ORIGINAL ARTICLE

Conductometric and volumetric studies of atorvastatin in aqueous solution of arginine from 298.15 to 313.15 K

M. M. R. Meor Mohd Affandi[1,2], Minaketan Tripathy[1,2], A. B. A. Majeed[2]

[1]Laboratory Fundamental of Pharmaceutics, Faculty of Pharmacy, Universiti Teknologi MARA, Selangor, [2]Pharmaceutical and Life Sciences Core, Universiti Teknologi MARA, Shah Alam, Selangor Darul Ehsan, Malaysia

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ABSTRACT

Categorized as a Biopharmaceutics Classification System Class II drugs, atorvastatin (ATV) exhibits low aqueous solubility and bioavailability thus presenting an obstacle and great challenge to formulation researchers. Numerous studies are available in regard to the solubility enhancement of ATV, but very few actually describe this phenomenon in terms of thermodynamics and the solute-solvent interaction. Arginine (ARG) is an amino acid that has been reported to enhance the solubility of the highly insoluble wheat protein gluten through hydrogen bonding and π electron-cation interaction. To our knowledge, ARG has never been investigated as a solubility enhancement agent of aqueous insoluble drugs. Thus, this study aimed to elucidate the solute-solvent and solute-cosolute interactions and derive thermodynamic parameters that bolstered the solubility of ATV in the presence of ARG. We examined the electrolytic conductance and densities of ATV-ARG binary system covering the temperature ranging from 298.15 K to 313.15 K. Conductometric and volumetric parameters such as limiting molar conductance, association constants, limiting partial molar volumes, and expansibility values were calculated. Additionally, thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0, and E_s) involved in the association process of the solute in the aqueous solution of ARG were also determined.

Key words: Atorvastatin-arginine, binary system, conductometric, volumetric

INTRODUCTION

Drugs with poor aqueous solubility characteristics have become one of the main technical issues highly discussed among pharmaceutical scientists. More than 70% of drug candidates and 40% of new chemical entities are poorly soluble or insoluble in water.[1,2] Atorvastatin (ATV), an inhibitor of 3-hydroxy-3-methlyglutaryl coenzyme A reductase is a member of statins, which are lipid lowering agents that have been widely used in the treatment of hypercholesterolemia. ATV has very good intestinal permeability but poor bioavailability due to its low aqueous solubility, crystalline nature, and exposure to hepatic first pass metabolism.[3] There are various approaches in which solubility of ATV can be enhanced. These include solid dispersion,[4-6] size reduction,[7] and use of surfactants.[8]

Arginine (ARG) (2-amino-5-guanidinopentanoic acid) is a conditional essential or semi-essential amino acid which plays an important role in several metabolic pathways in the human.[9] It has been reported to have a positive impact on hypertension,[10,11] reproductive physiology[12] muscle strength and mass,[13] renal and immune function,[14,15]

Address for correspondence:
Dr. Minaketan Tripathy,
Laboratory Fundamental of Pharmaceutics,
Faculty of Pharmacy, Universiti Teknologi MARA,
42300 Bandar Puncak Alam, Selangor, Malaysia.
E-mail: minaketantripathy@gmail.com

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and the release of growth hormone.[16] The role of ARG in solubility enhancement of proteins has been expansively reported by several researchers.[17,18] It is thought to increase the solubility of protein by disrupting the protein–protein and protein-surface interaction.[18]

The usage of ARG as a solubility enhancer for aqueous insoluble compounds and small molecules had been previously reported[18,19] which revealed that ARG was bound to the aromatic group of the drug through a π electron-cation interaction.[18,19] Although the role of ARG as a solubility enhancer has been described in detail by these authors, however, the fundamentals of the molecular interaction and thermodynamics involved in the binary mixture are still rather scarce in the current literature. Fundamental properties such as conductometric and volumetric studies at different temperature provide insight into the molecular interactions that occur in the binary mixture. In addition, this information contributes to a better understanding of the behavior of each component in the binary mixture. In this study, we investigated the conductometry and volumetry of several concentrations of ATV-ARG binary solution mixture at temperature of 298.15, 303.15, 308.15, and 313.15 K. Parameters related to this study such as association constants (K_A), limiting molar conductance (Λ_0), molar volume (Φ_v^0), molar expansibility (Φ_E^0), and related thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0 and E_s) were computed. These parameters were used to deliberate the possible solute-solvent, solute-cosolute, and solvent-solvent interaction, the behavior of liquid systems, structure making, and structure breaking phenomena and related structural changes.[20,21]

MATERIALS AND METHODS

Materials

ATV calcium was a gift from Hovid Berhad (Ipoh, Perak, Malaysia). ARG was purchased from Sigma Aldrich (St. Louis, MO, USA) while ethanol and methanol were purchased from HMBg Chemical (Germany). The water used was obtained from Select Bio O Purite (Oxfordshire, United Kingdom) water system. All other chemicals and reagents used in this study were of analytical grade unless otherwise stated.

Methods

Conductometric study

The electrical conductivity of each sample was measured with a cyber-scan conductivity meter with an accuracy of ± 0.5% and a conductivity cell (Model PC-510 – Eutech Instruments). The conductance cell was equipped with water circulating jacket, and the temperature was controlled within ± 0.02 K with a low-temperature thermostat. The cell constant is 1.01/cm, which was calculated by repeated measurements of KCl solutions. All data were corrected with specific conductivity of pure water at the experimental temperatures of 298.15 and 313.15 K. Six data points were recorded for each sample and results reported were mean values. Further, these data were used to define the equivalent conductance of the samples.

Volumetric study

The solution density of the blank, as well as solutions containing saturated concentrations of ATV at 4 different temperature ranging from 298.15- to 313.15 K, was determined with an Anton Paar digital density meter (Model DMA 60/602). An efficient constant temperature bath with stability within ± 0.02 K was used to regulate the temperature of water around the density meter cell. The density meter was calibrated daily at 298.15 K using dry air and water with conductivity of <1.0/μΩ/cm. All density measurements of the solutions were made relative to pure water. Densities of pure water at the experimental temperatures were taken from the literature.[22]

RESULTS AND DISCUSSION

Conductometric studies

The experimental value of specific conductance (K, μSm/cm) of ARG system in different molar concentrations, i.e., 0.1–7.34 mol/dm^3 saturated with ATV and the blank at 298.15, 303.15, 308.15, and 313.15 K was measured and presented in Tables 1 and 2. The molar conductance (Λ, Sm/cm) for all studied systems was evaluated using the following Equation 1:

$$\Lambda = 1000\ K/C \quad (1)$$

where C is the molar concentration and K is the measured specific conductance of the studied systems after solvent correction.

The limiting molar conductance (Λ_0) of the ARG system in the presence of ATV was derived from Equation 2 which is based on the Kohlrausch expression.[23]

$$\Lambda_0 = \Lambda + b \quad (2)$$

where b is a constant.

Values of molar conductance and limiting molar conductance are summarized in Tables 1 and 2. Further, these values were used to determine the degree of dissociation (α), which was assimilated into the mass action law for the ion association (K_A) in the form of Equation 3.[24]

$$K_A = 1-\alpha/\alpha^2\ c\ f_{\pm}^2 \quad (3)$$

where f ± is the mean activity coefficient. The values of K_A of ARG system in the presence and absence of ATV at 298.15 K are presented in Tables 3 and 4.

Table 1: Specific conductance (K), molar conductance (Λ), limiting molar conductance (Λ_0) and activation energy for each system (E_s) of arginine at different concentration and temperature

Sample	T/K=298.15		T/K=303.15		T/K=308.15		T/K=313.15		E_s (KJ/mol)
	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	
S1	6.7509	77.50	6.9861	80.20	7.1733	82.35	7.3040	83.85	66106.24
S2	4.7256	108.50	4.8454	111.25	5.0240	115.35	5.2156	119.75	58818.51
S3	3.1718	145.65	3.2339	148.50	3.3199	152.45	3.4397	157.95	31719.21
S4	2.0977	192.65	2.2213	204.00	2.3465	215.50	2.4118	221.50	38214.62
S5	1.3583	249.50	1.4290	262.50	1.4671	269.50	1.5379	282.50	20619.21
S6	0.9023	331.50	0.9540	350.50	0.9908	364.00	1.0330	379.50	15329.10
S7	0.5553	408.00	0.5913	434.50	0.6206	456.00	0.6424	472.00	10398.79
Λ_0 (Scm²/mol×10³)	8.6128		8.8446		9.0646		9.2805		

Table 2: Specific conductance (K), molar conductance (Λ), limiting molar conductance (Λ_0) and activation energy for each system (E_s) of arginine solution system with saturated presence of atorvastatin

Sample	T/K=298.15		T/K=303.15		T/K=308.15		T/K=313.15		E_s (KJ/mol)
	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	Λ (Scm²/mol×10³)	K (μS)	
S1	19.1638	220.00	19.2509	221.00	19.3380	222.00	19.4251	223.00	31124.02
S2	10.5836	243.00	10.6272	244.00	10.6707	245.00	10.7143	246.00	15562.20
S3	6.4460	296.00	6.4678	297.00	6.4895	298.00	6.5984	303.00	18894.30
S4	3.2665	300.00	3.2992	303.00	3.3101	304.00	3.3210	305.00	3956.00
S5	1.8945	348.00	1.9707	362.00	2.0252	372.00	2.0633	379.00	20079.52
S6	1.1677	429.00	1.2031	442.00	1.2494	459.00	1.2820	471.00	13910.60
S7	0.6628	487.00	0.6846	503.00	0.7390	543.00	0.7771	571.00	14179.87
Λ_0 (Scm²/mol×10³)	13.793		13.798		13.818		13.904		

Table 3: Ion association (K_A) of arginine at different concentrations and temperatures

Sample	K_A			
	T/K=298.15	T/K=303.15	T/K=308.15	T/K=313.15
S1	30.65109139	29.33881884	29.0210704	29.9503855
S2	65.29690037	65.61830094	63.20276212	60.40082904
S3	101.4383903	103.3345081	102.8875212	99.77184136
S4	138.8549307	129.2787536	120.4298753	119.3246417
S5	184.3733975	174.8433675	174.1745567	165.388705
S6	222.0171666	208.7074837	202.9329932	195.2537834
S7	306.3256677	284.1069335	270.4735637	264.4018462

Table 4: Ion association (K_A) of arginine solution system with saturated presence of atorvastatin at different concentration and temperature

Sample	K_A			
	T/K=298.15	T/K=303.15	T/K=308.15	T/K=313.15
S1	−17.57078871	−17.68474131	−17.76718238	−17.72133846
S2	17.21229238	16.87253258	16.6348416	16.82647762
S3	53.11138726	52.65295151	52.36328019	50.8054574
S4	148.1596735	144.9111351	144.2931253	145.2717063
S5	248.9305035	228.7545301	216.3035055	210.5356978
S6	347.6268487	326.8092235	302.8556348	290.638329
S7	561.0867723	525.4775612	450.3783495	411.3267322

Results presented in Tables 1 and 2 illustrate that the calculated molar conductance Λ of aqueous molar solutions of ARG in the absence and saturated presence of ATV decrease with the increase of ARG concentration. The increase in ARG concentration was due to the formation of ion pairs which promote stronger ion association thus decreasing molar conductivity. Further, the increase in ARG concentration resulted in a strong interaction between water molecule ions and $-NH_2$ charged end group of ARG. In addition, in saturated presence of ATV the molar conductivity values increased as compared to their counterparts without ATV. The above observation can be ascribed to the fact that reduced microscopic viscosity decreases the frictional coefficient of the medium and increases the species mobility. This phenomenon was due to a preferential interaction between the solute ATV and cosolute ARG in water hence increasing the solubility of the former. Additionally, the preferential affinity of ARG to ATV reduces the attraction between ARG ions and water molecules causing a decrease in hydrodynamic radii of these ions and an increase in their mobility.

Tables 1 and 2 show that the values of Λ_0 of ATV are high in the aqueous solution of ARG. The higher Λ_0 value of ATV can be attributed to the similar point of analogy as in the case of the molar conductance.[25] It can be seen from Tables 1 and 2 that Λ_0 of ATV and aqueous ARG solution increases with a rise in temperature which indicates less solvation or higher mobility of ions. In addition, an increased in thermal energy results in greater bond breaking and variation in vibrational, rotational, and translational energy of the molecules that leads to higher frequency and higher mobility of the ions.[26,27]

Tables 3 and 4 show that the association constant (K_A) of ARG increases with a concentration in the presence or absence of ATV. This was in line with the earlier claim which stated that the increase in ARG concentration resulted on the formation of ion pairs in the dilute region and possibly led to an increase in ion association. Additionally, it is interesting to note that at higher concentrations of ARG with saturated presence of ATV (S5 and S6) the K_A value decreases with the increased concentration of ARG. This phenomenon can be explained by the fact that at higher concentration of ARG more and more ATV will be bound with ARG resulting in the reduced attraction between the ions of the ARG and water molecules.[28]

Since the conductance measurements of an ion depend upon mobility,[29] it is quite reasonable to treat the conductance data similar to the one employed for the rate process taking place with the change of temperature (Equation 4):

$$\Lambda_0 = A\, e^{-Es/RT} \text{ (or) } \log\Lambda_0 = \log A - E_s/2.303RT \quad (4)$$

where A is the frequency factor, R is the gas constant, and E_s is the Arrhenius activation energy of the transport process. The E_s values were computed from the slope (=$-E_s/2.303R$) of $\log\Lambda_0$ vs. 1/T plot and recorded in Tables 1 and 2.

The free energy change, ΔG^0 for the association process is derived from Equation 5:

$$\Delta G^0 = -RT \ln K_A \quad (5)$$

The heat of association ΔH^0 is determined from the slope of the plot of $\ln K_A$ versus 1/T and the entropy change, ΔS^0 from Gibbs–Helmholtz Equation 6:

$$\Delta G^0 = \Delta H^0 - T\,\Delta S^0 \quad (6)$$

The values of ΔG^0, ΔH^0, and ΔS^0 at 298.15 K–313.15 K are presented in Tables 5 and 6.

As presented in Tables 1 and 2, the values of E_S are positive at all experimental concentration of ARG either in the absence or saturated presence of ATV. The negative ΔG^0 values for the systems of ARG with and without ATV indicate that the association process predominates over the dissociation process. It is interesting to note that for the system of ARG, the association is endothermic for all concentrations whereas there is no specific trend observed in the ARG system saturated with ATV. Depending on the concentration of ARG in the system, the association process is either endothermic or exothermic. Values of ΔS^0 are found to be

Table 5: Gibbs free energy (ΔG^0), entrophy (ΔS^0), and entalphy (ΔH^0) of arginine at different concentrations and temperatures

Sample	T/K=298.15		T/K=303.15		T/K=308.15		T/K=313.15		ΔH^0
	ΔG^0	ΔS^0	ΔG^0	ΔS^0	ΔG^0	ΔS^0	ΔG^0	ΔS^0	
S1	−8487.24	30.16	−8519.24	29.76	−8631.85	29.65	−8854.00	29.88	503.68
S2	−10362.59	37.39	−10548.75	37.39	−10626.61	37.04	−10680.93	36.62	786.05
S3	−11454.92	39.53	−11693.71	39.67	−11875.47	39.61	−11988.07	39.34	331.69
S4	−12233.49	45.42	−12258.48	44.75	−12278.95	44.09	−12454.17	43.95	1307.9
S5	−12936.57	45.59	−13019.71	45.11	−13224.63	45.05	−13304.40	44.58	656.78
S6	−13397.28	47.63	−13466.09	47.07	−13616.28	46.80	−13736.74	46.43	803.58
S7	−14195.49	51.45	−14243.70	50.76	−14352.60	50.29	−14526.34	50.04	1144.8

Table 6: Gibbs free energy (ΔG^0), entrophy (ΔS^0), and entalphy ΔH^0 of arginine solution system with saturated presence of atorvastatin

Sample	T/K=298.15		T/K=303.15		T/K=308.15		T/K=313.15		ΔH^0
	ΔG^0	ΔS^0	ΔG^0	ΔS^0	ΔG^0	ΔS^0	ΔG^0	ΔS^0	
S1	−7107.45	23.50	−7242.94	23.55	−7374.32	23.60	−7487.25	23.58	−102.2
S2	−7056.33	24.72	−7124.40	24.54	−7205.55	24.40	−7352.29	24.48	313.78
S3	−9850.39	33.99	−9993.73	33.90	−10144.42	33.84	−10230.36	33.58	284.56
S4	−12394.33	42.39	−12546.29	42.19	−12742.26	42.14	−12966.62	42.19	243.83
S5	−13681.01	50.22	−13697.33	49.45	−13779.81	48.91	−13933.01	48.62	1292.1
S6	−14509.12	52.40	−14596.75	51.83	−14642.41	51.13	−14772.75	50.73	1114.3
S7	−15696.28	59.17	−15794.19	58.52	−15659.44	57.13	−15677.31	56.28	1945.9

positive indicating the disorderedness of the solubilized species and its highly hydrated nature.

Volumetric studies

Density value along with limiting apparent molar volume (Φ_v^0) and limiting apparent molar expansibility (Φ_E^0) value of the ARG solution system in the absence and saturated presence of ATV in water at T= (298.15, 303.15, 308.15, 313.15) K are given in Table 7. Values of Φ_v^0 and Φ_E^0 were obtained from the intercept of the plot of Φ_v versus $C^{½}$ and of Φ_E versus C^{-1}, respectively, which was in turn derived from the experimentally measured densities (Equations 7 and 8).

$$\Phi_v = 1000(Cd_0)^{-1}(d_0 - d) + M_2/d_0 \quad (7)$$

and

$$\Phi_E = \alpha\Phi_v^0 + (\alpha - \alpha_0)\,1000C^{-1} \quad (8)$$

where C is the molar concentration of the solute, d_0 is the density of pure water, d is the density of the solution, M_2 is the molecular mass of the solute and α_0 and α are the coefficients of expansion of the solvent and solution (with or without drug), respectively, and determined by means of the relation available in the literature.[30]

The Φ_v and Φ_E showed linear dependence with square root of concentration and were found to obey the linear equation, Equations 9 and 10:

$$\Phi_v = \Phi_v^0 + S_v c^{1/2} \quad (9)$$

and

$$\Phi_E = \Phi_E^0 + S_E c^{-1} \quad (10)$$

Values of S_V and S_E obtained from slopes of the corresponding plots are also given in Table 7. Results presented in Table 7 illustrate that at the experimental temperature the values of Φ_v^0 are positive for the ARG systems in the absence and presence of ATV. The positive values of Φ_v^0 indicate strong drug-solvent interactions. Furthermore, a rise in temperature resulted in an increase

Table 7: Limiting apparent molar volume (Φ_V^0), limiting apparent molar expansibility (Φ_E^0), S_V and S_E constance of arginine, arginine solution system with saturated presence of atorvastatin (ATV-ARG)

System	Temperature (K)	S_v	Φ_V^0	S_E	Φ_E^0
ARG	298.15	233.35	31.072	0.1041	−0.037
ATV-ARG	298.15	−19.477	134.45	−0.0731	0.7904
ARG	303.15	−8.277	134.92	0.1041	0.0073
ATV-ARG	303.15	125.88	71.515	−0.0729	0.7576
ARG	308.15	−153.52	183.33	0.0576	0.3696
ATV-ARG	308.15	−2.3297	132.36	−0.0731	0.7893
ARG	311.15	−53.632	151.22	0.0576	0.3559
ATV-ARG	311.15	−3.1057	134.59	−0.0731	0.7904

ARG: Arginine, ATV: Atorvastatin

in the ion-solvent and the solute-solvent interactions except at 311.15 K. This phenomenon promotes the structure making the effect of the ATV in aqueous ARG systems.

As observed, S_V values are positive at the lower temperature except for ARG systems in the presence of ATV at 298.15 and ARG system at 303.15 K. The negative values of Sv at the higher temperature in all cases of ARG and ATV-ARG recommend the absence of ion-ion or solute-solute interaction in the system. Moreover, it is seen that values of S_V for the system in the presence of ATV are higher as compared to those ARG only systems which indicate that the solvent structure is not too much enhanced in the presence of the drug.

The standard partial molar volume of transfer, $\Delta_t \Phi_v^0$ at infinite dilution of ATV from water to aqueous ARG was determined from Equation 11:

$$\Delta_t \Phi_v^0 = \Phi_v^0 \text{ (in aqueous ARG solutions)} - \Phi_v^0 \text{ (in water)} \quad (11)$$

It is seen that at the experimental temperature the values of $\Delta_t \Phi_v^0$ are positive for all systems and decrease with a rise in temperature. This is because the dehydration of ions (the cation and anion of the ARG) and drug (ATV) molecules have taken place in the system. Moreover,

the destructive overlap of cospheres resulting in a net decrease in salvation thereby increasing the solute (drug) volume, and because of the strong interactions between the drug and the ARG the latter loses its effect on the water structure.[27]

Values of Φ_E^0 are low but positive for all the systems at all temperature except in the case of ARG at 298.15 K and vary irregularly with the increase in temperature. However, values of Φ_E^0 in the presence of ATV indicate the presence of a caging or packing effect[31] supporting the earlier argument that the solvent structure is not too much enhanced.

CONCLUSION

An extensive study of conductometry and volumetry of ATV-ARG binary solution system at different temperature has been conducted. It can be seen that the molar conductance, Λ, of an aqueous solution of ARG in the absence and saturated presence of ATV decreases with the increase of ARG concentration. Conversely, the molar conductivity is enhanced in ARG systems saturated with ATV as compared to their counterparts without ATV. It is also interesting to note that the values of limiting apparent molar volume (Φ_v^0) are positive for the ARG systems in the absence and presence of ATV at the experimental temperature. Based on the various evaluated volumetric and conductometric parameters, it is concluded that there is a strong solute-solvent, solute-cosolute, and solute-solute interaction taking place in the ATV-ARG binary solution system.

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Conflicts of interest
There are no conflicts of interest.

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