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RESEARCH PAPER

Aqueous Solubility of Diclofenac Diethylamine in the Presence of Pharmaceutical Additives: A Comparative Study with Diclofenac Sodium

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ABSTRACT

Aqueous solubility of diclofenac diethylamine (DDEA), a nonsteroidal anti-inflammatory drug currently formulated as a topical emulgel, was studied in the presence of pharmaceutical additives and compared with diclofenac sodium (DS). Electrolytes at low concentrations exhibited a salting-in effect on DDEA with peak solubility that was attributed to the association of DDEA into micelles, followed by a salting-out effect at higher concentrations, by which structure formation by DDEA molecules increased and precipitation occurred. For DS, which is not capable of forming micelles, the salting-out effect was dominant due to the common ion effect. Cosolvents displayed significant enhancement in solubility of both salts except glycerol, which showed a slight increase in solubility of DDEA and a decrease in solubility of DS due to transformation into the less soluble hydrate form. Ethanol and polyethylene glycol (PEG) 400 cosolvent systems at all concentrations showed positive deviations from the log-linear solubility equation. In the case of propylene glycol (PG) cosolvent systems, negative deviations were observed at low volume fractions of cosolvent, while positive deviations were observed at high volume fractions of cosolvent for DS and DDEA. The parent drug, being less ionizable and highly nonpolar, showed negative deviations up to 90% PG content. Thus, the positive deviations for DS and DDEA could be attributed to the more ionizable carboxylic group and its higher ability for hydrogen bonding at higher fractions of cosolvent. Polyvi-

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nylpyrrolidone (PVP) and PEG4000 or PEG6000 enhanced the solubility of DS and DDEA, with PVP exerting higher solubilizing efficiency and DS showing better solubility than DDEA. Solubilities of DS in Tween 80 (T80) and Pluronic F-127 (PF127) aqueous solutions were almost similar, while the solubility of DDEA in the presence of T80 was higher than the solubility in the presence of PF127. DS appeared to be located more in the polyoxyethylene mantle of the micelles, while DDEA was located more in the core of the micelles.

Key Words: *Cosolvents; Diclofenac salts; Effect of electrolytes; Hydrophilic polymers; Salting-in and salting-out; Solubility; Surfactants.*

INTRODUCTION

Many publications have dealt with the solubility of diclofenac sodium (DS) (1). However, there is little literature available related to the solubility of diclofenac diethylamine (DDEA), particularly in the presence of pharmaceutical additives like electrolytes, cosolvents, hydrophilic polymers, and nonionic surfactants, which are used extensively in formulations of topical dosage forms. DDEA is currently formulated by the innovator as an emulgel, which combines the properties of an emulsion cream with those of a gel in an aqueous alcoholic base.

DS and DDEA were reported as amphiphilic drug molecules and were able to form micelles and lyotropic crystals in the presence of water (2). The presence of electrolytes in the different media used in the pharmaceutical preparations are well documented to exert a significant effect on the solubility and dissolution rates of many drug salts, including DS, through the common ion effect (3–7). This study has investigated the effect of varying the concentration of sodium chloride (NaCl) and sodium citrate, as common ingredients in various formulations, on the solubility of DDEA relative to DS on the basis that DDEA has diethylamine cation, which is larger and more polarizable than the sodium ion (2). Considering this difference, the aqueous solubilities of DDEA in the presence of cosolvents, hydrophilic polymers, and nonionic surfactants were studied and compared to the corresponding solubilities of DS.

EXPERIMENTAL

Materials

Diclofenac acid (DA) along with DS and DDEA were pharmaceutical grade and were supplied by the Arab Pharmaceutical Manufacturing Company (Sult, Jordan). Polyvinylpyrrolidone (PVP) grade K25 (BASF, Ludwigshafen, Germany); polyethyleneglycol (PEG) grade 4000 and 6000 (E. Merck, Darmstadt, Germany); Pluronic F-127 (PF127) (BASF); Tween 80 (T80) (Croda, Goole, UK); NaCl (Nifor, Geneva, Switzerland); sodium citrate dihydrate (Janssen, Olen, Belgium); cosolvents like glycerol, ethanol, PEG400, and propylene glycol (PG) were pharmaceutical grade and were obtained from E. Merck. Distilled water for injection was used in all experiments.

Methods

Solubility Determinations

Solubilities of DS and DDEA were determined in a series of cosolvent-water mixtures and in a series of additive-water mixtures. Ratios were expressed as either percentage weight/weight for glycerol-water binary mixtures or percentage volume/volume for other systems, and molar concentrations were used for NaCl and sodium citrate. Excess drug powder was placed in crimped stoppered glass vials containing 10 ml of solvent system. The vials were placed in a shaking water bath equilibrated at 25°C (±2°C) and agitated continuously for 48 hr to achieve saturation solubility. Each run was done at least in duplicate. Samples were withdrawn through 0.45-μm filters and assayed for drug content. Spectrophotometric technique was used (Beckman DU7 spectrophotometer, Fullerton, CA) by measuring absorbance of the diluted sample solution at 275 nm versus a standard solution. Most of the additives after the dilution step did not interfere significantly. In the case of the minimal interference, blank solution containing the same concentration of the additive in water was prepared, and its absorbance was measured at 275 nm and considered during calculation of the drug content.

Thermal Analysis

The thermograms were recorded on a Mettler TA 3000 DSC 20 unit (Mettler, Greifensee, Switzerland), calibrated with 6 mg of indium sample (mp 155°C) heated

at a rate of 10°C/min in a closed pierced aluminum crucible from 50°C to 350°C. By thermogravimetric analysis (TGA), the mass loss of a 1 mg sample was recorded using the Mettler TA 3000 TG 50 unit at 10°C/min in a TGA crucible.

RESULTS AND DISCUSSION

Solubility in the Presence of Cosolvents

The solubilities of DS and DDEA in various cosolvent-water systems are shown in Figs. 1 and 2. DS, being a more ionizable salt, produced a higher aqueous solubility than DDEA, 1.92% and 1.13% w/v, respectively. It was reported previously that some salts of drugs had higher solubility and others had lower solubility in cosolvent-water systems than in water alone (8). In the present study, the reduction in solubility was only observed for DS in glycerin-water cosolvent systems (30–90% glycerin) (see below). The other solubility profiles indicated solubility enhancement of different degrees as shown in Figs. 1 and 2. Furthermore, the maximum solubility for both drugs appeared at 80% cosolvent concentration, except for DDEA in glycerol-water systems, for which maximum solubility was not observed.

The highest solubility of DDEA was attained with ethanol-water binary mixtures because ethanol was the least polar of the cosolvents investigated. DS, a more polar salt, had maximum solubility in the presence of PEG400, for which hydrogen bonding interaction was dominant, particularly above 40% cosolvent concentration. The solubility profiles of DDEA and DS in different cosolvent systems were then plotted semilogarithmically against cosolvent concentration. In the case of ethanol-water binary mixtures, linear relationships were observed up to 40% ethanol content (r^2 = 0.9872, slope = 0.0219, and intercept = 1.95% w/v for DS; r^2 = 0.9989, slope = 0.0355, and intercept = 1.22% w/v for DDEA). While for PEG400–water binary mixtures linear relationships were observed up to 60% PEG content (r^2 = 0.9895, slope = 0.0225, and intercept = 2.24% w/v for DS, r^2 = 0.9972, slope = 0.0144, and intercept = 1.22% w/v for DDEA). Nonlinear or poor regression correlation coefficients were obtained outside the ranges outlined for each binary system. It was also noticed that PG-water binary mixtures produced nonlinear relationships, but alternatively sigmoidal plots were observed for both DS and DDEA.

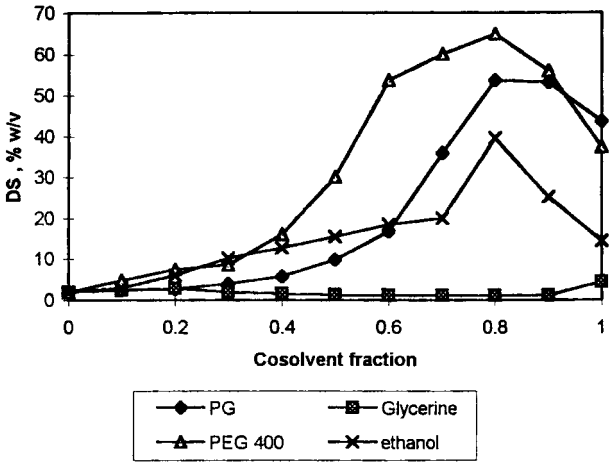

Figure 1. Solubility of DS in the presence of cosolvents at 25°C.

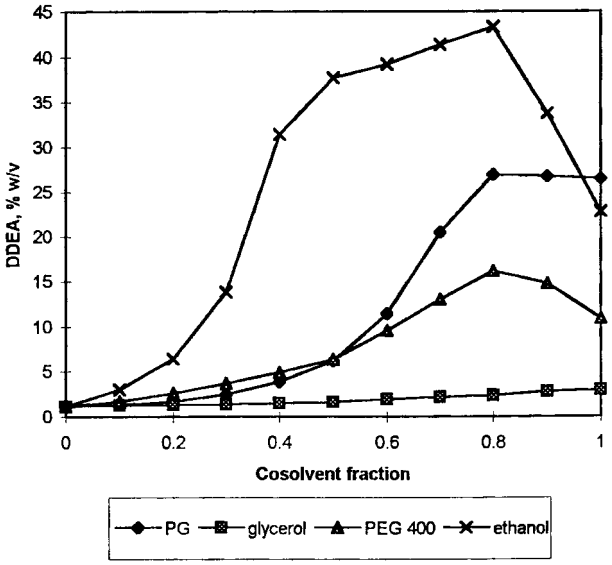

Figure 2. Solubility of DDEA in the presence of cosolvents at 25°C.

Deviations from the Log-Linear Solubility Equation

The following equation (9) was used in this study to calculate deviations from linearity:

$$\log Sc = \phi \log Sn + (1 - \phi)\log Sw$$

where *Sc* is the calculated solubility, *Sn* is the solubility in the neat cosolvent, *Sw* is the equilibrium solubility in water, and ϕ is the volume fraction of the cosolvent. The solubility of DS and DDEA in either PEG-water or eth-

anol-water systems produced positive deviations from linearity in all volume fractions of the cosolvents. The PG-water cosolvent system behaved differently, with negative deviations observed at low volume fractions of PG and positive deviations observed at high volume fractions of PG (Fig. 3). This phenomenon was characteristic for PG-water binary mixtures, as already shown for various drugs (9,10) and related to water-cosolvent interactions and changes in the solvent structures (9). Furthermore, the degrees of deviation in DS and DDEA plots were not clearly different, although DS was a more ionizable salt than DDEA. However, when the solubility of DA, the parent drug, was determined in water-PG binary mixtures, negative deviations were observed up to approximately 90% PG content as shown in Fig. 3. Therefore, the higher values of positive deviations observed for DS and DDEA at the higher fractions of PG could be related to the more ionizable carboxylic groups of the salts and their ability for hydrogen bonding. Furthermore, the highest negative deviations were observed for DA, which indicated a strong interaction between water and PG molecules, and a weak interaction between water and the nonpolar DA molecules resulted in a lower solubility than predicted by calculation using this equation.

Solubility in the Presence of Glycerol

The DS solubility profile in glycerol-water systems produced an unusual pattern; in order to be highlighted, a plot of log (*S*/*Sw*) versus cosolvent content was chosen as shown in Fig. 4, and *S* represents the observed solubility in the aqueous cosolvent mixture. DDEA also was similarly treated and plotted with DS. The solubility profile of DDEA (Fig. 2) did not exhibit maximum solubility, which means that the solubility parameter of DDEA

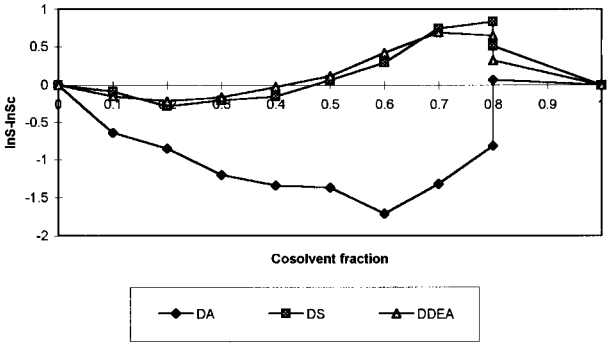

Figure 3. Deviations of observed solubility (ln *Sc*) values from log-linearity relationship for DA, DS, and DDEA in PG-water binary mixtures.

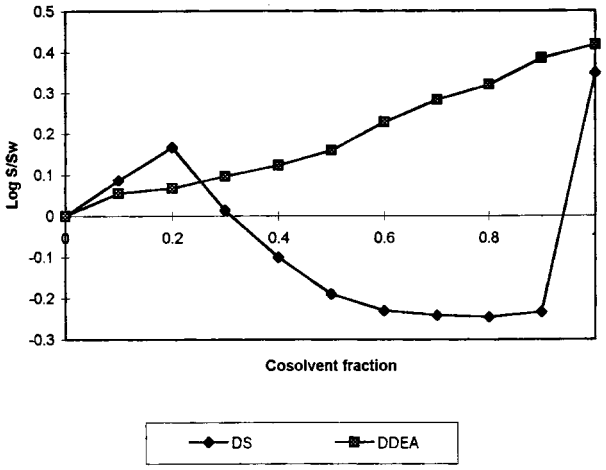

Figure 4. Solubility of DS and DDEA in the glycerol-water mixture at 25°C.

did not fall between the solubility parameter values of glycerol and water. On a semilogarithmic scale, the plot showed a typical log-linear relationship ($r^2 = 0.9896$). The solubility efficiency represented by the slope of the plot was 0.0042, a very low value when compared with the solubility efficiencies of other cosolvent systems. In the case of DS, the solubility was first increased, with a maximum at 20% glycerol, and then decreased gradually, reaching a value lower than *Sw* at a cosolvent content above 30% and a minimum value at 90% glycerol content. After that, the solubility started to increase, reaching double the value of *Sw* at 100% glycerol content, as shown in Fig. 4. This unusual solubility profile was due to a change in the solid state of the drug. The solid phase of DS in equilibrium with mixtures of water and glycerol (50%) was found to be a hydrate when examined by thermal analysis, and the water content determined by a Karl Fischer test was 3.8% w/w. The peak temperature of dehydration was relatively high (120°C) and was related to the weight loss in TGA. While the solid phase of DS in equilibrium with water alone did not exert any solid-state change (water content was 0.73%, while it was 0.51% before it came into contact with water or with the aqueous cosolvent systems). Hydrate formation decreased the solubility of DS in glycerol-water binary mixtures (30–90%) and distorted the solubility curve.

Solubility in the Presence of Surfactants and Hydrophilic Polymers

The solubility profiles of DS and DDEA in two nonionic surfactants at 25°C are shown in Fig. 5. At a concentration of surfactant lower than 0.1% w/v, no signi-

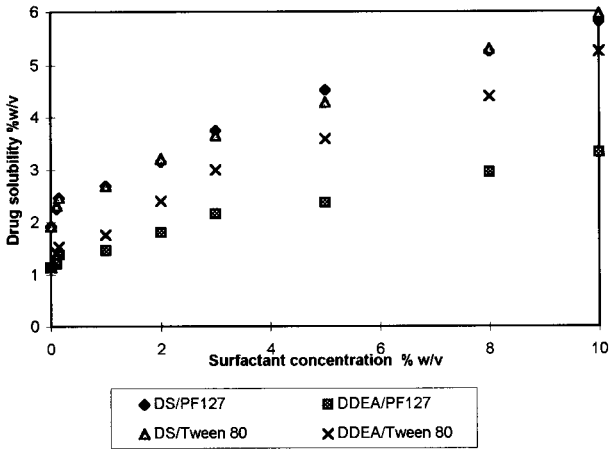

Figure 5. Aqueous solubility of DS and DDEA in the presence of different surfactants at 25°C.

ficant increase in the solubility of DS or DDEA was observed. In each case, the solubility was proportional to the surfactant concentration within the two distinct ranges 0–3% and 3–10% w/v after linear regression, with a smaller value of slope for the range 3–10% w/v surfactant indicating that a negative deviation in the solubility occurred that could be due to some interaction that took place between surfactant molecules and both drugs. The solubilization of drug in a surfactant solution is generally due to increasing partitioning of the drug molecules into the hydrocarbon core of the micelles. Nevertheless, it was reported that phenol in large quantities used to dissolve in the polyoxyethylene mantle of the micelles of Pluronic PF68 after saturation of the micelle hydrophobic core occurred (11). The solubilization efficiency of the additive was indicated by the slope of the solubility curve and is presented as millimoles of drug solubilized per gram of additive. Although DS was more soluble in water than DDEA, T80 exhibited average solubilization efficiency of similar magnitude for both salts, 1.38 and 1.23, respectively. DDEA has more hydrophobic characteristics and consequently is expected to have more solubility in the hydrophobic core of the micelles, which might have higher solubility in T80. However, DS solubility could be attributed to its higher affinity toward the polyoxyethylene mantle of the micelles. It was reported that the greater dissociation constant of the acidic group, the greater the hydrogen bonding to the oxyethylene (OE) group in the micelles of nonionic surfactant like T80 (11, p. 299). Thus, these results suggested that DS and DDEA were distributed between both the hydrophilic and hydrophobic regions of the micelles with variable ratios. In contrast to T80, the average solubilization efficiency of PF127 showed dissimilarity, with a higher solubility for DS than for DDEA (1.32 and 0.67, respectively). Taking into consideration that T80 and PF127 have a similar number of OE groups per 1 g of the surfactant (0.0153 and 0.0155, respectively) (12); this would support that DS molecules appeared to be located more in the polyoxyethylene mantle of the micelles of the surfactant and hence showed higher solubility than DDEA in PF127 aqueous solutions.

Solubility in the Presence of Hydrophilic Polymers

Figure 6 shows the solubility of DS and DDEA in solutions of PVP, PEG4000, and PEG6000. The solubility of DS in PVP exhibited a linear relationship with the concentration of PVP up to 30% w/v ($r^2 = 0.9968$), and the solubility plot can be generally classified as A-L (13). The solubility of DDEA in PVP and the solubility of DS and DDEA in PEG4000 and PEG6000 solutions exhibited a negative deviation, which represented a decreasing dependence on polymer added at higher concentrations. This could be attributed to the self-association of the polymer at high concentrations (14). PVP up to 15% w/v concentrations showed a solubilizing efficiency that was almost similar for DS and DDEA (0.99 and 0.96 mmol drug/g polymer, respectively). Above a concentration of 15% w/v, the solubilizing efficiency of PVP for DDEA decreased significantly, to 0.41 mmol/g, as a result of the negative deviation, by which PVP molecules have a greater tendency to associate, rather than to interact, with DDEA molecules. Similarly, DS showed a stronger interaction with PEG4000 and PEG6000 than DDEA, as indicated by its higher solubilizing efficiency (almost double), and the negative deviation occurred at concen-

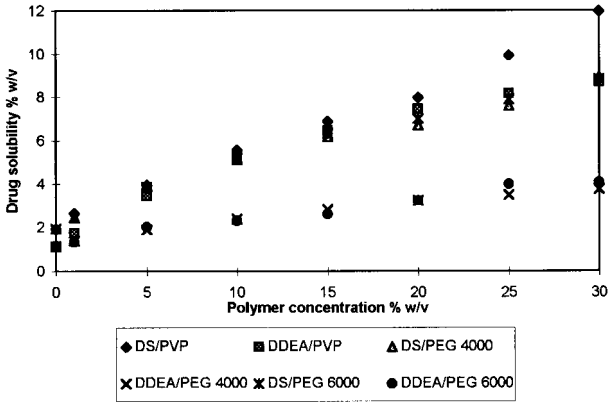

Figure 6. Aqueous solubility of DS and DDEA in the presence of hydrophilic polymers at 25°C.

trations of PEG above 10% w/v compared to DDEA, which occurred above 5% w/v of the polymer. Furthermore, in the case of PEG400, DS showed much higher solubility than DDEA did in the same polymer solution.

The solubilizing efficiency of T80 for DDEA was much higher than that of PEGs of a similar concentration range. It was approximately five times that of PEG6000, six times that of PEG4000, and nine times that of PEG400. Taking into account that T80 has the fewest OE groups per gram (0.0218, 0.0198, 0.0229, 0.0153, and 0.0155 for PEG400, PEG4000, PEG6000, T80, and PF127, respectively), then the higher solubility of DDEA in T80 could be due to that DDEA was located mostly within the hydrocarbon core of T80 micelles. This was further confirmed by the lower solubility of DDEA in PF127. When the solubilizing efficiency of T80 for DS was compared with that of PEGs, that for T80 was more than twice the value for PEGs; one could conclude that the solubilization of DS in the nonionic surfactants did depend to some extent on the location within the hydrocarbon core of the micelles. However, the solubilizing efficiency of OE groups was higher for the nonionic surfactants polyoxyethylene mantle than that of polyoxyethylene glycols, as reported previously and related to the type of arrangement of these groups with respect to the whole molecule in solutions (15).

Solubility in the Presence of Electrolytes

The results of aqueous solubility (mmol/L) of DS and DDEA in the presence of different concentrations (mol/L) of either sodium chloride or sodium citrate are presented semilogarithmically (Fig. 7). The effect of electrolytes on the solubility of DS was prominent and indicated a salting-out phenomenon. An empirical quantification of the effect of an electrolyte on the solubility of a solute may be obtained by the Steschenow equation (16):

$$\log S^*/S = K \cdot C_e$$

where S^* is the solubility in the presence of an electrolyte having C_e concentration, S is the solubility in its absence, and K is the salting coefficient. A positive K means a salting-out effect, while a negative value means a salting-in effect. This equation holds up to electrolyte concentrations of 1 mol /L. In this study, the relationship was found to be fairly linear from C_e 0.2 up to 0.6 M (in the case of DS, $r^2 = 0.9900$ and 0.9888 for NaCl and sodium citrate, respectively). Furthermore, the K values were 1.163 and 1.634 for NaCl and sodium citrate, respectively, which indicated that sodium citrate, being a trisodium salt, was stronger as a salting-out agent, as expected.

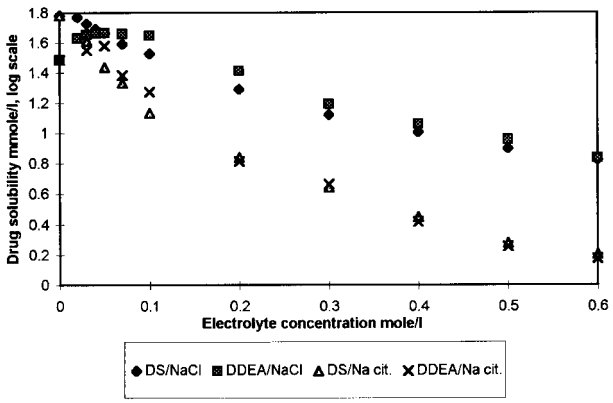

Figure 7. A semilogarithmic presentation of the aqueous solubility of DS and DDEA in the presence of NaCl and sodium citrate at 25°C.

The effect of electrolytes on the solubility of DDEA was different from that of DS, which could be attributed to the absence of common ion effect and also due to the fact that DDEA cation is larger and more polarizable than the sodium ion (2). In a recent report (17), it was shown that DS has a surface activity, but no micelle formation. With DDEA, on increasing concentration of electrolytes, the phenomenon was progressively converted from an effective salting-in (negative K) to an effective salting-out (positive K) effect. In a previous report, the combination of a lipophilic palmitate side chain and a protonated head group in clindamycin 2–palmitate HCl (18) was responsible for the enhanced solubility through association into micelles. DDEA behaved similarly, and its solubility was maximum in the presence of 0.05 M of electrolytes (46.4 mmol/L and 38.0 mmol/L in the presence of NaCl and sodium citrate, respectively), with NaCl being more efficient in enhancing the solubility of DDEA than sodium citrate (K values were -3.548 and -1.858, respectively). The critical aggregation concentration of DDEA was equal to 20 mmol/L at 20°C (2), much lower than the maximum solubility in the presence of either NaCl or sodium citrate. Micelles have a much higher solubility in water than single surfactant molecules because the hydrophobic moieties in the micelles are well shielded from contact with water by the polar moieties (11, p. 92). Thus, a salting-in effect took place as a direct result of more efficient formation of micelles. At room temperature, a 2% DDEA solution already existed as a vesicle dispersion because the region of existence of the micellar solution of DDEA was small (2). The vesicle dispersion of DDEA was reported as an unstable system and started to recrystallize within a few hours. In this study, above 0.05

M C_e, DDEA started to decrease in solubility, and sodium citrate exhibited a stronger salting-out effect than NaCl (K values were 1.394 and 1.681 for NaCl and sodium citrate, respectively). Under high electrolyte concentrations, the aggregation number became fairly large, which might facilitate precipitation of DDEA.

CONCLUSION

DS was not able to tolerate low concentrations of electrolytes, and the salting-out effect was dominant due to the common ion effect. In contrast, DDEA showed two phases for which the salting-in effect was observed at low electrolyte concentrations, followed by the salting-out effect at high concentrations. The cosolvents ethanol, PG, and PEG400 were useful in enhancement of DS and DDEA solubility. Glycerol was a poor cosolvent for DDEA and caused transformation of the anhydrous DS to the less soluble hydrate form. Since DS is a more ionizable salt, it exhibited higher complexing tendency than DDEA, which resulted in higher aqueous solubility in the presence of hydrophilic polymers (PVP and PEGs) and nonionic surfactants (T80 and PF127). DS was more likely to be located in the polyoxyethylene mantle of the micelles, while DDEA was more likely to be located in the core of the micelles.

ACKNOWLEDGEMENT

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