound. This analytical approach aimed to detect potential physicochemical interactions between the active pharmaceutical ingredient and excipients, while also verifying the structural integrity of the developed formulation.

Differential Scanning Calorimeter (DSC)

Thermal behavior analysis of Atorvastatin (ATS), its physical mixture, and solid dispersion was performed using a METTLER DSC-3/500/3297 instrument. Samples (~1.1 mg) were loaded into aluminum crucibles and heated from 30°C to 250°C under a nitrogen purge (50 mL/min) at a rate of 10°C/min. Thermograms were recorded to assess thermal transitions, crystallinity, and potential drug-excipient interactions.

Table 1: Composition and Solvent Systems Used in the Formulation of Solid Dispersions of Atorvastatin.

Formulation Code	Atorvastatin (mg)	Soy Lecithin (mg)	Aluminium Magnesium Metasilicate (mg)	Croscarmellose (mg)	Solvent System	Volume (mL)
SD1	100	100	-	-	Methanol	-
SD2	100	100	-	-	Methanol + Chloroform (1:1)	-
SD3	100	100	-	-	Methanol + Ethanol (1:1)	-
S1	100	30	200	50	Methanol + Ethanol (1:1)	2
S2	100	50	200	50	Methanol + Ethanol (1:1)	2
S3	100	100	200	50	Methanol + Ethanol (1:1)	2
S4	100	150	200	50	Methanol + Ethanol (1:1)	2
S5	100	200	200	50	Methanol + Ethanol (1:1)	2
ASD	100	-	200	50	Methanol + Ethanol (1:1)	2
SD	100	100	-	-	Methanol + Ethanol (1:1)	2
PM	100	200	200	50	Methanol + Ethanol (1:1)	2

Abbreviations: SD: Solid Dispersion; ASD: Aqueous Solid Dispersion; PM: Physical Mixture; mg: Milligram; mL: Milliliter.

Powder X-ray Diffraction (PXRD)

Crystallinity assessment of ATS, soy lecithin, physical mixture, and the optimized solid dispersion was conducted using a Bruker D2 Phaser diffractometer (2nd Generation, Germany). The system operated at 30 kV voltage and 10 mA current, equipped with a nickel-filtered Cu-Kα radiation source. Diffraction patterns were collected across a 2θ angular range of 1-60°, with a step size of 0.02° and a dwell time of 0.3 sec per step. Data were analyzed to evaluate phase transformations and amorphous content in the formulation.

Preparation of Oral Dispersible Tablet

For preparation of oral dispersible tablet The orodispersible tablet formulations F1 and F2 were prepared with a total tablet weight of 100 mg. In formulation F1, 10 mg of pure atorvastatin was used as the active pharmaceutical ingredient. In contrast, formulation F2 contained 33.94 mg of solid dispersion S4, equivalent to 10 mg of atorvastatin. Both formulations included mannitol as a diluent (63.5 mg in F1 and 39.56 mg in F2), microcrystalline cellulose (8.5 mg), croscarmellose (8 mg) as a superdisintegrant, and aluminium magnesium metasilicate (2 mg) as an adsorbent. Talc (3 mg), aspartame (3 mg), and magnesium stearate (2 mg) were also incorporated uniformly in both formulations as glidant, sweetener, and lubricant, respectively., the solid dispersion batch S4 showing maximum solubility and dissolution rate was selected. Pure ATS was also formulated into ODT. Oro dispersible tablet was prepared by direct compression using the respective powders, weighed blended thoroughly with mortar and pestle using MCC and mannitol as directly compressible agent. Aspartame was used as sweetening agent. Talc and magnesium stearate were added as lubricant and glidant and tablet were compressed using flat faced punches. The hardness of tablets was kept constant and was measured with a hardness tester. Tablet mixture and tablets were evaluated for various pre-compression and post-compression parameters.

Stability Studies

The orodispersible tablet formulation underwent stability testing in accordance with International Council for Harmonisation (ICH) guidelines. Formulations F1 and F2 were stored under accelerated conditions (40°C temperature and 75% relative humidity) for 90 days. Post-storage, tablets were assessed for critical quality attributes, including weight variation, mechanical strength (hardness), friability, disintegration time, drug content uniformity, and dissolution efficiency to evaluate physicochemical stability.

Statistical Analysis

Experimental data derived from triplicate measurements were expressed as mean±standard deviation (Mean±SD). Statistical comparisons were performed using Student's *t*-test and one-way analysis of variance (ANOVA) via GraphPad Prism 8 software. A p-value < 0.05 was deemed statistically significant to validate differences between experimental groups.

RESULTS

Since the ATS was freely soluble in methanol, a solution of 2 ug/mL concentration in methanol was scanned in the 200-400 nm range. The absorption maxima (λ_{max}) of a pure drug in methanol was found to be 246 nm, which corresponded with the λ_{max} reported for ATS.[26] λ_{max} of pure ATS in water and phosphate buffer were obtained at 240 nm and 242.6 nm, respectively. The regression coefficient values (r^2) confirm that the solution of ATS in methanol, water, and phosphate buffer 6.8 obeyed the Beers-Lambert Law.

Saturation solubility

The saturation solubility of pure ATS in distilled water was found to be 110±15 µg/mL, and that in phosphate buffer was 200±6 µg/mL. Solubility properties of ATS from solid dispersions, analyzed in distilled water, are depicted in Figure 1(A). Solid dispersions SD1, SD2, and SD3 were prepared without adsorbent using different solvent systems. The solubility values suggested that SD3 prepared using methanol and ethanol (1:1) showed significantly higher solubility 352±21 µg/mL than SDs prepared with other solvent systems. Therefore, it was selected to prepare solid dispersion with the adsorbent further.

The solid dispersion (ASD), prepared with adsorbent material without phospholipid, showed increased aqueous solubility compared to ATS. Solid dispersion, containing soy lecithin (SD) prepared without adsorbent, showed better solubility than ASD. However, it was lower than S3, a solid dispersion prepared with adsorbent. The physical mixture increased aqueous solubility compared to the pure drug. However, it was lower compared to the aqueous solubility of solid dispersions.

Figure 1(A) shows that the solid dispersion formulations (S1-S5) showed an increase in the aqueous solubility of the drug with an increase in the proportion of soy lecithin. Batch S4 demonstrated the highest water solubility of 614±24 µg/mL among all the solid dispersion formulations. The saturation solubility of ATS from solid dispersion significantly increases up to 6 folds compared to ATS. There was a significant difference among the solubility values of solid dispersions, physical mixture, and pure ATS with p value less than 0.05.

Drug content

The results of drug content are given in Table 2, solid dispersions containing soy lecithin prepared with the adsorbent (S1 to S5) showed drug content ranging from 78.75±0.89% to 90.39±0.49%. At the same time, the Physical Mixture (PM) and the solid dispersion prepared without adsorbent (SD) exhibited a drug content of 62.45±0.56% and 83.25±0.79%, respectively. The batch devoid of phospholipid (ASD) was found to have a drug

content of 81.34±0.67%. The drug content was increased with an increase in phospholipid content. These findings suggest that the proportion of phospholipid to adsorbent might influence/ the extent to which the drug is adsorbed into the porous structure.[22,23]

In vitro dissolution studies

The drug release characteristics of ATS and solid dispersions of ATS are shown in Figure 1(B). The drug release for all the solid dispersions was higher than that of pure drug. Maximum drug release of 91.20±2.27% in 90 min was demonstrated by S4 containing ATS and soy lecithin in the proportion of 2:3. S4 showed about 50% of drug release in 30 min. The drug release from all the solid dispersions was higher than that of a formulation devoid of phospholipid (ASD). The drug release of all the formulations containing soy lecithin (S1-S5) was higher than that of the physical mixture throughout 90 min. There was an increase in drug release with an increase in drug-to-phospholipid proportion. Solid dispersion containing soy lecithin prepared without adsorbent (SD) demonstrated lower drug release than that prepared with adsorbent. Solid dispersion containing soy lecithin prepared without adsorbent (SD) demonstrated lower drug release compared to that prepared with adsorbent. The Dissolution Efficiency (DE) of S1 to S5 solid dispersion formulations ranged from 30.50±1.41% to 57.16±1.6% and that of ATS, ASD, PM, and SD were 9.98±1.73%, 18.96±1.81%, 24.91±1.57%, and 34.78±1.53% respectively. All the Solid dispersions formulation including formulation devoid of phospholipid (ASD) showed higher Dissolution Efficiency (DE) than that of pure atorvastatin. Dissolution Efficiency (DE) of S4 was found to be higher that is 57.16±1.6 compared to that of all other solid dispersions (Table 2).

The drug release data was subjected to a kinetic study. The formulation S4 followed zero oder kinetics for the drug release. The release exponent (*n* value) from the Korsmeyer-Peppas model was observed to be greater than 0.5, indicating non-Fickian diffusion. Thus, the results of the dissolution study confirmed phospholipids to be a promising carrier for the enhancement of the dissolution of ATS. The hydrophilic material croscarmellose and PL-based matrix contribute to the dissolution of ATS due to its desorption capacity and amphiphilic nature respectively.

FTIR

FTIR study investigated the possible physiochemical interaction between ATS and excipients,[17,18] FTIR spectra of ATS shown in Figure 2(A1) illustrates N-H stretching (aromatic) at 3363.56 cm^{-1}, C=O stretching (amide) at 1650.01 cm^{-1}, C-C aromatic stretching at 1510.17 cm^{-1} and 1435.82 cm^{-1}, C-N stretching at 1317.79 cm^{-1} and 1216.09 cm^{-1}, C-F stretching at 1159.80 cm^{-1} and O-H bending at 1111.61 cm^{-1}, C-Cl stretching (halo compound) at 842.58 cm^{-1}, C-H bending at 746.12 cm^{-1}, C=C bend at 691.92 cm^{-1}. Major vibrational frequencies of ATS in solid dispersion complex were identical to that of ATS. In case of solid dispersions, low-intensity peaks of C-C stretching at 1432.45 cm^{-1}, C-N

Table 2: Drug Content and Dissolution Efficiency of Various Solid Dispersion Formulations of Atorvastatin.

Formulation	S1	S2	S3	S4	S5	ASD	SD	PM	ATS
Drug Content (%)	78.75±0.89	82.50±0.95	87.81±0.77	89.46±0.43	90.39±0.49	81.34±0.67	83.25±0.79	62.45±0.56	-
Dissolution Efficiency (%DE)	30.50±1.41	38.21±1.56	52.13±1.42	57.16±1.60	43.60±1.57	18.96±1.81	34.78±1.53	24.91±1.57	9.98±1.73

Note: Results are shown as Mean±S.D (*n=3).

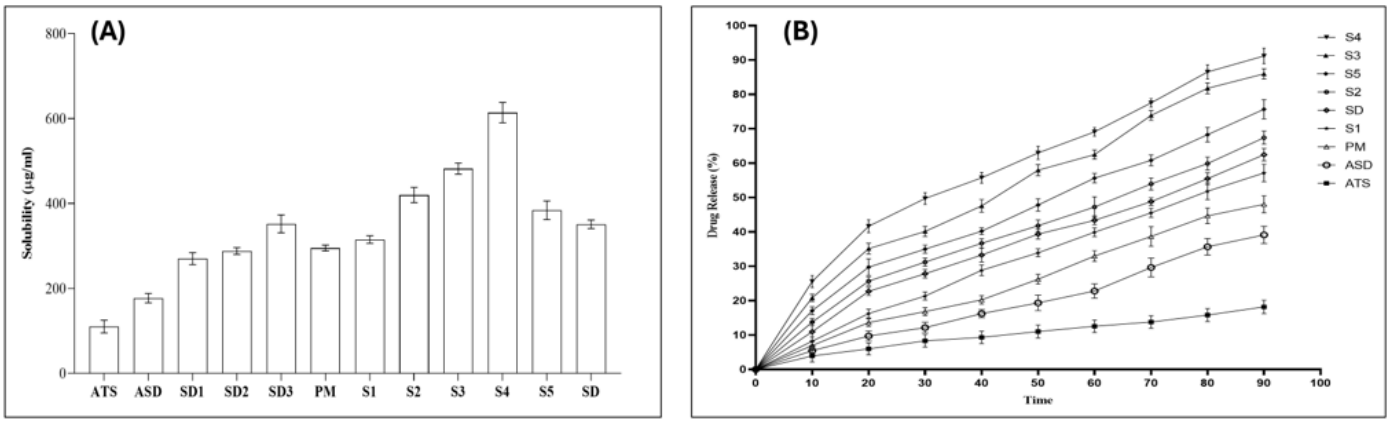

Figure 1: (A) Solubility of pure Atorvastatin (ATS), Solid dispersions, and Physical Mixture (PM). Solubility values are expressed as Mean±S.D (n=3), *p<0.05, t-test. (B) *In vitro* dissolution profile of atorvastatin from solid dispersion. Amounts of drug released are expressed as Mean±S.D. (n=3), *p<0.05, Two-way ANOVA.

Stretching at 1312.82 cm^{-1}, C-C aromatic stretching at 1509.40 cm^{-1}, C-O stretching at 1014.51 cm^{-1}, C-H bending at 751.70 cm^{-1}, C-CL stretching (halo compound) at 844.30 cm^{-1}, C=C bend at 692.83 cm^{-1} were retained. A broader peak was observed at 1014.51 cm^{-1}. Characteristic peaks of N-H stretching and C=O stretching disappeared. It indicates molecular interaction between ATS and phospholipid.[12,27]

DSC

The DSC analysis was used to investigate the thermal behavior, physicochemical characteristics, and chemical degradation of ATS.[6] Figure 2(A2) illustrates the DSC thermogram of ATS, physical mixture, and ATS solid dispersion S4. The thermogram of the pure drug showed a distinguished peak at 104.49°C that indicated a loss of water as it is a trihydrate and another sharp endothermic peak at 152.96°C[13] in the thermogram corresponds to the melting temperature of ATS suggesting the crystallinity of ATS. Moreover, an endothermic low-intensity peak was observed in a thermogram of pure ATS at 193.56°C, possibly attributed to its degradation.[12,27] The thermogram of the physical mixture displayed an endothermic peak at 254.66°C. However, the thermogram of solid dispersion showed no characteristic peak of ATS. Therefore, it confirmed the dispersion of the ATS in amorphous form in phospholipid-based matrices.[15,17,27]

PXRD

Powered X-ray Diffraction pattern of ATS, soy lecithin, physical mixture, solid dispersion S4 are shown in Figure 3. Diffractogram of ATS demonstrated characteristic peaks at 2θ of 9.028°, 9.339°, 10.448°, 10.151°, 11.716°, 12.069°, 15.053°, 16.899°, 19.334°,

Table 3: Composition of atorvastatin Oro Dispersible tablet.

Ingredients (mg)	F1	F2
Atorvastatin	10	--
S4 (Equivalent to atorvastatin 10 mg)	--	33.94
Mannitol	63.5	39.56
MCC	8.5	8.5
Talc	3	3
Aspartame	3	3
Magnesium stearate	2	2
Croscarmellose	8	8
Aluminium magnesium metasilicate	2	2
Total	100	100

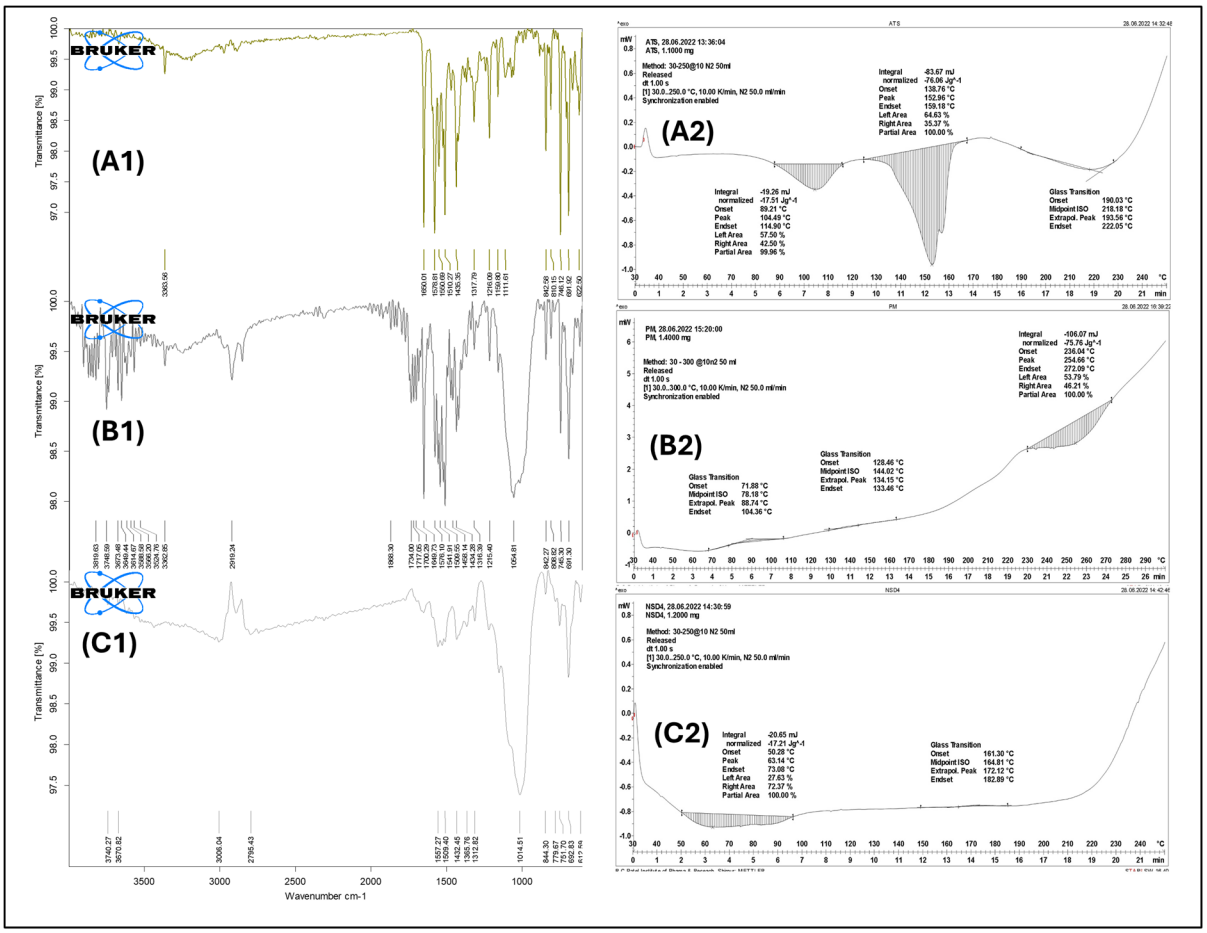

Figure 2: FT-IR spectra of (A1) Atorvastatin; (B1) Physical mixture; and (C1) Solid dispersion S4. DSC thermogram of (A2) Atorvastatin; (B2) Physical mixture; and (C2) solid dispersion S4.

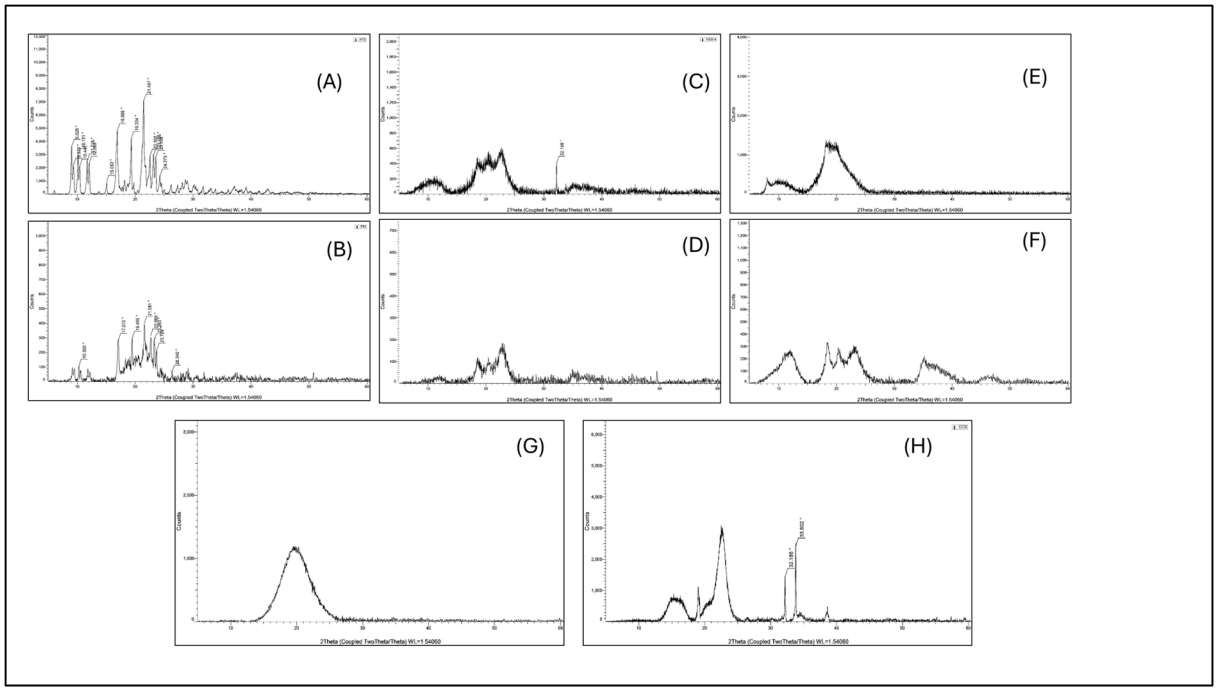

Figure 3: Powder X-ray diffraction patterns of (a) Atorvastatin; (b) Physical mixture; (c) Solid dispersion S4; (d) ASD; (e) SD; (f) Magnesium aluminium metasilicate; (g) Soy lecithin; (h) Croscarmellose.

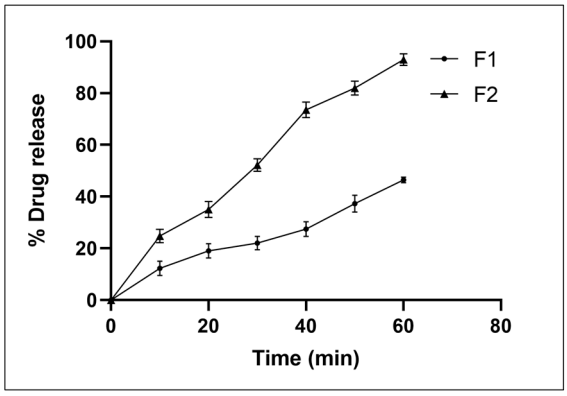

Figure 4: Percent drug release from atorvastatin oro-dispersible tablets. Amounts of drug released are expressed as Mean±S.D. (n=3), *p<0.05 Two-way ANOVA.

21.457º, 22.565º, 23.188º, 23.358º, 23.358º, 24.273º. These sharp and intense peaks indicate the crystalline nature of the drug in pure form. Physical mixture exhibited characteristic peaks at 2θ of 10.300º,17.075º, 19.485º, 21.581º, 22.665º, 23.263º, 23.724º, and 26.34º. The intensity of peaks in the diffractogram solid dispersion S4 was significantly reduced. Thus, it indicates the dispersion of ATS in phospholipid matrices in an amorphous form, ensuring the enhancement and dissolution of ATS.[15,17]

Characterization of oro-dispersible tablets

Solid dispersion S4 was obtained as uniform and non-greasy particles indicated maximum drug solubility, better dissolution profile as compared to other batches so it was selected for the formulation of Oro dispersible tablets. The tablet blend was prepared as given in Table 3 using MCC and mannitol as directly compressing agents, aspartame was added as sweeting agent. The powder blend was evaluated for the various precompression properties. The compressibility and the flowability of the powder blend were determined by calculating Carr's index and Hausner's ratio. Results of Hassner's ratio was less than 1.5 indicates the good flow property, and Carr's index reveals the good compressibility of the prepared powder mixture. Results of post compression parameters of ATS Oro dispersible tablets are given in Table 4. For both the batches, hardness was found to be 3.54 and 3.23 kg/cm^2. The hardness test revealed favourable mechanical strength. The obtained friability was less than 1%, signifying excellent mechanical resistance of both the batches. The disintegration time for both the batches F1 and F2 was 24 and 22 s respectively. The drug content of the formulation was 43.39±2.73% and 90.58±1.42% indicating maximum entrapment of drug in the formulation containing soy lecithin solid dispersion. The formulation F2 containing soy lecithin solid dispersion of ATS showed 92.92±2.37% dissolution in 60 min as compared to F1 containing ATS which showed only 46.43±1.09% release in 60 min (Figure 4). Thus, the results suggested that the formulation of solid dispersion of ATS in soy lecithin as phospholipid carrier increased the dissolution rate of the ATS.

Stability studies

Accelerated stability study were conducted on F1 and F2 formulations of Oro-dispersible tablet. The change in friability of F1 0.98±0.02% and F2 0.89±0.08% and dissolution of F1 41.28±2.47% and F2 88.50±1.33% were observed which might be

Table 4: Evaluation and Stability Study Parameters of Orodispersible Tablets of Atorvastatin.

Evaluation Parameters	F1 (Initial)	F2 (Initial)	F1 (After Stability Study)	F2 (After Stability Study)
Weight Variation$ (mg)	98.8±1.81	99.11±1.5	-	-
Thickness (mm)*	3.45±0.23	3.38±0.45	-	-
Hardness (mg/cm³)*	3.54±0.42	3.23±0.86	-	-
Friability# (%)	0.75±0.02	0.88±0.05	0.98±0.02	0.89±0.08
Disintegration Time (s)*	24±1.23	22±1.59	23±1.36	23±1.55
Drug Content (%)*	43.39±2.73	90.58±1.42	42.43±0.45	89.29±0.21
Dissolution (%)*	-	-	41.28±2.47	88.50±1.33

Results are shown as Mean±S.D. *n*=3 (Thickness, Hardness, Disintegration Time, Drug Content, Dissolution). $*n*=20 (Weight Variation). #*n*=6 (Friability).

due to Aluminium magnesium metasilicate added as excipient in tablet (Table 4).

Solid dispersion may experience physical instability over time, leading to aggregation of the phospholipid matrix due to temperature change and drug crystallization which can negatively impact the drug release profile. Traces of residual solvent may pose potential toxicity. *In vitro* dissolution study does not reflect therapeutic efficacy of solid dispersion, insufficient data on *in vivo* study necessitates further research. Detailed *in vivo* studies to assess the pharmacokinetics of atorvastatin-soy lecithin solid dispersion using a suitable animal model can be conducted. Hybrid matrices combining soy lecithin with biodegradable polymers like HPMC or PEG could improve the atorvastatin solubility and stability. The long term and/or accelerated stability study assessment as per ICH guideline (Q1A R2) under various stress condition can be investigated. Formulation can be optimized using various QbD based approaches to get best formulation under given set of conditions. We can also investigate the influence of different formulation variable on characterization of solid dispersion.

DISCUSSION

The study demonstrated that soy lecithin-based solid dispersions significantly enhanced the solubility and dissolution of Atorvastatin (ATS), a BCS class II drug with poor aqueous solubility. Among various formulations, SD3 using methanol:ethanol (1:1) showed superior solubility and was selected for further development. Incorporating soy lecithin and adsorbents notably improved solubility, with S4 achieving the highest value (614±24 µg/mL). Overall, the optimized solid dispersion increased ATS solubility by up to six-fold compared to the pure drug attributed to the amorphous state of ATS confirmed via DSC and XRD. The amphiphilic nature of soy lecithin likely facilitated drug dispersion, while adsorbents (aluminum magnesium metasilicate) and disintegrants (croscarmellose) improved flowability and hydration, accelerating dissolution.

The drug release study revealed a substantial improvement in the dissolution of ATS from all solid dispersion formulations compared to the pure drug. Among them, S4 demonstrated the highest release (91.20±2.27% in 90 min) and rapid initial release (50% in 30 min), attributed to its optimal drug-to-phospholipid ratio (2:3). Solid dispersions containing soy lecithin consistently showed better results than both the physical mixture and the formulation without phospholipid (ASD), indicating the vital role of phospholipids in enhancing drug release. The presence of adsorbent further improved release, as evidenced by higher performance of formulations with adsorbent compared to SD. The Dissolution Efficiency (DE) of S4 was also highest (57.16±1.6%), confirming its superior performance. Kinetic studies indicated that S4 followed zero-order release and exhibited non-Fickian diffusion, suggesting a combined mechanism of diffusion and erosion, aided by the amphiphilic nature of phospholipids and the desorption ability of croscarmellose.

These findings align with prior studies using phospholipids for solubility enhancement but extend the approach to ATS, previously unexplored in such matrices. The FTIR study showed that most characteristic peaks of ATS were retained in the solid dispersion, but the disappearance of N-H and C=O stretching peaks indicated molecular interactions between ATS and phospholipid. DSC analysis confirmed the crystalline nature of pure ATS with a melting peak at 152.96°C, while the absence of this peak in S4 suggested the drug was present in an amorphous form in the dispersion. PXRD further supported this, as the sharp crystalline peaks of pure ATS were significantly reduced in the solid dispersion, indicating successful amorphization, which contributes to improved solubility and dissolution.

Solid dispersion S4 was selected for tablet formulation due to its superior solubility and dissolution profile. The prepared tablet blend showed good flow and compressibility, as confirmed by Hausner's ratio (<1.5) and Carr's index. Post-compression results showed acceptable hardness, low friability (<1%), and rapid disintegration (22-24 s), indicating good mechanical and performance characteristics. Drug content was significantly higher in F2 (with soy lecithin solid dispersion) than F1. F2 also showed a much higher drug release (92.92±2.37%) compared to F1 (46.43±1.09%) in 60 min, confirming that soy lecithin-based solid dispersion greatly enhanced the dissolution of ATS.

However, stability studies revealed minor dissolution declines in F2, likely due to residual solvent or phospholipid aggregation over time. While *in vitro* results are promising, the lack of *in vivo* data limits clinical relevance. Additionally, QbD-based optimization and pharmacokinetic studies in animal models are necessary to validate therapeutic efficacy.

CONCLUSION

In conclusion, solid dispersion using the solvent evaporation method was successfully prepared. The solvent system, methanol and ethanol (1:1) contributed to the maximum solubility of atorvastatin from the solid dispersion compared to others. Solid dispersion prepared with adsorbent has shown better solubility and drug release than a formulation devoid of adsorbent. The XRD and DSC analyses confirmed the decreased crystallinity of ATS. Solid dispersion containing drug and soy lecithin in the ratio 2:3 was found to be optimized batch showing significantly better solubility and higher dissolution compared to all other formulations, $p<0.05$ based on student *t* test and two-way Anova respectively. Additionally, dissolution efficiency of this batch was higher than other solid dispersions which confirmed its selection as optimised batch. Oro-dispersible tablet of the optimized batch of solid dispersion was successfully prepared. The tablet containing solid dispersion exhibited higher drug content and better dissolution than pure atorvastatin tablet. Thus, it was concluded that the solid dispersion prepared using phospholipid matrix can sufficiently enhance the aqueous solubility of ATS, which in turn may improve its efficiency, reducing the dose of the drug required. The findings highlight phospholipids as effective carriers for hydrophobic drugs, potentially reducing therapeutic doses however, further optimization of storage stability and *in vivo* pharmacokinetic assessments to convert it into clinical practice. This work underscores the promise of phospholipid-based solid dispersions in addressing solubility challenges for BCS class II drugs.

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ABBREVIATIONS

ADS: Atorvastatin Solid Dispersion; **ANOVA:** Analysis of Variance; **ATS:** Atorvastatin; **AUC:** Area Under the Curve; **BCS:** Biopharmaceutics Classification System; **D.E.:** Dissolution Efficiency; **DSC:** Differential Scanning Calorimetry; **FT-IR:** Fourier Transform Infrared Spectroscopy; **HDL:** High-Density Lipoprotein;**HMGCoA:**3-Hydroxy-3-Methylglutaryl-Coenzyme A; **HPMC:** Hydroxypropyl Methylcellulose; **ICH:** International Council for Harmonisation; **LDL:** Low-Density Lipoprotein; **MCC:** Microcrystalline Cellulose; **ODT:** Orodispersible Tablet; **PEG:** Polyethylene Glycol; **PM:** Physical Mixture; **PXRD:** Powder X-ray Diffraction; **PVP:** Polyvinylpyrrolidone; **QbD:** Quality by Design; **rpm:** Revolutions per Minute; **SD:** Solid Dispersion; **SLS:** Sodium Lauryl Sulfate; **USP:** United States Pharmacopeia; **UV:** Ultraviolet; **VLDL:** Very Low-Density Lipoprotein.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study aimed to enhance the aqueous solubility and dissolution rate of ATS, a BCS class II drug with poor bioavailability, by developing a soy lecithin-based solid dispersion. The solvent evaporation method using methanol and ethanol (1:1) was employed to prepare solid dispersions with varying ATS-to-soy lecithin ratios. Adsorbent (aluminum magnesium metasilicate) and disintegrant (croscarmellose) were incorporated to improve flow properties and dissolution. Formulation S4 (ATS: soy lecithin ratio 2:3) demonstrated optimal performance, achieving a sixfold increase in saturation solubility (614±24 µg/mL vs. 110 µg/mL for pure ATS) and 91.2% drug release in 90 min. Characterization via DSC and XRD confirmed the transition of crystalline ATS to an amorphous state within the phospholipid matrix, enhancing solubility. ODTs formulated with S4 exhibited superior drug content (90.58%) and dissolution (92.92% in 60 min) compared to tablets containing pure ATS (43.39% drug content, 46.43% dissolution). Stability studies under accelerated conditions (40°C/75% RH) showed minimal changes in ODT properties, indicating robustness. The use of soy lecithin as a carrier offered advantages over polymers, including reduced recrystallization risk and effective drug dispersion. However, the dissolution of the developed ODTs remained lower than marketed formulations, highlighting the need for further optimization. The study underscores phospholipid-based solid dispersions as a promising strategy to overcome solubility limitations of ATS, potentially reducing therapeutic doses. Future work should focus on *in vivo* studies, hybrid matrices with biodegradable polymers, and quality-by-design approaches for scalable production.

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