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Combined effect of SLS and $(SBE)_{7M}$-β-CD on the solubilization of NSC-639829

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Abstract

Complexation and micellization are two effective ways of solubilizing drugs. In this study, the combined effect of surfactant and complexant on the solubilization of a poorly water soluble compound (NSC-639829) is investigated. With increasing concentration of sodium lauryl sulphate (SLS) in solutions of fixed concentration of $(SBE)_{7M}$-β-CD, the total solubility of the drug decreases linearly, reaches a minimum and then increases linearly. At each minimum, the molar ratio of SLS to $(SBE)_{7M}$-β-CD is close to unity. The above observation is attributed to the fact that the surfactant molecule competes with the drug to "fit" in the non-polar cyclodextrin cavity. The surfactant depletes cyclodextrin to form a 1:1 complex. Once the concentration of free SLS reaches the CMC, it starts forming micelles and hence, solubilizes the drug. A slight decrease of the solubilizing power is noticed in the presence of SLS/$(SBE)_{7M}$-β-CD complex. The combined use of two solubilizing agents, a surfactant and a complexant, results in a much lower solubility than when either one is used alone at the same concentration. The surfactant molecule acts as a competitive inhibitor in the solubilization of the drug by the complexant. Similarly the complexant "pulls" the surfactant out of solution, making it unavailable for solubilizing the drug.

Keywords: Solubilization; Combined effect; Complexation; Micellization; NSC-639829

1. Introduction

Solubilizing a certain dose of drug in a limited volume of aqueous solution is a frequently encountered challenge in parenteral formulation design. pH adjustment, cosolvent addition, surfactant addition, and complexation are the most commonly utilized solubilization techniques in the formulation of poorly water soluble pharmaceutical compounds (Yalkowsky, 1999). Certain combinations of solubilization techniques show synergistic effects, resulting in greater solubility enhancement than if they were used alone. pH adjustment in combination with either cosolvency, micellization, or complexation is frequently highly effective for solubilization of ionizable compounds (Tinwalla et al., 1993; Johnson et al., 1994; Li et al., 1998, 1999a).

According to Stella et al. (1999), it has been suggested that the combination of complexant and cosolvent or surfactant might have a synergistic effect on solubilization. Studies (Pitha and Hoshino, 1992; Li et al., 1999b) indicate that the combined use of cosolvent and complexant can result in either decreased and/or enhanced solubility compared with

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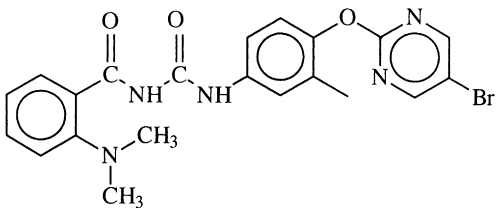
either method used alone. Li et al. proposed that the decrease in solubility is due to the competitive displacement of drugs from their complexes by cosolvents and that the increase is due to the formation of a drug–ligand–cosolvent ternary complex (Li et al., 1999b). They developed a simple mathematical model that describes both phenomena.

Given the fact that the cyclodextrins can incorporate ionic and nonionic surfactant molecules into their cavities in aqueous solutions (Yunus et al., 1992; Junquera et al., 1997), it will be interesting to study the effects of the interaction between surfactants and complexants on their solubilization ability of pharmaceutical compounds. Among limited literature, Müller and Albers noticed the competitive displacement of methyltestosterone from the cyclodextrin cavity by sodium deoxycholate (Müller and Albers, 1991). Veiga and Ahsan reported that the co-presence of Brij 35 or sodium lauryl sulphate in the solution with β-CD lowered the solubility of tolbutamide (Veiga and Ahsan, 1998). However, the low solubility of the complex formed by tolbutamide and natural β-CD complicated the study.

In this study, we studied the combined effect of the surfactant, sodium lauryl sulfate, and the complexant, $(SBE)_{7M}$-β-CD, on the solubilization of NSC-639829 (*N*-[4(5-bromo-2-pyrimidoxyl)-3-methylphenyl]-(2-dimethylamino)-benzoylurea), an investigative antitumor compound (Okada et al., 1999). A semi-quantitative relationship to describe the combined effect of surfactant and complexant on the solubilization of poorly soluble drug is developed.



2. Background

2.1. Solubilization by complexation

Cyclodextrins and their derivatives can form complexes by the inclusion of a nonpolar molecule, or the nonpolar part of a molecule, in their nonpolar cavities. Some of them have been widely used for enhancement of the aqueous solubility of drugs. The total solubility of a solute that forms a 1:1 complex is

$$S_{\text{total}}^{\text{comp}} = S_{\text{w}} + \tau_{\text{u}} C_{\text{L}} \tag{1}$$

where C_{L} is the concentration of the ligand added, and τ_{u} (the slope of the solubilization curve) is its solubilization power for the unionized solute (Yalkowsky, 1999). The formation (or stability) constant, K_{u}, can be calculated using the Higuchi/Connors method (Higuchi and Connor, 1965) by

$$K_{\text{u}} = \frac{\tau_{\text{u}}}{S_{\text{w}}(1 - \tau_{\text{u}})} \tag{2}$$

2.2. Solubilization by micellization

Due to their amphiphilic nature surfactant micelles have been widely used to solubilize drugs. The total solubility of the solute in a surfactant solution can be described by

$$S_{\text{total}}^{\text{surf}} = S_{\text{w}} + \kappa_{\text{u}} C_{\text{mic}} \tag{3}$$

where S_{w} is the intrinsic solubility of the drug, κ_{u} is the surfactant solubilization capacity for the unionized form of the drug, and C_{mic} is the concentration of the micellar surfactant,

$$C_{\text{mic}} = C_{\text{total}} - \text{CMC} \tag{4}$$

where C_{total} is the total surfactant concentration and CMC is the critical micelle concentration of the surfactant (Yalkowsky, 1999).

3. Materials and methods

3.1. Materials

NSC-639829 (*M*w: 470) was used as received from the National Cancer Institute (NCI). Sodium lauryl sulfate USP was purchased from Fisher (Fair Lawn, NJ). Sulfobutyl ether β-cyclodextrin ($(SBE)_{7M}$-β-CD) with an average molecular weight of 2162 and an average degree of substitution of 7 was a generous gift from Cydex, LC (Overland Park, KS). HPLC grade solvents purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA) were used.

3.2. Solubility determinations

Solutions containing different concentrations of SLS (w/v %: 0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0) and $(SBE)_{7M}$-β-CD (w/v %: 0, 1, 2, 5, 10) were prepared in Millipore water. The solutions are not buffered or ionic-strength controlled. Excess amount of NSC-639829 powder was added to sample vials containing the above solutions. The samples were equilibrated for 5 days at room temperature. Samples with remaining crystals were considered to have reached equilibrium. The samples were then filtered through a 0.45 μm filter (Gelman Acrodisc LC13) and analyzed by HPLC. All the samples were prepared in duplicate.

3.3. HPLC analysis

The HPLC assay for NSC-639829 was used as reported by the National Cancer Institute (Report 98, 2001). A Beckman Gold HPLC system with a 168 detector was used. A Lichrosorb RP-18 column (250 mm × 4.6 mm with particle size of 10 μm) was used with a mobile phase comprised of 90% methanol and 10% water. A flow rate of 1 ml/min was maintained and the effluent was detected at a wavelength of 254 nm. None of the solubilizing species interfered with the assay.

3.4. Data analysis

All the data are plotted using Microsoft Excel. Slope information for Fig. 3a and b is obtained using SPSS 10.0 for Windows.

4. Results and discussion

NSC-639829 has an intrinsic solubility of 3×10^{-5} mg/ml (6.5×10^{-5} mM) and an approximate basic p*K*a of 5 (Jain et al., 2001). The phase solubility diagrams with $(SBE)_{7M}$-β-CD and SLS are shown in Fig. 1a and b, respectively. At neutral pH the drug is primarily uncharged. The total solubility of NSC-639829 increases linearly with $(SBE)_{7M}$-β-CD concentration up to 10% (46.2 mM) as shown in Fig. 1a. Using the slope of the solubilization curve, i.e. τ_u (0.006), the formation constant of NSC-639829/$(SBE)_{7M}$-β-CD complex is calculated as 92 mM^{-1} via Eq. (2). The solubilization by the surfactant follows a linear dependence upon SLS concentration above critical micelle concentration (7.98 mM, Handbook of Pharmaceutical Excipients, 1994). The solubilization capacity κ_u of the surfactant is calculated as 0.049 using Eq. (3).

When SLS and $(SBE)_{7M}$-β-CD are used in combination, V-shaped solubilization curves are observed (Fig. 2a). The total drug solubility decreases linearly with increasing SLS concentration at fixed $(SBE)_{7M}$-β-CD concentration. The curves reach a minimum before going up again linearly with increasing SLS concentration. At each of the three minimum, the molar ratio of SLS to $(SBE)_{7M}$-β-CD is close to unity (0.95, 0.75, 0.94, respectively), suggesting the formation of 1:1 SLS/$(SBE)_{7M}$-β-CD complex. Similar results are obtained when the data in Fig. 2a are replotted as S_{tot} versus $(SBE)_{7M}$-β-CD concentration for fixed SLS concentration series (Fig. 2b). Similar V-shaped solubilization curve was also observed in the study using 2-HP-β-CD and sodium deoxycholate (Müller and Albers, 1991).

Assuming both NSC-639829 (D) and SLS (S) form 1:1 complex with the ligand $(SBE)_{7M}$-β-CD (L), the following equilibria exist in the system.

$$D + L \Leftrightarrow DL$$

$$S + L \Leftrightarrow SL$$

The formation constants of DL and SL can be expressed as

$$K_D = \frac{[DL]}{[D][L]}$$

$$K_S = \frac{[SL]}{[S][L]}$$

As can be seen from the following equation, the concentration ratio between DL and SL depends on not only the formation constants but also the concentrations of free drug and free surfactant.

$$\frac{[DL]}{[SL]} = \frac{K_D[D][L]}{K_S[S][L]} = \frac{K_D[D]}{K_S[S]}$$

Unfortunately, the formation constant of the SLS/$(SBE)_{7M}$-β-CD complex is not found in the literature. Based on the reported SLS/β-CD formation constant of 21 mM^{-1} (Lin et al., 2001) and that

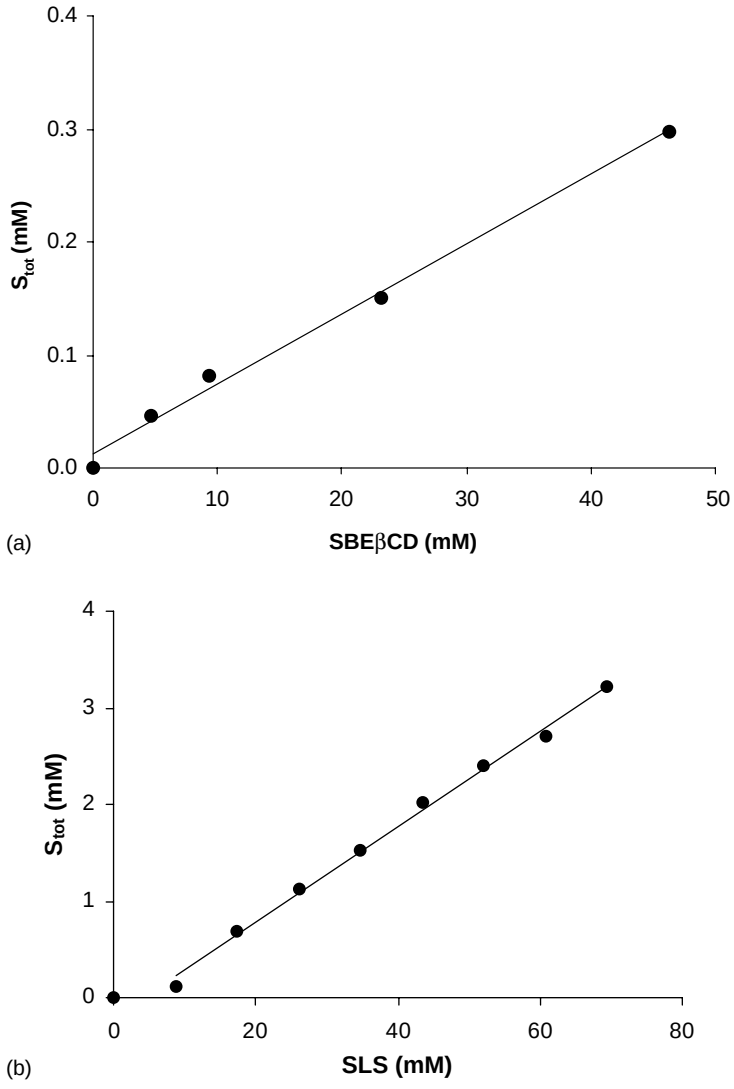


Fig. 1. Solubilization curves of NSC-639829 by $(SBE)_{7M}$-β-CD (a) and SLS (b).

substitution can lead to weakened binding due to steric hindrance and possible charge repulsion, the formation constant of SLS/$(SBE)_{7M}$-β-CD complex is expected to be lower than 21 mM^{-1}. Although the NSC-639829/$(SBE)_{7M}$-β-CD complex may have a higher formation constant (92 mM^{-1}) than the SLS/$(SBE)_{7M}$-β-CD complex, SLS/$(SBE)_{7M}$-β-CD complex can predominate due to the very low concentration of free NSC-639829, which is approximately the intrinsic solubility of the drug.

Assuming that the formation constant for the SLS/$(SBE)_{7M}$-β-CD complex is in the same order of magnitude as or one order of magnitude lower than that of the SLS/β-CD complex, an excess of less than 1 mM or a few mMs of either SLS or $(SBE)_{7M}$-β-CD will drive the complexation of the other to over 90% completion. It may be assumed that SLS and $(SBE)_{7M}$-β-CD sequester each other at 1:1 ratio when either one of them is in excess. To explore whether the formation of

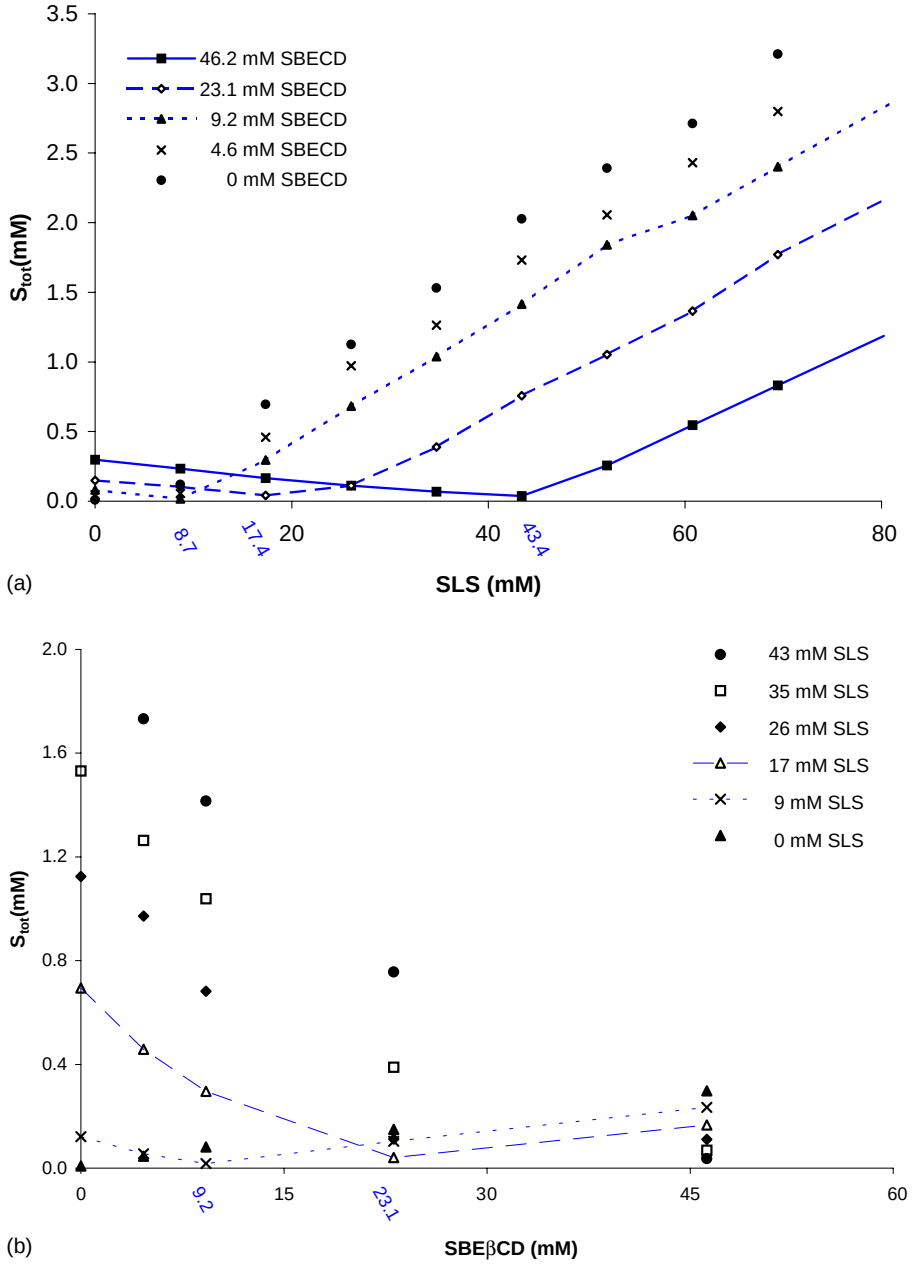
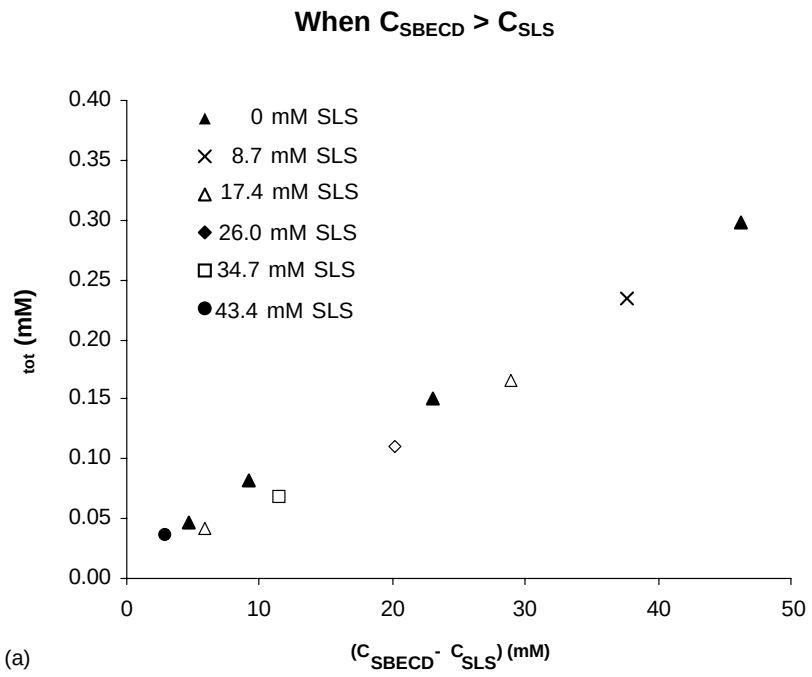
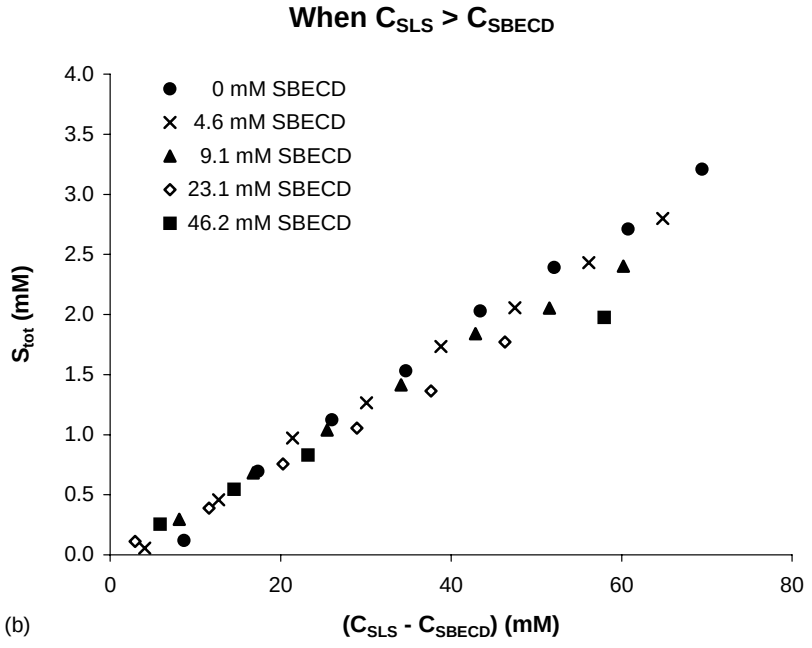


Fig. 2. Solubilization profile of NSC-639829 by combined use of $(SBE)_{7M}$-β-CD and SLS. (a) S_{tot} vs. SLS concentration; (b) S_{tot} vs. $(SBE)_{7M}$-β-CD concentration.

SLS/$(SBE)_{7M}$-β-CD complex will influence the solubilization of the drug by the solubilizer in higher concentration, the total solubility of NSC-639829 is plotted against the concentration difference between SLS and $(SBE)_{7M}$-β-CD. The data for the total concentration of $(SBE)_{7M}$-β-CD being higher than that of SLS are given in Fig. 3a while the data for the total concentration of SLS being higher than that of



(a)



(b)

Fig. 3. Total solubility plotted against concentration difference between $(SBE)_{7M}$-β-CD and SLS: (a) when $C_{(SBE)\text{-}\beta\text{-}CD} > C_{SLS}$ and (b) when $C_{SLS} > C_{(SBE)\text{-}\beta\text{-}CD}$.

Table 1
Slope information for curves in Fig. 3a

	C_{SLS} (mM)		
	0	8.7	17.4
Slope (±S.E.)	0.060 ± 0.000	0.058 ± 0.000	0.054 ± 0.000
R^2	0.997	0.999	1.000

$(SBE)_{7M}$-β-CD are given in Fig. 3b. As can be seen in the figures, the total drug solubility is linearly related to the difference between SLS and $(SBE)_{7M}$-β-CD concentrations. The slopes of each concentration series seem to be close. However, a slight decrease of the slopes with increasing SLS/$(SBE)_{7M}$-β-CD complex concentrations is observed as shown in Tables 1 and 2. This suggests that the co-existence of SLS/$(SBE)_{7M}$-β-CD complex may slightly decrease the solubilization power of $(SBE)_{7M}$-β-CD and that of SLS micelles.

Fig. 4a and b provide schematic concentration profiles for the following drug components in the system (note that free ligand ($(SBE)_{7M}$-β-CD) and free surfactant (SLS) are not shown).

D: free drug
DL: drug–ligand complex
SL: surfactant–ligand complex
MD: micellar drug

With the increased concentration of SLS at fixed ligand concentration, complexation of the drug decreases until most of the ligand is tied up with surfactant. Additional surfactant then forms micelles that solubilize the drug. The total solubility of the drug in the system is the sum of free drug (D), drug/complexant complex (DL), and micellar drug (MD) concentrations. Therefore, it exhibits the V-shape curve. On the other hand, when SLS concentration is fixed, addition of ligand depletes SLS and then solubilizes drug through formation of drug/ligand complex.

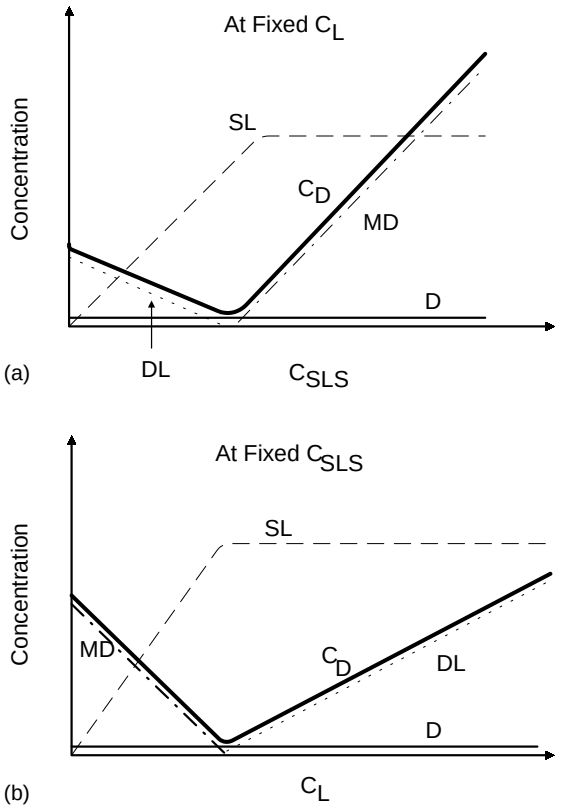


Fig. 4. Schematic concentration profiles of some of the various drug components in the system at fixed $(SBE)_{7M}$-β-CD concentration (a) and at fixed SLS concentration (b).

Depending on the intrinsic solubility of the drug and the association constants of the drug/ligand and surfactant/ligand complex, the degree of completeness of depletion of surfactant or ligand by the other is expected to be different. For a drug with relatively high intrinsic solubility and high drug/ligand association constant, significant amount of drug/ligand complex may still exist when the surfactant starts forming micelles and there is a chance for a less than additive

Table 2
Slope information for curves in Fig. 3b

	$C_{(SBE)\text{-}\beta\text{-}CD}$ (mM)				
	0	4.6	9.1	23.1	46.2
Slope (±S.E.)	0.048 ± 0.001	0.045 ± 0.001	0.041 ± 0.001	0.038 ± 0.001	0.033 ± 0.000
R^2	0.994	0.997	0.996	0.997	1.000

effect on solubilization by combined use of surfactant and complexant.

5. Conclusions

The combined use of SLS and $(SBE)_{7M}$-β-CD on the solubilization of NSC-639829, a poorly soluble drug, results in a much lower solubility than when either is used alone. The SLS molecule acts as a competitive inhibitor in the solubilization of the drug by the $(SBE)_{7M}$-β-CD molecule while the $(SBE)_{7M}$-β-CD increases the apparent CMC of the surfactant and decreases the solubilization of the drug by micellization.

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References

Handbook of Pharmaceutical Excipients, 1994. American Pharmaceutical Association, Washington, DC.

Higuchi, T., Connors, K.A., 1965. Phase solubility techniques. In: Advances in Analytical Chemistry and Instrumentation. Interscience, New York, pp. 117–212.

Jain, N., Yang, G., Tabibi, S.E., Yalkowsky, S.H., 2001. Solubilization of NSC-639829. Int. J. Pharm. 225, 41–47.

Johnson, M.D., Hoesterey, B.L., Anderson, B.D., 1994. Solubilization of a tripeptide HIV protease inhibitor using a combination of ionization and complexation with chemically-modified cyclodextrins. J. Pharm. Sci. 83, 1142–1146.

Junquera, E., Peña, L., Aicart, E., 1997. Micellar behavior of the aqueous solutions of dodecylethyldimethylammonium bromide. A characterization study in the presence and absence of hydroxypropyl-β-cyclodextrin. Langmuir 13, 219–224.

Li, P., Tabibi, E., Yalkowsky, S.H., 1998. Combined effect of complexation and pH on solubilization. J. Pharm. Sci. 87, 1535–1537.

Li, P., Tabibi, E., Yalkowsky, S.H., 1999a. Solubilization of flavopiridol by pH control, combined with cosolvents, surfactants, or complexants. J. Pharm. Sci. 88, 945–947.

Li, P., Zhao, L., Yalkowsky, S.H., 1999b. Combined effect of cosolvent and cyclodextrin on solubilization of nonpolar drugs. J. Pharm. Sci. 88, 1107–1111.

Lin, C.E., Huang, H.C., Chen, H.W., 2001. A capillary electrophoresis study on the influence of beta-cyclodextrin on the critical micelle concentration of sodium dodecyl sulfate. J. Chromatogr. A 917, 297–310.

Müller, B.W., Albers, E., 1991. Effect of hydrotropic substances on the complexation of sparingly soluble drugs with cyclodextrin derivatives and the influence of cyclodextrin complexation on the pharmacokinetics of the drugs. J. Pharm. Sci. 80, 599–604.

Okada, H., Kato, M., Koyanagi, T., Mizuno, K., 1999. Synthesis and antitumor activity of water-soluble benzoylphenylureas. Chem. Pharm. Bull. 47, 430–433.

Pitha, J., Hoshino, T., 1992. Effects of ethanol on formation of inclusion complexes of hydroxypropylcyclodextrins with testosterone or with methyl-orange. Int. J. Pharm. 80, 243–251.

Report 98, 2001. RPT-130 from the Analytical Contractor to the National Cancer Institute, NIH, Bethesda, MD.

Stella, V.J., Rao, V.M., Zannou, E.A., Zia, V., 1999. Mechanisms of drug release from cyclodextrin complexes. Adv. Drug Delivery Rev. 36, 3–16.

Tinwalla, A.Y., Hoesterey, B.L., Xiang, T.X., Lim, K., Anderson, B.D., 1993. Solubilization of thiazolobenzimidazole using a combination of pH adjustment and complexation with 2-hydroxypropyl-beta-cyclodextrin. Pharm. Res. 10, 1136–1143.

Veiga, M.D., Ahsan, F., 1998. Solubility study of tolbutamide in monocomponent and dicomponent solutions of water. Int. J. Pharm. 160, 43–49.

Yalkowsky, S.H., 1999. Solubility and Solubilization in Aqueous Media. Oxford University Press, New York.

Yunus, W.M.Z.W., Taylor, J., Bloor, D.M., Hall, D.G., Wynjones, E., 1992. Electrochemical measurements on the binding of sodium dodecyl-sulfate and dodecyltrimethylammonium bromide with alpha-cyclodextrin and beta-cyclodextrins. J. Phys. Chem. 96, 8979–8982.