Solubility and Dissolution Enhancement of Atorvastatin Calcium using Phospholipid Solid Dispersion Technique. #

Bashar K. K. Ghyadh*1 and Eman B. H. Al-Khedairy1

*2nd Scientific Conference for Postgraduate Students Researches. 
1Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Atorvastatin (ATR) is a poorly water-soluble anti-hyperlipidemic drug. The drug belongs to the class II group, according to the biopharmaceutical classification system (BCS), with low bioavailability due to its low solubility. Solid dispersion is an effective technique for enhancing the solubility and dissolution of drugs. Phosphatidylcholine (PC) was selected as an unusual carrier for ATR due to its lipid-lowering effect to prepare phospholipid solid dispersion (PSD) with or without adsorbent (magnesium aluminium silicate, silicon dioxide 15nm, silicon dioxide 30nm, calcium silicate) was used to prepare ATR PSD using different drug: PC; adsorbent ratios by solvent evaporation method. The resulted PSD was evaluated for its percentage yield, drug content, solubility, dissolution rate, Fourier transformation infrared spectroscopy (FTIR), powder X-ray diffraction study (PXRD), and differential scanning calorimetry (DSC). The prepared (PSD) showed improvement in drug solubility in all prepared formulas. The best result was obtained with F5 (ATR: PC: MAS 1:3:4). The solubility was increased by 21 folds compared to the pure drug with enhanced dissolution and decreased crystallinity, as confirmed by DSC and PXRD. While FTIR results indicate compatibility between the drug and the excipients.

Keywords: Atorvastatin, Phospholipid Solid dispersion, Phosphatidylcholine, Magnesium aluminium silicate.

Introduction

Poor aqueous solubility is one of the most frequently encountered problems for drug substance formulation. The low solubility leads to a very slow drug dissolution rate and poor intestinal absorption [1]. The bioavailability of BCS class II drugs is likely to be dissolution rate limited. The BCS class II drugs have been on focus for solubility enhancement researches, and several formulation approaches for this class of compounds have been developed [2].

Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor; it is a lipid-regulating drug with actions on plasma lipids similar to those of simvastatin. It is also used for primary and secondary prophylaxis of cardiovascular events [3]. Atorvastatin (Figure 1) is a white or almost white powder. Very slightly soluble in water, slightly soluble in alcohol, practically insoluble in dichloromethane. It has log P 6.36 and an absolute oral bioavailability of 12 %. The poor oral bioavailability is attributed to pre-systemic clearance in the gastrointestinal mucosa, high hepatic first-pass metabolism, and low water solubility [4,5]. Many techniques were utilized to enhance the aqueous solubility of ATR including nanosuspension and complexation with cyclodextrin [6,7].
Solid dispersion (SD) is the most generally used technique for bioavailability enhancement of poorly water-soluble drugs, as the drug is dispersed in a freely soluble carrier (9).

Due to their amphiphilic nature, phospholipids can be technically used in oral dosage forms as emulsifiers, wetting agents, solubilizers, and liposome former. In addition, unsaturated phospholipids can be used as a carrier for solid dispersions when solubilization and fast release of the API are required, whereas saturated phospholipids may be suitable for slow-release tablet formulations (10). The aqueous solubility of celecoxib and that of aprepitant was found to be enhanced using phospholipids (especially phosphatidylcholine) as a carrier for the preparation of solid dispersion (11,12).

Phospholipids may exhibit high levels of adhesiveness and poor flow properties in their formulation as solid dosage forms, making them more challenging to work when compared to polymer-based solid dispersion systems. As a result, transforming phospholipid-based dispersion systems into a solid state by adding adsorbent is necessary to enhance their ease of handling and processability (13).

In the present work, phospholipid-based solid dispersions (PSD) of ATR were prepared using phosphatidylcholine as a carrier as a trial to improve its solubility and dissolution rates in the solid state.

This carrier was selected as it has a lipid-lowering effect so that a synergistic effect may be obtained with ATR (14).

To impart solid-state properties to the ATR-PSD system, inorganic mesoporous excipients were employed as adsorbents.

**Materials and Method**

**Materials**

Atorvastatin calcium (ATR) was supplied by Pioneer pharmaceutical company, Iraq, as a gift sample. Phosphatidylcholine was purchased from Shanghai, Meryer biochemical technology, China. Magnesium aluminium silicate (MAS), silicon dioxide (SiO2) 30nm, silicon dioxide 15nm and Calcium silicate were purchased from Hangzhou, Hyperchem, China.

**Method**

**Preparation of phospholipid solid dispersion**

Phospholipid solid dispersions (PSD) of ATR were prepared by solvent evaporation technique. A predetermined amount of ATR and PC were dissolved in methanol. Then adsorbent was added gradually to the solution with gentle stirring using a magnetic stirrer for 1 h, in weight equal to 50% w/w to the total weight of solid dispersion (Table 1). The resulting mixture was left for 24 hours in a 40°C oven for removal of solvent. Finally, the mass was pulverized and sieved using no. 60 mesh sieve and stored in a desiccator for further use (12).

**Preparation of the physical mixture (PM)**

By using the same ratio of the best formula, the PC and the adsorbent were mixed together by using a mortar and pestle till we get a fine powder. Then ATR was added to the resulting powder and mixed well. The PM powder was sieved using no. 60 mesh sieve to get uniform particle size.

**Evaluation of phospholipid-solid dispersion**

**Determination of percentage yield (PY %) of the prepared PSD**

The practical percentage yield (PY%) was determined for all the prepared PSD formulations. The PY% was calculated by dividing the actual mass of the PSD formula by the theoretical mass of PSD, using the equation below (15).

\[
PY\% = \frac{\text{Practical weight (PSD)}}{\text{Theoretical weight (PSD)}} \times 100
\]

**Determination of drug content of the prepared PSD**

Using a 50 ml volumetric flask, an accurately weighed amount of PSD equivalent to 10 mg of ATR was dissolved in 50 ml methanol. Then after suitable dilution the solution was assayed for drug content using UV spectrophotometric method at 246 nm. The percentage of drug content in the PSD was calculated by using the equation below (7).

\[
\text{drug content} \% = \frac{\text{Actual ATR amount in PSD}}{\text{Theoretical ATR amount in PSD}} \times 100
\]
Table 1. Composition of different ATR-PSD formulas.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>ATR (g.)</th>
<th>PC (g.)</th>
<th>MAS (g.)</th>
<th>SiO2 30nm (g.)</th>
<th>SiO2 15nm (g.)</th>
<th>Ca. Silicate (g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>0.5</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>0.5</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F4</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F5</td>
<td>0.5</td>
<td>1.5</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F6</td>
<td>0.5</td>
<td>2.5</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F7</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F8</td>
<td>0.5</td>
<td>1.5</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F9</td>
<td>0.5</td>
<td>2.5</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F10</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>F11</td>
<td>0.5</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>F12</td>
<td>0.5</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>F13</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>F14</td>
<td>0.5</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>F15</td>
<td>0.5</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

**Determination of saturation solubility**

Saturated solubility was determined by adding an excess amount of pure ATR and ATR-PSDs into 10 ml of water, and incubated in a water bath at 25 °C for 48 hours. The samples were filtered using a 0.45μm filter syringe and diluted when necessary. (16,17). The dissolved ATR was analyzed using UV-spectrophotometry at 240 λ max. The procedure was done in triplicate. 

**In-vitro dissolution studies**

The in-vitro dissolution of pure ATR and PSDs was assessed using a USP apparatus II (RC-6, China) An equivalent amount of 10 mg of ATR was dispersed in 900 ml of 0.05M phosphate buffer (pH 6.8) as a dissolution media, and the temperature was maintained at 37±0.5°C using a thermostatic water bath. The apparatus was set to rotate at a speed of 75 rpm. Samples were collected at regular intervals and replaced with a fresh dissolution medium. The samples were filtered and measured using spectrophotometry at 240 nm. This evaluation was conducted on the PSD formulations that exhibited the highest solubility in triplicate.

The dissolution profile was statistically analyzed using a similarity factor (f2) as calculated by the following equation.

\[
f_2 = 50 \cdot \log \left\{ 100 \cdot \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} \left( \frac{R_t - T_t}{T_{max}} \right)^2 \right]^{-0.5} \right\}
\]

At time t, (Rt) represents the dissolution value of the reference, (Tt) represents the dissolution value of the test, and (n) denotes the number of dissolution time points. Dissolution profiles are deemed similar when f2 values exceed 50 (ranging from 50 to 100), while dissolution profiles are deemed dissimilar if the f2 value falls below 50 (19).

**Fourier Transforms Infrared Spectroscopy (FTIR)**

The FTIR spectra of pure ATR, PC, selected adsorbent, the optimal formula, and its PM were analyzed to investigate potential interactions between the drug and the component of the formula. An infrared spectrophotometer (IRAffinity-1, Shimadzu, Japan) was employed to obtain these spectra over a scanning range of 400-4000 cm⁻¹ (20).

**Powder x-ray diffraction (PXRD)**

Powder X-ray diffraction (DX2700BH, China) was used to evaluate the crystalline state of the pure ATR, PC, selected adsorbent, the selected PSD formula, and its PM. The target metals Cu, filter Kα, 40kV, and 30mA. The scan was over a 2θ range of 5-80° at 1.5406 Å wavelength (21).

**Differential scanning calorimetry (DSC)**

Thermal characteristics were analyzed using an automatic thermal analyzer system (Setaram, DSC-131 evo, France) of the pure ATR, MAS, the selected PSD formula, and its PM. Each sample (10 mg) was placed in none hermetically aluminum pan and heated at a rate of 10°C/ min over temperatures 30°C to 300°C. The analysis was carried out under the atmosphere flow conditions (22).

**Statistical analysis**

The mean and standard deviation (SD) of the triplicate samples were calculated and presented as the outcomes of the experiments. The statistical analysis was performed using one-way analysis of variance (ANOVA) and the test level of significance was set at (P < 0.05). The statistical software used for the analysis was SPSS version 26.

**Results and Discussion**

**Percentage yield (PY %) and drug content of prepared PSD**

Without adding adsorbent, the prepared PSDs formulas resulted in sticky mass that was...
unable to sieve. Except for Calcium silicate, a high percentage yield ranging between 88.65-97.21% was obtained by adding adsorbents (Table 2). This result indicates that this method was suitable and efficient when using MAS or SiO2. Due to the lower silicon dioxide content in calcium silicate, it may have fewer available silanol groups on its surface compared to MAS and SiO2 (14), resulting in a reduced adsorption capacity for phospholipids due to a limited number of interaction sites. Therefore, this adsorbent was canceled from further study (23).

On the other hand, the findings of percentage drug content fell within the range of (98.31-101.55%) w/w for all yielded formulas (Table 2), aligning with the USP guidelines of (98-102%) (18). These observations suggest that the preparation process resulted in minimal loss of ATR with uniform dispersion within ATR-PSD formulas.

Table 2. The practical yield percent (PY %) and drug content of ATR-PSDs using different adsorbents.

<table>
<thead>
<tr>
<th>Formula Code</th>
<th>Percentage yield (PY %)</th>
<th>Drug content (w/w) (%) (Mean ±SD (n=3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
<tr>
<td>F4</td>
<td>92.57%</td>
<td>100.6% ±0.9</td>
</tr>
<tr>
<td>F5</td>
<td>88.65%</td>
<td>98.55% ±0.33</td>
</tr>
<tr>
<td>F6</td>
<td>94.10%</td>
<td>99.23% ±0.09</td>
</tr>
<tr>
<td>F7</td>
<td>96.10%</td>
<td>98.36% ±0.08</td>
</tr>
<tr>
<td>F8</td>
<td>95.80%</td>
<td>98.35% ±0.01</td>
</tr>
<tr>
<td>F9</td>
<td>97.21%</td>
<td>101.55% ±0.03</td>
</tr>
<tr>
<td>F10</td>
<td>90.60%</td>
<td>99.58% ±0.14</td>
</tr>
<tr>
<td>F11</td>
<td>97.01%</td>
<td>99.1% ±0.06</td>
</tr>
<tr>
<td>F12</td>
<td>93.23%</td>
<td>100.2% ±0.17</td>
</tr>
<tr>
<td>F13</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
<tr>
<td>F14</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
<tr>
<td>F15</td>
<td>Sticky mass</td>
<td>-</td>
</tr>
</tbody>
</table>

Saturation solubility of pure ATR and ATR-PSD and ATR-PSD formulas are presented in Table 3. The saturation solubility study results for pure ATR.

Table 3. The Saturation solubility of pure ATR and ATR-PSDs formulas using different Drug: PC: adsorbent ratios in distilled water at 25°C

<table>
<thead>
<tr>
<th>Formula code</th>
<th>(ATR: PC) and (ATR: PC: adsorbent) ratio</th>
<th>Saturated solubility µg/ml, Mean ±SD (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR</td>
<td></td>
<td>150.8±6.19</td>
</tr>
<tr>
<td>F1</td>
<td>ATR: PC (1:1)</td>
<td>193.9±2.59</td>
</tr>
<tr>
<td>F2</td>
<td>ATR: PC (1:3)</td>
<td>942.67±22.12</td>
</tr>
<tr>
<td>F3</td>
<td>ATR: PC (1:5)</td>
<td>1246±24.25</td>
</tr>
<tr>
<td>F4</td>
<td>ATR: PC: MAS (1:1:2)</td>
<td>1805.33±27.01</td>
</tr>
<tr>
<td>F5</td>
<td>ATR: PC: MAS (1:3:4)</td>
<td>3151.33±49.36</td>
</tr>
<tr>
<td>F6</td>
<td>ATR: PC: MAS (1:5:6)</td>
<td>2496.67±23.03</td>
</tr>
<tr>
<td>F7</td>
<td>ATR: PC: SiO2 30nm (1:1:2)</td>
<td>657.67±6.5</td>
</tr>
<tr>
<td>F8</td>
<td>ATR: PC: SiO2 30nm (1:3:4)</td>
<td>1603.67±5.13</td>
</tr>
<tr>
<td>F9</td>
<td>ATR: PC: SiO2 30nm (1:5:6)</td>
<td>2455.33±14.01</td>
</tr>
<tr>
<td>F10</td>
<td>ATR: PC: SiO2 15nm (1:1:2)</td>
<td>228.6±2.86</td>
</tr>
<tr>
<td>F11</td>
<td>ATR: PC: SiO2 15nm (1:3:4)</td>
<td>500.02±13.95</td>
</tr>
<tr>
<td>F12</td>
<td>ATR: PC: SiO2 15nm (1:5:6)</td>
<td>993.30±36.29</td>
</tr>
</tbody>
</table>

Except for F1 and F10; the solubility of ATR was significantly improved (P-value <0.05) in all PSD formulations as compared to the solubility of the pure drug.

A significant enhancement in solubility was obtained (P<0.05) by using a higher ratio of PC in PSDs. PC being an amphiphilic surfactant, increased the solubility of the drug by the action of wetting and dispersion (11,24).

Furthermore, a significant enhancement in solubility (P<0.05) was obtained by using an adsorbent in the formulation. This result was in alignment with the study by Rajesh S. J et al who found enhancement in solubility of nifedipine when adsorbed onto porous adsorbent (25). This can be
attributed to the adsorption of the dispersion system, consisting of the drug and phosphatidylcholine, onto the high surface area and hydrophilic adsorbent material. This adsorption results in an increased surface area of the drug that is exposed to the solvent, improved wettability of the drug particles, prevention of agglomeration, and an increase in the solubility of the drug (26). For all ATR: PC: adsorbent ratio, the order of the impact of adsorbents on improving solubility was observed to be MAS > SiO2 30nm > SiO2 15nm. This is because MAS has a multilayer of silicate resulted in a large surface area (27).

The higher solubility of SiO2 30nm compared to SiO2 15nm can be attributed to a greater loading of ATR: PC dispersion system on silica, as it has been demonstrated that increasing pore size leads to increased drug loading (23).

**In-vitro dissolution studies**

Comparative in-vitro dissolution of the pure ATR, F5, F9, and F12 was studied (Figure 2). These formulas were selected on the base of the solubility of the best ART: PC: adsorbent ratio for each adsorbent type. The results indicated that F5, F9, and F12 exhibited improved dissolution rates, with respective f2 values of 27.62, 38.59, and 40.04, in comparison to pure ATR.

F5 which is composed of ATR: PC: MAS in a 1:3:4 ratio showed the highest release profile (91.65%) after 15 minutes as compared with F9 (79%), F12 (76.5%), and pure ATR (61%).

This enhancement of the dissolution profile can be explained by multiple factors, including the solubilizing effect of PC, improved wettability and dispersibility of the drug, adsorption onto MAS which has hydrophilic properties, in addition to its disintegration effect in aqueous media (13,28,29).

**Figure 2. Comparison between in-vitro dissolution profile of the ATR, F5, F9, and F12 in 0.05M phosphate buffer (pH 6.8) at 37°C±0.5.**

To prove the effectiveness of such type of solid dispersion, a comparison between F5 and its PM was conducted. A significant improvement in dissolution rate (f2=37.66) demonstrates the effectiveness of the technique as shown in Figure (3) (30).

![Figure 3. Comparison between the in-vitro dissolution profile of the F5 and its PM in 0.05M phosphate buffer (pH 6.8) at 37°C±0.5.](image)

**Selection of the best PSD**

The (F5) formula, which combines ATR, PC, and MAS in a 1:3:4 ratio, was chosen as the best formula. It had the highest solubility and released the greatest amount of ATR in 15 minutes. This formula was subjected to further in-vitro evaluation studies.

**Evaluation of best PSD**

**X-ray powder diffraction (XRD)**

The XRD diffractogram of ATR, PC, MAS, F5, and its PM are shown in Figure 4. Distinctive peaks with high intensity were observed in the diffraction pattern (Braggs peaks) of the pure drug at 2θ of 9.06°, 10.27°, 11.7°, 16.79°, 19.22°, 21.39°, 22.4°, and 23.18°, which suggests that the drug is in a crystalline state. These results were in agreement with the previous studies (26). A notable reduction or absence of the characteristic ATR peaks was evident by comparing the XRD diffractogram of F5 with that of pure ATR and PM, suggesting the predominant presence of an amorphous state within the phospholipid solid dispersion (31). Since the amorphous form is easier to dissolve than the crystalline form, this may explain the solubility enhancement of F5 (32).

**Differential scanning calorimetry (DSC)**

Thermograms of ATR, MAS, F5, and its PM are shown in Figure 5. The DSC plot for ATR demonstrates an endothermic peak observed at 168.36°C, which corresponds to its melting point (33). This indicates the crystallinity and purity of the ATR. While the DSC thermogram of magnesium silicate exhibited a wide and gradual dehydration peak ranging between 100.6 to 140.1°C (34), whereas no thermogram was obtained for PC as it is soft and tacky material to be operated by DSC.

While for PM, the intensity and melting point of the ATR peak decreased to 164.6°C which can be attributed to dilution with other components. This result was in agreement with that obtained by Samer A. et al (26). The thermogram of F5 shows the disappearance of the ATR peak which may be due to its complete dispersion in the PC and conversion of the drug from crystalline to an amorphous state (11).
phospholipid solid dispersion

Figure 4. X-ray powder diffraction of pure ATR (Atorvastatin), PC (Phosphatidylcholine), MAS (Magnesium aluminum silicate), F5, and its PM (physical mixture).

Figure 5. DSC of pure ATR (Atorvastatin), MAS (Magnesium aluminum silicate), F5, and its PM (physical mixture).

Fourier transform infrared

The ATR spectrum shows peaks at 3363 cm\(^{-1}\) (O–H stretching), 3236 cm\(^{-1}\) (N–H stretching), 3055 cm\(^{-1}\) (aromatic C–H stretching), 2970 and 2920 cm\(^{-1}\) (aliphatic C–H stretching), 1651 cm\(^{-1}\) (amide C=O stretching), 1577 and 1550 cm\(^{-1}\) (aromatic C=C stretching), 1508 cm\(^{-1}\) (N–H bending), 744 cm\(^{-1}\) (out of plane N-H wagging)\(^{(35)}\) as shown in Figure 6.

While the MAS spectrum shows peaks at 3614 cm\(^{-1}\) (free O–H stretching), 1635 cm\(^{-1}\) (Si=O stretching), and 987 cm\(^{-1}\) (Si–O stretching)\(^{(36)}\).

The FTIR spectrum of PC shows peaks at 1743 cm\(^{-1}\) (C=O stretching), 1450 and 1419 cm\(^{-1}\) (CH\(_2\) scissoring), and 1022 cm\(^{-1}\) (C–O–P stretching)\(^{(37)}\).
Moreover, all ATR characteristic peaks are present in the PM FTIR spectrum with lower intensity. This contributed to the dilution and predominant peaks of other components.

Figure 6. FTIR Spectrum of pure ATR (Atorvastatin), PC (Phosphatidylcholine), MAS (Magnesium aluminum silicate), F5, and its PM (physical mixture).

The stretching of the C=O bond in PC, at 1743 cm\(^{-1}\), showed a shift towards a lower wavenumber of 1735 cm\(^{-1}\) in F5. Additionally, this peak exhibited reduced intensity, suggesting an electrostatic interaction between the carboxyl group of PC and positively charged sites located at the edges of the MAS structure. Which confirms the adsorption process\(^{(38)}\).

The characteristic peaks of the ATR spectrum can still be observed but with a reduction in intensity, in the FTIR spectrum of F5. This suggests that there is no chemical incompatibility between the drug, PC, and MAS.
Conclusion
PSD formulations for enhancing the aqueous solubility and dissolution rate of ATR were developed using the solvent evaporation technique with acceptable production yield. While dispersing ATR in PC alone demonstrated a significant improvement in ATR's aqueous solubility, the waxy texture of PC made it unsuitable for developing solid dosage forms. Therefore, adding adsorbent was necessary for handling the product. MAS was the best adsorbent and gave additional enhancement of aqueous solubility. In conclusion, the PSD technique demonstrates its effectiveness and efficiency technique for enhancing the solubility and dissolution rate of hydrophobic drugs.

Acknowledgement
The authors sincerely thank the College of Pharmacy, University of Baghdad, for their valuable support in providing education and facilities that facilitated this work. An acknowledgement to Pioneer Pharmaceutical Industry for generously gifting the atorvastatin calcium and other materials used in this research.

Conflicts of Interest
The authors declare that they have no conflicts of interest related to this work.

Funding
The authors declare that this research received no financial support from any institution.

Ethics Statements
According to the research integrity rules in our country, the study does not require ethical approval from an ethics committee as it’s an in-vitro study.

Author Contribution
All authors have actively participated in the research process and have reviewed the results. Additionally, they have approved the final version of the manuscript before submission.

References
16. Hussain HAM, Al-Khedia EBH. Preparation and in vitro evaluation of cyclodextrin based effervescent and dispersible granules of...
