

Influence of Valsartan on the thermodynamics of micellization of anionic surfactant Sodium Dodecyl Sulphate

Original research article

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Abstract In this manuscript was investigated behaviour of drug valsartan by micellar media of anionic surfactant sodium dodecyl sulphate. As the method was used electrical conductivity for the determination of critical micelle concentration at different temperatures ($T = 293.15 - 313.15$ K), as well as calculated thermodynamic parameters like standard Gibbs free energy, enthalpy and entropy of micellization. According to contribution of Gibbs free energy is the process of micellization primarily controlled by entropy. Solubilization of valsartan was studied in surfactant system at 298.15 K and physiological conditions pH 7.4 using UV-spectrophotometry at different concentration range (0.001 - 0.07 mol/l) of sodium dodecyl sulphate. The solubilization of drug was observed with increasing concentration of surfactant in aqueous solution.

Keywords Valsartan – sodium dodecyl sulphate – critical micelle concentration – micellization – thermodynamics – solubilization

INTRODUCTION

Amphiphilic molecules such as surfactants may be spontaneously self-assemble in aqueous solutions to form thermodynamically stabile layers. These layers may close on themselves to form aggregates in solutions, known as micelles (Bergström, 2006; Kabir-ud-Din et al., 2010).

The driving force needed for amphiphilic molecules to spontaneously self-assemble into micelles and bilayers is usually called as hydrophobic effect. As a result, in order to decrease the hydrocarbon–water contact in an aqueous solution, the hydrophobic tails self-assemble to form liquid-like cores with the hydrophilic head groups located at the aggregated interface pointing towards the aqueous bulk solvent phase (Bergström, 2011).

The threshold concentration of amphiphilic molecules, in a solution above which micelles are formed, is defined as the critical micelle concentration (CMC). Above the CMC, the biological activity of micelle-forming solutes changes potentially. It is well known that amphiphile's molecular structure, as well as physico-chemical conditions such as

pH, temperature, ionic strength, nature and concentration of additives and so on, changes the CMC of amphiphiles (drugs or surfactants) (Kabir-ud-Din et al., 2010).

The physico-chemical interactions of drugs with surfactant micelles can be considered as an approximation for their interactions with biological surface. One of the most important aspects associated with this phenomenon is the relative participation of hydrophobic and electrostatic interactions between the drug and surfactant molecule. This may explain the location of drug molecule in the micellar interior. The combination of intermolecular hydrophobic and hydrophilic interactions between surfactant and drug molecules is considered to affect the self-aggregation of surfactant molecules that leads to the formation of surfactant – drug molecular complexes (Kaushal et al., 2015).

An important property of micelles that has particular meaning in pharmacy is their ability to enhance the solubility of water-insoluble molecules by a process known as solubilisation (Mohammad Amin Mir et al., 2011).

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Micellar system can solubilise poorly soluble drugs and thus increase their bioavailability and can be used as a model system for biomembrane, as well as for drug delivery vehicle and drug targeting systems. Micelles are known to have an anisotropic water distribution within their structure. Consequently, the water concentration decreases from the surface towards the core of micelle, with completely hydrophobic core. As a result, the spatial position of solubilised drug in micelle depends on its polarity: nonpolar molecules are solubilised in the micellar core, and substances with intermediate polarity are associated along the surfactant molecules in accurate intermediate positions (Göktürk et al., 2012).

Valsartan (VAL) lowers blood pressure by antagonising the renin-angiotensin-aldosterone system because it is a potent, highly selective and orally active antihypertensive drug belonging to the group of angiotensin II type 1 (AT₁) receptor antagonists, of which it plays an integral role in hypertension. The main function of VAL in human body, as AT₁ receptor antagonists, is relaxing blood vessels and initiating them to widen, which lowers blood pressure and improves blood flow (Nalluri et al., 2012; Lee et al., 2014; Mak et al., 2015). It is used as a first-line agent to treat uncomplicated hypertension, isolated systolic hypertension and left ventricular hypertrophy, where it can lower blood pressure for 24 successive hours, which renders once-daily administration of VAL's effect for the treatment of hypertension (Antil et al., 2013; Lee et al., 2014). Unfortunately, the drug is poorly water soluble, which is responsible for its low bioavailability. The absolute oral bioavailability is determined to be 25%, and as a result, it defends its therapeutic efficacy (Nalluri et al., 2012; Chadha et al., 2014). VAL differs structurally from losartan by an alkylated amino acid that substitutes the heterocyclic moiety of compound. Its chemical title is *N*-(1-Oxopentyl)-*N*-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-*L*-valine (Potamitis et al., 2011; Sanad & Borai, 2014).

VAL contains, in its molecular structure, two weak acidic centres, the COOH group and tetrazole ring. The higher value ($pK_a = 4.70$) can be linked to the prevalent ionisation of tetrazole ring, whilst the lower value ($pK_a = 3.60$) is consequently ascribed to the prevalent ionisation of COOH group. The ionization profile of VAL shows that at $pH < 1.60$, this drug exists almost specifically in the undissociated form, and at $pH > 6.70$ and accordingly at physiological $pH 7.4$, the drug exists almost as dianion (Tosco et al., 2008).

The solubility of VAL increases in the pH range 4–8, and its lipophilicity decreases in the same range. VAL is soluble in water at 25 °C to the extent of 0.18 g/L, and in buffered solutions, its solubility is increased because the dianion salt is formed. As VAL has pH -dependent solubility, it presents to a special case in a suggested general classification system, which categorises drugs with respect to their biopharmaceutical and absorption properties (Criscione et al., 1995; Saydam & Takka, 2007).

According to the Biopharmaceutical Classification System (BCS), VAL belongs to the special group and has been classified

as Class III drug with low permeability, poor metabolism and high solubility at higher pH values (Siddiqui et al., 2011).

The aim of this work was to study the thermodynamics of micellisation of anionic surfactant sodium dodecyl sulphate (SDS) with VAL and the solubilisation of VAL by micellar media of SDS (Fig. 1). We have discussed how drug does behave in this solution and also we have estimated and analysed various thermodynamic parameters, for example, Gibbs free energy, enthalpy and entropy of micellisation.

MATERIALS AND METHODS

Materials

The drug VAL with molecular weight ($M_r = 435.52$) from the group of sartans was obtained from Huahai Pharmaceuticals Co, Ltd., China, and anionic surfactant SDS with molecular weight ($M_r = 288.38$) was purchased from Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Phosphate buffer solution that consisted of potassium dihydrogen phosphate (KH_2PO_4 , $M_r = 136.09$) and sodium phosphate dibasic dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$, $M_r = 358.14$) at physiological $pH 7.4$ was prepared as a solvent for single measurements. Both of them were obtained from Lachema N.P. Brno, Czech Republic. The acidity of VAL solutions was adjusted by addition of NaOH ($c = 0.5 \text{ mol/l}$).

Methods and apparatus

Stock phosphate buffer solution was prepared according to Pharmacopoeia Bohemoslovaca (PhBs, IV. Ed.) in concentration of 0.003 mol/l for all measurements, and the pH value of the solution was determined and regulated potentiometrically (Inolab- pH meter, Germany) to the desired pH value 7.4.

Conductivity measurements of CMC in the presence of VAL and SDS were carried on digital conductivity meter WTW inoLab 720i (Switzerland) with thermostat Julabo ED 4 (Germany) and were based on the conductivity change (κ) with surfactant concentration. This instrument can measure in the range from 0.01 μS to 199.9 mS. The electrode was coated with platinum black to avoid the polarisation effect. The conductivity measurements were performed at temperature range of 293.15–313.15 K with temperature stability of ± 0.1 C. For the conductivity measurements, solutions of SDS ($c = 0.014 \text{ mol/l}$) with VAL ($c = 0.0005 \text{ mol/l}$) in phosphate buffer solution were prepared and then poured into 25-ml calibrated flask. Experiment was initiated to measure herewith solution and the subsequent concentrated solutions were obtained by adding previously prepared VAL stock solution ($c = 0.0005 \text{ mol/l}$). After ensuring thorough mixing and temperature equilibration, the specific conductance was measured.

The calibration curve of VAL was measured using UV spectrophotometric method by UV-1800 Spectrophotometer (Japan). The stock solution of VAL was dissolved using

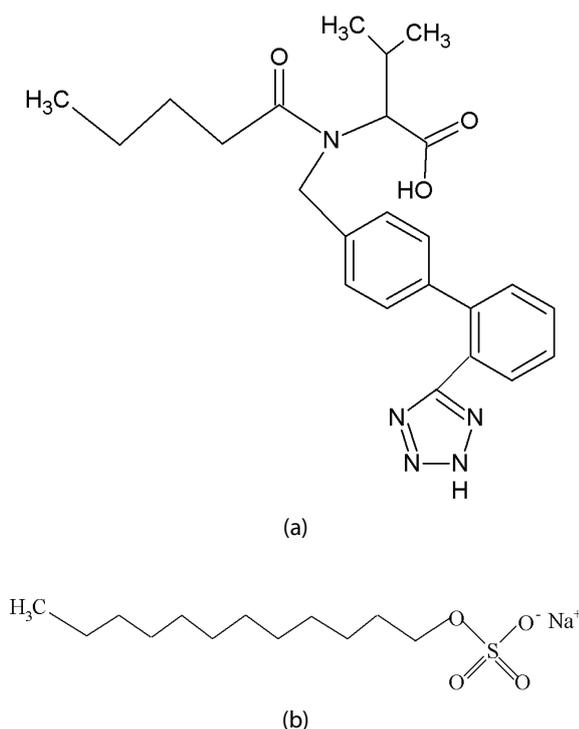


Figure 1. Structure of (a) valsartan and (b) sodium dodecyl sulphate

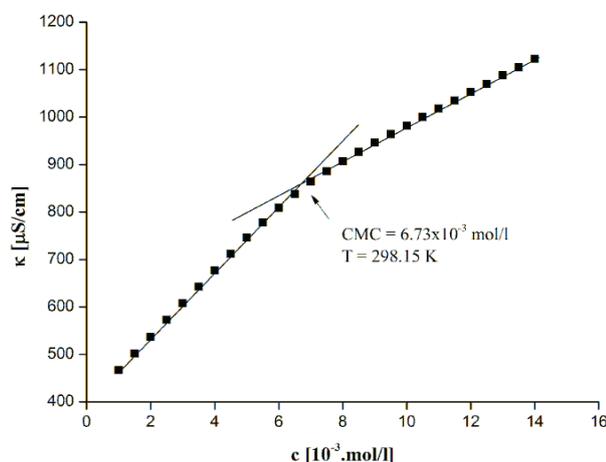


Figure 2. Plot of conductivity versus concentration of SDS in the presence of VAL at 298.15 K. CMC, critical micelle concentration; SDS, sodium dodecyl sulphate; VAL, valsartan

ultrasound Sonorec Digitec Bandelin DT 31H (Germany) and adjusted to pH value of 7.4. A different amounts of volume 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0 and 1.1 ml of VAL stock solution ($c = 0.0005$ mol/l) were pipetted into 10-ml calibrated flasks and subsequently diluted to volume with buffer solution. The calibration graph was measured at $\lambda_{\max} = 249$ nm for VAL. Through the studies of solubilisation, we used an excess amount of the studied VAL (constant concentration, $c = 0.055$ mol/l) in the presence of SDS surfactant solutions in the concentration range of 0.001–0.07 mol/l (0.028– 2.02 % w/v).

The prepared solutions, with excess amount of VAL and various concentrations of SDS, in a medium of buffer solutions, were added to Erlenmeyer flasks. The samples were then succussed in a shaker Kavalier LT3 (Czech Republic) at 298.15 K for 8 h. After this period, the samples were filtered and the concentration of solubilisation of VAL was determined by UV spectrophotometry. The samples were prepared in phosphate buffer solution and diluted further so that the maximum absorbance may not have exceeded 1 and the Lambert–Beer law may have been obeyed. All the experiments were repeated twice.

RESULTS AND DISCUSSION

Electrical conductivity measurements

The electrical conductivity of the SDS–VAL in aqueous solutions at different temperatures (293.15–313.15 K) were measured to characterise the thermodynamic properties of micellisation. Figure 2 shows the variation of electrical conductivity versus the concentration of SDS–VAL system at 298.15 K. The experimental results fit into two straight lines with a substantial change in slope. The break point of the curve corresponds to the CMC. The CMC values at different temperatures are summarised in Table 1.

Calculation of thermodynamic parameters

The temperature dependence of $\ln \text{CMC}$ (Fig. 3) was fitted to the function of the second-degree polynomial: $\ln \text{CMC} = A + B.T + C.T^2$, which was used to determine the values of A, B and C. The obtained results were $A = 6.80617 \pm 7.09248$, $B = -0.08123 \pm 0.04681$ and $C = 0.0001397 \pm 0.0000772034$. The fit was quite less good with the coefficient of determination 0.937.

Regarding our study, the minimum of the curve is close to 290.65 K according to the fit. For ionic and amphoteric surfactants, micellisation is affected by the temperature, as the hydrophobic and head group interactions change with temperature. Accordingly, CMC versus temperature studies have been performed to obtain information on these interactions (Goto et al., 1985). For ionic surfactants in an aqueous solution, the CMC decreases to a certain minimum value and then increases, displaying a U-shaped behaviour (Lee, 1995; Rosen, 2004). In nonionic surfactants, CMC decreases as the temperature is increased. This is due to an increase in the destruction of hydrogen bonds between water molecules and hydrophilic groups of the surfactants. The log CMC versus $1/T$ plot is nearly linear (Hall, 1967). However, other studies show something else, the nonionic surfactants such as polyoxyethylene glycol monoether in an aqueous solution exhibited a minimum in the CMC–temperature curve. The temperature of the minimum in the CMC–temperature curve is around 323.15 K and increases as the chain length of the oxyethylene increases. Though, most of the previous

Table 1. Critical micelle concentration (CMC), enthalpy of micellisation (ΔH_m^0), Gibbs free energy of micellisation (ΔG_m^0), entropy of micellisation (ΔS_m^0), degree of counterion binding (α) and degree of dissociation (β) for aqueous solutions of SDS in the presence of VAL at different temperatures

T [K]	CMC ^a .10 ³ [mol/l]	CMC.10 ³ [mol/l]	ΔG_m^0 [kJ/mol]	ΔH_m^0 [kJ/mol]	ΔS_m^0 [kJ/mol.K]	$-T\Delta S_m^0$ [kJ/mol]	α	β
293.15	7.94	6.76	-18.27	-1.33	0.057	-16.93	0.489	0.511
298.15	8.05	6.73	-18.13	-2.24	0.053	-15.88	0.465	0.535
303.15	8.50	6.91	-18.53	-3.91	0.048	-14.61	0.477	0.523
308.15	8.97	7.04	-18.60	-7.40	0.036	-11.20	0.449	0.551
313.15	9.57	7.21	-18.64	-9.28	0.029	-9.36	0.440	0.560

^aRefs – CMC of SDS in doubly distilled water (Shah et al., 2001)

experiments have been carried out only up to temperature 318.15 K. It is fair to assume that 318.15 K is too low to observe the minimum CMC behaviour in the CMC–temperature curve (Chen et al., 1998). The observed process of micellisation and the value of CMC depending on temperature are a complicated system, because the increase in temperature causes dehydration of hydrophilic and also hydrophobic parts. Dehydration of hydrophobic parts favours micellisation because it causes an increase in entropy, whilst dehydration of hydrophilic groups disfavours micellisation because it causes repulsion between charged hydrophilic groups. The relative size of both factors decide whether CMC will increase or decrease with temperature (Usman et al., 2013; Hanif et al., 2015). Figure 3 shows that the increase in CMC value with temperature is due to the degree of hydrophilic dehydration which is greater than that of the hydrophobic dehydration. The decrease in the value of CMC, in the presence of VAL in comparison to the value of CMC for pure SDS in doubly distilled water (Table 1), is mainly due to the decrease in the thickness of electric double layer surrounding the ionic head groups and due to the responsible decrease in the electrical repulsion between them in the micelle (Rangel-Yagui et al., 2005). From the above-mentioned fitting parameters, the thermodynamics magnitudes as function of temperature, Gibbs free energy ΔG_m^0 , enthalpy ΔH_m^0 , and entropy of micellisation ΔS_m^0 have been calculated by using the following equations (Andriamainty et al., 2004; Khan et al., 2014):

$$\Delta G_m^0 = (2 - \beta)RT \ln CMC \quad (1)$$

where β is the degree of dissociation, R is the universal gas constant having value $8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ and T is the absolute temperature. β can be calculated from the equation

$$\beta = \frac{S_2}{S_1} \quad (2)$$

where S_1 and S_2 are the slopes in the pre-micellar and post-micellar phases, respectively.

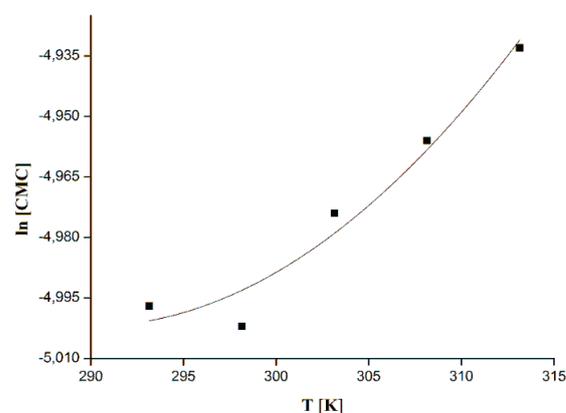


Figure 3. Plot of $\ln CMC$ versus temperature of SDS in the presence of VAL

The degree of counterion binding α can be expressed as

$$\alpha = 1 - \beta \quad (3)$$

The enthalpy of micellisation is defined by the equation

$$\Delta H_m^0 = -(2 - \beta) RT^2 \left[\frac{\partial(\ln CMC)}{\partial T} \right] \quad (4)$$

and the entropy contribution of micellisation can be calculated as follows:

$$\Delta S_m^0 = \frac{(\Delta H_m^0 - \Delta G_m^0)}{T} \quad (5)$$

Different parameters calculated from electrical conductivity are given in Table 1 as Gibbs free energy (ΔG_m^0), enthalpy (ΔH_m^0), entropy (ΔS_m^0) of micellisation, degree of dissociation (β) and degree of counterion binding (α) for solutions of SDS–VAL system at different temperatures.

As shown in Table 1, the values of ΔG_m^0 are negative, and with increasing temperature, there is almost no change. More significant in values is the depression of standard molar enthalpy ΔH_m^0 . It is due to the spontaneous process of micellisation.

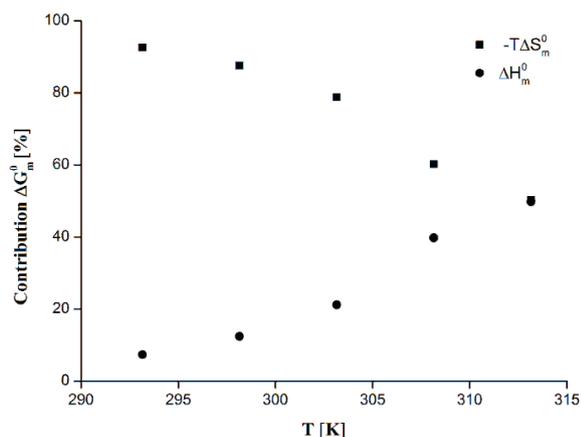


Figure 4. Contribution of enthalpy (●) and entropy $-T$ (■) to the Gibbs free energy of micellisation for SDS in the presence of VAL

The ΔH_m^0 is the sum of change in enthalpies arising from hydrophobic interactions, electrostatic interactions, hydration of polar head groups and counterion binding to micelles (Usman et al., 2013). The values of negative enthalpy indicate that the London dispersion interactions represent the major attractive force in the micelle formation (Del Rio et al., 1995). With increasing temperature, the enthalpy contribution to free energy increases, whereas the entropic contribution decreases as depicted in Fig. 4. The values of $|\Delta H_m^0|$ are lower than those of $|-T\Delta S_m^0|$. It suggests that the process of micellisation is primary driven to gain the entropy. The decrease in ΔS_m^0 values with temperature is due to the decrease in the degree of hydrophobic groups hydration at high temperature (Usman et al., 2013). It indicates that the process of micellisation is reduced at higher temperature and the micellisation inclined to be enthalpy controlled with the rise in temperature, because at high temperature, the kinetic energy of VAL and SDS molecules is higher and the probability of association of these molecules to form the complex is less. The negative values of ΔH_m^0 and positive values of ΔS_m^0 are probably caused by the flexible structure of SDS, which makes the micellisation easily (Usman et al., 2013).

In the following part of work, we examined solubilisation of in the presence of anionic surfactant SDS. Solubilisation is generally used as an alternative method for the dissolution of poorly soluble drugs, depending on the drug hydrophobicity. The solubilisation effect of drugs can occur in the inner core of micelle, on the surface of micelle or at an intermediate location in the palisade layer (Seedher & Kanojia, 2008).

For the experiments of VAL solubility, the concentration of SDS in range 0.001–0.07 mol/l at temperature 298.15 K was selected and the concentration of drug was kept constant (0.055 mol/l). All the samples were determined spectrophotometrically (Table 2) and they refer to data of VAL solubility. The parameters of solubility S (in mg/ml) were acquired from calibration curve of VAL, which is shown in Fig. 5 (a). As can be seen from Table 2 and Fig. 5 (b) for SDS–

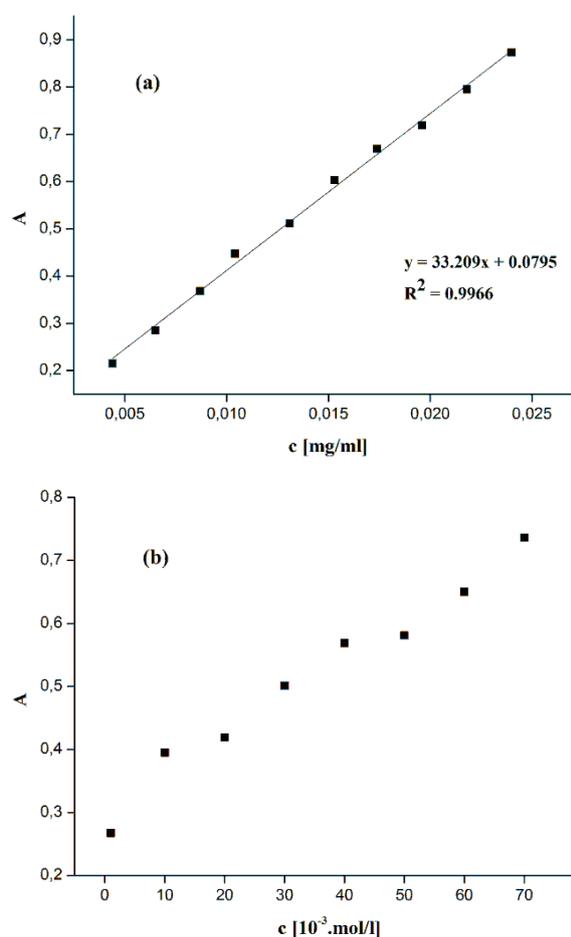


Figure 5. (a) Calibration curve of valsartan in buffer solution. (b) Plot of absorbance versus concentration of SDS in the presence of VAL (0.055 mol/l)

VAL system, the increase in drug solubility is observed for surfactant concentration above CMC and can be supposed that the micellar solubilisation is taking place.

CONCLUSION

The results obtained from conductivity enabled us to conclude that the interaction of VAL molecule with SDS and its micellisation are spontaneous processes. The values of ΔG_m^0 are negative in all considered temperatures. This shows that the micellisation process is spontaneous in the studied temperature range. Depression of standard molar enthalpy ΔH_m^0 is more significant compared with ΔG_m^0 values. It means that the micellisation process becomes more exothermic with increasing temperature. The process of SDS–VAL system micellisation is entropy driven in the studied temperature interval.

Conflicts of interest: none.

Table 2. Solubilisation of VAL (0.055 mol/l) in the presence of various concentrations of SDS

Concentration of SDS [mmol/l]	A [$\lambda_{\max}=249$ nm]	S [mg/ml]	S [mmol/l]	Log S
1	0.267	0.564	1.296	0.113
10	0.395	1.900	4.363	0.640
20	0.419	3.067	7.042	0.869
30	0.501	4.442	10.201	1.009
40	0.569	5.896	13.539	1.132
50	0.581	7.551	17.338	1.239
60	0.650	8.590	19.724	1.295
70	0.736	9.886	22.698	1.356

VAL, valsartan; SDS, sodium dodecyl sulphate; S, solubility

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