



Effect of Surfactants on the Solubility of Atorvastatin Calcium

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How to cite this paper: Liang, G.Y., Sun, W.J., Ai, Z.W., Liu, J.P., Ruan, C.Y. and Jiang, C.J. (2025) Effect of Surfactants on the Solubility of Atorvastatin Calcium. *Open Access Library Journal*, **12**: e12613. <https://doi.org/10.4236/oalib.1112613>

Received: November 11, 2024

Accepted: January 27, 2025

Published: January 30, 2025

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Abstract

Atorvastatin calcium (ATC) is a widely prescribed synthetic cholesterol-lowering agent classified as BCS class II. This study aimed to investigate the solubility of ATC in a methanol-water mixture, which was illustrated through a ternary phase diagram. Additionally, the influence of varying concentrations of Tween 20 on the solubility of ATC in this aqueous methanol mixture was examined. ATC exhibits maximum solubility in pure methanol, and the incorporation of surfactants significantly modifies the drug's solubility profile depending on its concentration.

Subject Areas

Chemical Engineering & Technology

Keywords

Atorvastatin Calcium, Solubility, Ternary Phase Diagram, Surfactant

1. Introduction

Hyperlipidemia represents a significant global health challenge due to its strong association with cardiovascular diseases, including cardiovascular disease and peripheral vascular disease [1]. This condition can lead to the development of atherosclerotic plaques that obstruct blood flow to critical organs such as the brain, limbs, and heart [2]. The primary objective in mitigating atherosclerotic cardiovascular disease (ASCVD) is to lower LDL cholesterol levels through statin therapy [3].

Atorvastatin calcium (ATC), a widely used synthetic cholesterol-lowering agent, is employed in the treatment of hypercholesterolemia and is classified as a Class II BCS formulation. However, its water solubility and absolute bioavailability are notably low, with an oral bioavailability of only 14% [4]-[6]. Various strategies

have been explored to enhance its solubility. These approaches include salt formation, crystal modification, solid dispersion techniques, nanosuspension development, complexation methods, and self-emulsifying drug delivery systems [10]. Among these strategies, co-crystallization utilizing inactive conformations has emerged as a commonly adopted method for improving the solubility of ATC [5]. Additionally, cocrystal formulations and eutectic mixtures present alternative avenues for enhancing the solubility profile of ATC [6]-[9].

There is currently limited data available regarding the solubility of ATC in various solvent mixtures. In recent years, the solubility of ATC in pure solvents such as water, n-propyl alcohol, 2-propyl alcohol, acetone, and acetone-water mixtures using a shaker method across different temperature ranges from 293.15 K to 328.15 K was measured [11].

Surfactants play a crucial role in enhancing the solubility of insoluble drugs, improving the wettability of their crystalline surfaces, and increasing their dissolution rates. These compounds can be categorized into various classes based on their dissociation properties in water. Tween 20 is a notable surfactant characterized by its large molecular structure, which contains both hydrophilic and lipophilic components. Consequently, it facilitates the absorption of large molecules that are otherwise insoluble in water by plants and aids in the permeation of water through biofilms with high lipid content. Tween 20 is extensively utilized as an emulsifier and solubilizer for certain insoluble drugs in aqueous environments. For instance, it is frequently employed in Chinese herbal injections to prevent the precipitation of minor amounts of insoluble constituents and has gained widespread application for solubilizing drugs with poor water solubility [12].

For a three-component system, the ternary phase diagram can effectively illustrate the distribution of each phase. Additionally, methanol-water serves as a suitable solvent for preparing crystal form I of Atorvastatin Calcium [13]. Therefore, the objective of this paper is to investigate the solubility of Atorvastatin Calcium in a methanol-water mixture using both ternary phase diagrams and absorption spectrophotometry. Furthermore, we discuss the impact of Tween 20 on ATC solubility. This study aims to provide insights for developing further formulations of Atorvastatin Calcium.

2. Experimental Section

2.1. Reagents

Atorvastatin calcium (Crystal form I), purchased from Zhejiang Lepu Pharmaceutical Co., LTD. Anhydrous ethanol (analytical pure) was purchased from Shanghai Lingfeng Chemical Reagent Co., LTD. Tween 20 was purchased from Anhui Zesheng Technology Co., LTD.

2.2. Instruments

Electronic balance (Shanghai Balance Instrument, Model: FA2204). Ultraviolet-Visible Spectrophotometer (Shanghai Yuan Analysis Instrument Co., LTD.,

Model: UV-5100). Constant temperature shaking Table (Hangzhou Chuanyi Experimental Instrument Co., LTD., Model: TS-2102C).

2.3. Preparation of Ternary Phase Diagram of ATC-Methanol-Water System

ATC solid-liquid equilibrium data were obtained at 303.15, 313.15, and 323.15 K using a static method, specifically gravimetry. Excess solid atorvastatin calcium was added to varying proportions of a methanol-water solvent mixture in a 15 mL centrifuge tube to create a suspension. The centrifuge tube was then placed in an air shaker, where the rotational speed and temperature were set; it remained there for full agitation over a period of 24 hours. Following the solid-liquid phase separation, the supernatant was carefully extracted and filtered through an organic filter membrane to yield the saturated solution of atorvastatin calcium. The saturated solution was transferred into a small beaker and allowed to evaporate until dry before being placed in an oven for further drying. Throughout all experiments, mass measurements were conducted using an electronic balance with an accuracy of ± 0.001 g. Each experiment was repeated three times to minimize errors, with the mean value representing the solid-liquid equilibrium data for atorvastatin calcium under the specified conditions.

2.4. Influence of Tween 20 on the ATC Solubility

At 303.15 K, excess solid atorvastatin calcium was added to a 15 mL centrifuge tube along with varying proportions of a methanol-water solvent mixture. Different amounts of Tween 20 were then incorporated to create a suspension. The centrifuge tube was placed on an air shaking table, where the rotational speed and temperature were set for thorough shaking over a period of 24 hours. Following the solid-liquid phase separation, the supernatant was carefully removed and filtered through an organic filter membrane to obtain the saturated solution of atorvastatin calcium, which was subsequently diluted. The absorbance of this solution was measured at a wavelength of 245 nm, allowing for the calculation of drug content.

3. Results and Discussion

3.1. Ternary Phase Diagram of ATC-Methanol-Water System

The phase diagram of the ATC-methanol-water system at temperatures of 303.15 K, 313.15 K, and 323.15 K is presented in **Figure 1**. Each phase diagram is categorized into four distinct regions: the unsaturated homogeneous region (Region I), the liquid-liquid region (Region II), the solid-liquid-liquid equilibrium region (Region III), and the solid-liquid region (Region IV). As the temperature increases, the liquid-liquid region (Region II) expands progressively, while the solid-liquid region (Region IV) diminishes. It is observed that the solubility of ATC in the binary mixture decreases with a reduction in temperature and an increase in the mass fraction of water (See **Table 1** and **Figure 1**).

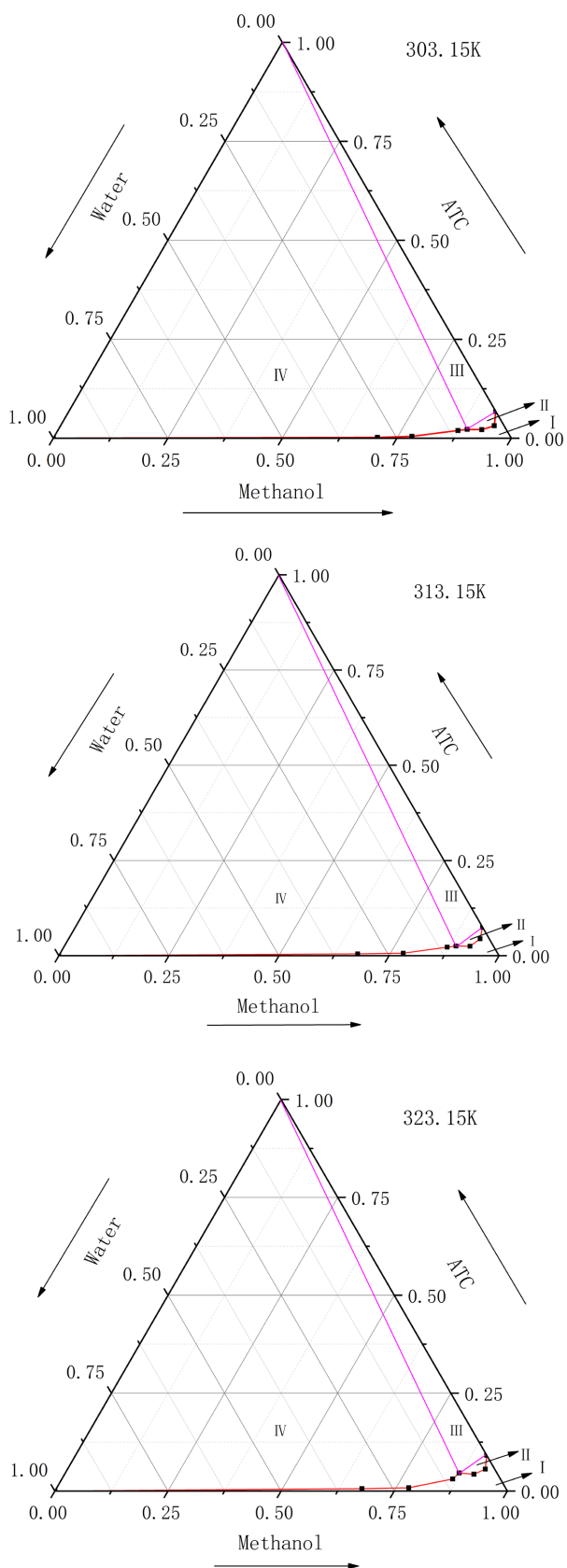


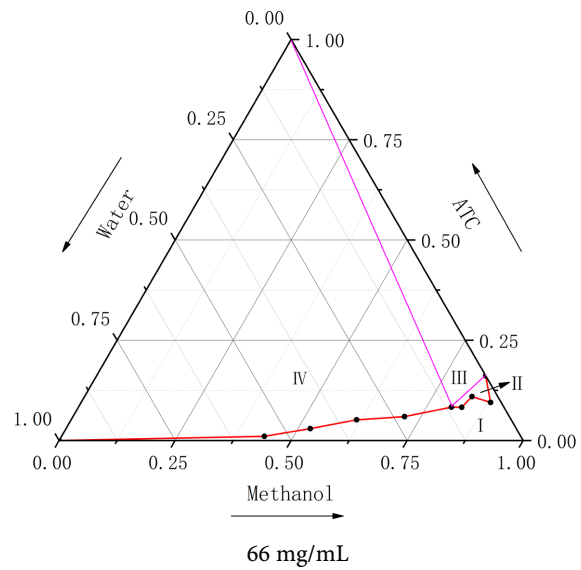
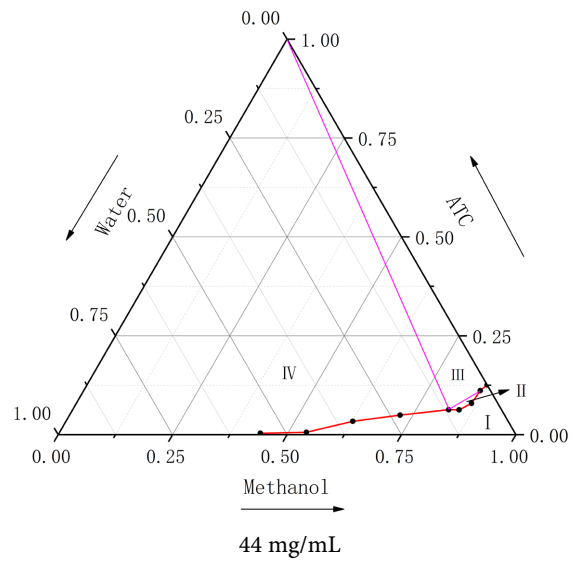
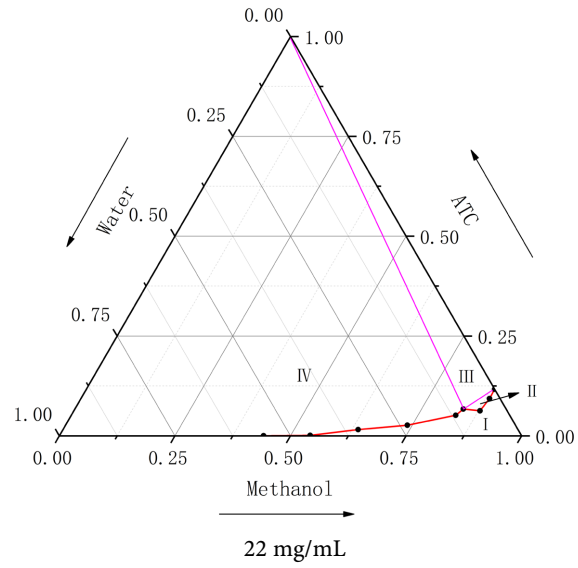
Figure 1. Phase diagram of ATC-methanol-water system at different temperatures.

Table 1. Solid-liquid equilibrium composition of ATC at different temperatures.

303.15 K		
W_{Methanol}	W_{ATC}	W_{Water}
0.9325	0.0675	0
0.9470	0.0318	0.0212
0.9252	0.0215	0.0535
0.8923	0.0224	0.0853
0.8738	0.0195	0.1067
0.7809	0.0046	0.2145
0.7752	0.0022	0.3194
313.15 K		
0.9253	0.0747	0
0.9347	0.0443	0.0210
0.9218	0.0248	0.0534
0.8994	0.0256	0.0850
0.8710	0.0226	0.1063
0.7793	0.0066	0.2141
0.6766	0.0047	0.3187
323.15 K		
0.9087	0.0913	0
0.9234	0.0559	0.0207
0.9047	0.0430	0.0523
0.8618	0.0458	0.0824
0.8636	0.0309	0.1054
0.7780	0.0082	0.2137
0.6757	0.0060	0.3182

3.2. Influence of Tween 20 on the Phase Diagram

The phase diagram of the ATC-methanol-water system at 303.15 K, with Tween 20 concentrations of 22 mg/mL, 44 mg/mL, 66 mg/mL, and 88 mg/mL, is depicted in **Figure 2**. Each phase diagram is divided into four distinct regions: unsaturated homogeneous region (Region I), liquid-liquid region (Region II), solid-liquid-liquid equilibrium region (Region III), and solid-liquid region (Region IV). A comparison with the phase diagram lacking Tween 20 clearly indicates that the solubility of ATC increases. As the concentration of Tween 20 rises, both the unsaturated homogeneous region and the liquid-liquid region gradually expand, while the solid-liquid region decreases. This suggests that the overall solubility of ATC in the binary mixture increases with higher amounts of Tween 20 (See **Table 2** and **Figure 2**).



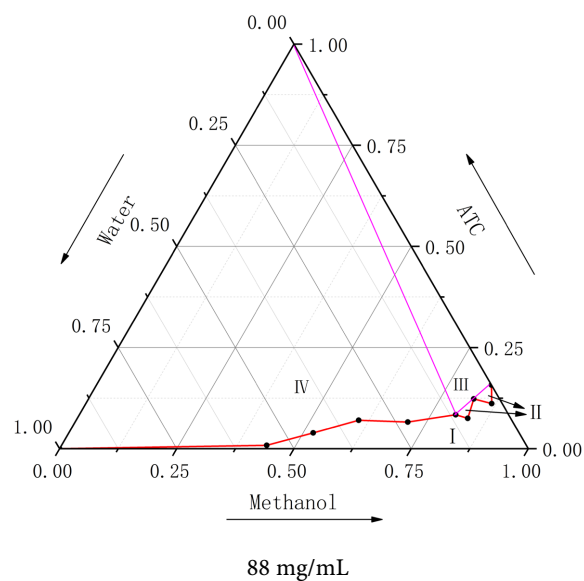


Figure 2. Phase diagram of the ATC-methanol-water system at different concentration.

Table 2. Influence of Tween 20 concentration on the phase diagram.

Tween 20 22 mg/mL			Tween 20 44 mg/mL		
W_{Methanol}	W_{ATC}	W_{Water}	W_{Methanol}	W_{ATC}	W_{Water}
0.8833	0.1167	0	0.8743	0.1257	0
0.8840	0.0932	0.0228	0.8664	0.1112	0.0224
0.8787	0.0628	0.0585	0.8635	0.0791	0.0574
0.8403	0.0673	0.0924	0.8444	0.0628	0.0928
0.8318	0.0514	0.1168	0.8214	0.0632	0.1154
0.7396	0.0266	0.2338	0.7223	0.0494	0.2283
0.6385	0.0156	0.3459	0.6267	0.0337	0.3396
0.5420	0.0011	0.4569	0.5395	0.0058	0.4547
0.4415	0.0004	0.5581	0.4400	0.0036	0.5564
Tween 20 66 mg/mL			Tween 20 88 mg/mL		
0.8385	0.1615	0	0.8425	0.1575	0
0.8825	0.0947	0.0228	0.8659	0.1117	0.0224
0.8349	0.1095	0.0556	0.8221	0.1232	0.0547
0.8263	0.0829	0.0908	0.8333	0.0751	0.0916
0.8038	0.0833	0.1129	0.8031	0.0841	0.1128
0.7146	0.0595	0.2259	0.7097	0.0660	0.2243
0.6152	0.0514	0.3334	0.6028	0.0706	0.3266
0.5266	0.0296	0.4438	0.5214	0.0392	0.4394
0.4371	0.0104	0.5525	0.4380	0.0082	0.5538

3.3. Influence of Tween 20 on ATC Solubility

Table 3 illustrates the impact of surfactants on the solubility of drugs in binary solutions of methanol and water. The solubility of the drug in pure water was found to be the lowest, at 0.181 mg/mL, when no surfactant was added. In contrast, the highest drug solubility was observed in methanol, reaching 68.315 mg/mL. When Tween 20 was added at concentrations of 22 mg/mL and 44 mg/mL, the solubility of ATC increased with the rising methanol-water ratio, similar to the pattern observed when no Tween 20 was present. However, at concentrations of 66 mg/mL and 88 mg/mL of Tween 20, the solubility of ATC exhibited fluctuations without any discernible trend corresponding to the mass ratio of the solvent composition. Notably, when the concentration of Tween 20 was 88 mg/mL, there was a decline in the solubility of ATC in both water and methanol.

Table 3. Influence of Tween 20 concentration on ATC solubility.

Methanol:Water (V:V)	C (mg/mL)				
	Tween 20 (0)	Tween 20 (22 mg/mL)	Tween 20 (44 mg/mL)	Tween 20 (66 mg/mL)	Tween 20 (88 mg/mL)
Water	0.181	1.030	1.520	2.457	2.237
1:9	0.478	0.687	1.018	1.890	2.970
2:8	0.687	1.068	1.544	1.652	2.312
3:7	1.106	1.662	2.305	3.107	3.741
4:6	2.712	2.297	3.177	3.484	4.720
5:5	4.534	3.788	3.279	9.430	9.287
6:4	10.150	9.433	5.197	8.971	7.495
7:3	14.297	13.201	8.803	15.258	22.193
8:2	23.645	28.366	39.225	23.115	39.201
9:1	27.473	32.186	68.280	58.351	35.914
Methanol	68.315	104.565	131.725	152.374	147.955

Additives can influence the nucleation and growth of drug molecules, thereby affecting their crystal morphology [14]. Surfactants, in particular, play a significant role in altering the solubility and crystallization processes of drugs. The form of the Active Pharmaceutical Ingredient (API) depends on the concentration of the surfactant used. Different surfactants exhibit varying physical and chemical properties, which arise from their distinct molecular structures and self-organizing behaviors. Classic nucleation theory predicts that crystal nucleation increases with decreasing interfacial tension.

Research indicates that the influence of solvents on crystallization behavior can be attributed to the interactions between solute and solvent. These interactions lead to a preferential adsorption of the solute onto the surface, altering the behavior of the crystals [15]. This alteration results in an increase in both the crystal surface and surface area, which in turn enhances the dissolution rate.

4. Conclusion

The solubility of ATC in a methanol-aqueous solution was investigated using a ternary phase diagram and absorptiometry, incorporating Tween 20 at various concentrations. The highest solubility was observed when the drug was dissolved in pure methanol. The ternary phase diagram clearly indicates that the solubility of ATC in the methanol-aqueous solution is relatively low, confirming its overall low solubility. However, the introduction of Tween 20 resulted in a notable increase in the drug's solubility. At lower concentrations of Tween 20, an increase in the methanol-water ratio corresponded with enhanced solubility of ATC. Conversely, at higher concentrations of Tween 20, the solubility of ATC exhibited fluctuations in relation to the mass ratio of the solvent components, lacking a consistent pattern. The conclusion could benefit from a brief mention of potential areas for future research. Identifying avenues for further investigation would contribute to the ongoing scholarly discourse in this domain.

Conflicts of Interest

The authors declare no conflicts of interest.

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