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Review Article

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Drug Solubilization by Means of Partition/Association Equilibrium Using a Modified Nanosized Dendrimeric Biopolymer

Hwee Jing Ong[1] and Rodolfo Pinal[1,2]

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Abstract. The objective of this study is to elucidate the combined effects of a novel type of material being investigated as a new excipient, an octenylsuccinate-modified dendrimer-like biopolymer (OS-DLB) and poloxamer (PLX), on the solubility of poorly water-soluble compounds. Phenytoin (PHT), griseofulvin (GSF), ibuprofen (IBU), and loratadine (LOR) were used as model compounds. Phase solubility measurements were conducted to determine the relative proportions of API, OS-DLB, and PLX that result in the most stable dendrimeric complexes. The solubilizing power of OS-DLB increases with increasing hydrophobicity of the solute. In the presence of PLX, the solubilization effect of OS-DLB is modestly accentuated for the most hydrophobic drugs (IBU and LOR) but has no effect on the least hydrophobic one (PHT). The maximum potentiation effect of PLX on the solubilizing properties of OS-DLB was observed for GSF, the drug of intermediate hydrophobicity. Three different types of solubilization profiles were obtained in the study. All three different profiles can be appropriately described by a single solubilization model, depending on the specific parameter values. The defining parameters of the model reflect the hydrophobicity of the drug on the one hand and, on the other hand, the inherent tendency of the drug (crystal lattice energy) toward crystallization.

KEY WORDS: solubility; solid dispersion; solution phase; model; excipients.

INTRODUCTION

Drug solubility is one of the most persistent challenges in pharmaceutical development. Traditional solubilization approaches can be broadly divided into two categories: solute modification and solvent modification. Solute modification strategies typically involve either the alteration of the physical properties of the crystal, such as salt formation, change of polymorphic form, and amorphization, or the incorporation of a second component in the solid solute phase in small concentration as an impurity, or in comparable amounts as the active as in a eutectic, or alternatively in large excess as a carrier (1). These strategies are effective in increasing the apparent solubility and dissolution rate of organic compounds in aqueous media. However, when dealing with metastable crystal forms or amorphous systems, the increase in apparent solubility is the result of a thermodynamically unstable system; when dissolved in aqueous media, there will be a natural driving force (tendency) toward precipitation as the most stable (least soluble) solid form, thereby posing the critical limitation of potentially eliminating the very advantages offered by these solid modification strategies (2).

Solvent modification strategies are comparatively more effective in producing thermodynamically stable enhancements in solubility. Solvent modification approaches typically involve the use of solubilizing agents such as cosolvents, buffers, complexing ligands, and surfactants. The use of organic cosolvents is one of the most powerful means of altering the solubility of a crystalline organic compound in aqueous media. Cosolvents facilitate drug solvent mixing in the liquid phase by decreasing the activity coefficient, γ, of the solute in the particular solvent mixture, thus decreasing the free energy of mixing, ΔG_{mix}. Mechanistically, cosolvents disrupt water structure; the less strongly water self-associates, the less able it is to "squeeze out" nonpolar solutes. Consequently, higher solubility (easier mixing) of the nonpolar solutes in the water-cosolvent mixture is obtained. Solubilization by means of buffers, complexing ligands, and surfactants is attained through the creation of a secondary liquid phase equilibrium acting in parallel (simultaneously) with the solid-liquid solubility equilibrium. Many poorly soluble active pharmaceutical ingredients (APIs) are weak electrolytes. For this type of solutes, pH modification can increase the solubility, as long as it is used as a control variable. Specifically, the use of buffers to control the pH of a system provides a means of increasing the solubility of weak electrolytes in aqueous media. This is achieved by incorporating

Guest Editors: Philip J. Kuehl and Stephen W. Stein

[1] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana 47907, USA.
[2] To whom correspondence should be addressed. (e–mail: rpinal@purdue.edu)

and controlling the acid-base equilibrium as a contributor toward the overall solubility equilibrium. When surfactants are used to increase solubility, surfactant concentrations above the critical micelle concentration (CMC) are necessary. Surfactant-based solubilization of nonpolar solutes in aqueous media is achieved *via* incorporation (partition equilibrium) of solute molecules into the nonpolar core of the micelles, which is largely composed of the hydrophobic chains of the surfactant. Solubilization by molecular complexation is achieved by means of "reversible (noncovalent), stoichiometric association of two or more molecules into a distinct, well-defined structural entity" (1). Another type of complexation is the formation of nonstoichiometric stacking complexes or hydrotropes (3). The driving force for hydrotrope formation is of the same nature as the driving force for micelle formation. That is, the nonpolar solute molecules are arranged so, as to minimize the molecular surface area of contact with water. Because of the similarity between minimum hydrotropic concentration (MHC) and CMC, the molecular basis of hydrotropic cooperativity has been largely attributed to the self-aggregation of the hydrotrope, analogous to the aggregation of surfactant molecules to form micellar aggregates (4,5). Both micelles and complexing agents (inclusion and stacking compounds) provide a favorable nonpolar microenvironment—a secondary liquid phase equilibrium—that is well suited to accommodate nonpolar molecules otherwise being squeezed out of water. A limitation of solvent modification techniques is that there is a maximum solubility enhancement that can be achieved for a given concentration of a solubilizing agent.

One way to circumvent the abovementioned limitation of solvent modification techniques is the use of multiple of solubilizing agents, either multiple solubilizing agents, each from a different class, or different solubilizing agents all from the same class. The use of combinations of solubilizing agents allows formulation scientists to minimize the unfavorable characteristics of any single solubilizing agent, as well as to expand the solubilization range of the solubilizing agents. Hoye and Myrdal (6) demonstrated the versatility of ethanol as cosolvent in hydrofluoroalkane (HFA)–based metered dose inhalers, with the solubility enhancement for various solutes ranging from 1.2 to 99.4-fold when 20% (w/w) ethanol was added compared to pure HFA-134a. He et al. (7) showed that the solubility of fluasterone can be increased or decreased by varying the concentrations of cosolvent and cyclodextrin, as well as the type of cosolvent. Li et al. (8) found that pH control, when used in combination with cosolvents, surfactants, or complexing ligands, is effective in enhancing the solubility of both the ionized and unionized forms of flavopiridol.

The use of amorphous solid dispersions for enhancing the apparent solubility and dissolution rate of poorly soluble drugs has been shown effective, although the effectiveness of this general approach requires specific considerations for each active pharmaceutical ingredient (API) (9,10).

BIODENDRIMERIC SOLID DISPERSIONS

Biodendrimeric solid dispersions (BDSDs) have been shown to increase the apparent solubility and dissolution rate of poorly soluble drugs while preserving the crystalline state of the API, thus alleviating the thermodynamic instability issue (11). However, the solubilization mechanism of BDSDs has not been established. The present report is aimed at understanding the combined solubilization effect of the excipients used in the preparation of BDSDs, in relation to the effect of each excipient alone. The formulation and manufacturing process for BDSDs has been reported elsewhere (11). Briefly, BDSDs are drug-polymer dispersions made by (low temperature) hot melt extrusion (HME). BDSDs use a dendrimer-like biopolymer (DLB) as the backbone of the polymeric carrier matrix. DLB is a glycogen-like α-D-glucan, naturally produced in plant mutants such as those of sweet corn, sorghum, and algae, with roughly spherical shape and typical diameter range of 30 to 100 nm (12). In BDSDs, the drug is not molecularly dispersed through the polymer. Instead, drug crystals are intimately mixed with the solid DLB nanoparticles in the formulation. The effect of BDSDs is expected to be 2-fold: increasing the apparent aqueous solubility of these drugs and potentially enhancing the permeability and retention effect *in vivo* (13), owing to the nanoscale of the dendrimeric assemblies. As obtained from its natural source, the DLB material has negligible solubilizing ability. However, a modification involving the covalent linking of octenylsuccinate (OS) groups to the original plant-derived DLB nanoparticles confers the material significant solubilizing power. The OS-substituted DLB, or OS-DLB, and its solubilizing properties are the subject of this report, for its potential as a novel pharmaceutical excipient. We should point out that neither the source (DLB) nor the derivatized (OS-DLB) nanosized particulates are fully space-filling solid particles. The DLB particles are dendrimers (12). Therefore, when placed in an aqueous environment, the OS-DLB material exists as colloidal corpuscles resembling dendrimeric micelles (5). The manufacturing process of BDSDs involves no melting of either the drug or the OS-DLB. Indeed, in order to maintain the level of crystallinity of the drug as high as possible, melting of either the API or the OS-DLB is best avoided. This situation elicits a processing issue: HME of solid API mixed with dry powder OS-DLB without any melt results in torque levels that are too high for practical applications. Consequently, in order to bring the torque generated during HME to practicable levels, a processing aid needs to be added to the formulation. There are numerous materials that can be used as processing aids for producing BDSDs. However, for purposes of the particular study presented in this report, the choice of processing aid was limited to poloxamer 338 (PLX). The reason for the choice of processing aid in this report is that at the concentrations used, PLX has a negligible solubilizing effect on the APIs used in the study. This is important, because the objective is to investigate the solubilization mechanism of OS-DLB, but free from any potential confounding effects brought about by the solubilizing properties of other materials such as the processing aid. However, even though OS-DLB by itself is an effective solubilizer of poorly soluble drugs, while PLX is not, this investigation includes the combined solubilization effect of the two materials.

Four poorly soluble APIs were used as model compounds. They are phenytoin (PHT), griseofulvin (GSF), ibuprofen (IBU), and loratadine (LOR). The experimentally determined melting properties and calculated solubility properties (crystallinity and hydrophobicity) of the drugs have been reported previously (11). Briefly, the order of

crystal lattice energy of the model drugs is IBU < LOR < GSF < PHT. The lower the crystal lattice energy, the higher the ideal solubility; hence, IBU and PHT exhibit the highest and lowest ideal solubility values, respectively, of the group. The rank order of hydrophobicity of the solutes, quantified by means of their aqueous activity coefficients, is PHT < GSF < IBU < LOR.

PLX was selected as processing aid because it does not have an appreciable solubilizing effect on the model APIs used in this study. The lack of solubilizing effect of PLX is due in part to its concentrations being maintained below the CMC value (~ 3.5% w/v) (14). Figure 1 shows the effect of PLX on the solubility of the four model compounds, where $[A]_t$ and $[A]_o$ denote the total (with PLX present) and plain (without PLX) water solubility values, respectively. PLX has no solubilizing effect on PHT, GSF, and IBU. There is some solubilizing effect on LOR. A possible explanation for the observed solubilizing effect of PLX on LOR is the highly hydrophobic character of LOR (the most hydrophobic of the drugs in this study), such that the interaction between poloxamer and the highly hydrophobic solute can alter the CMC value (15). It is possible that the highly hydrophobic LOR promotes the formation of micelles or proto-micellar bodies, thus attaining concentrations above $[A]_o$. Nonetheless, the results in Fig. 1 show that any potential confounding effects from PLX, on the solubilizing effect of OS-DLB, are of moderate magnitude for LOR but negligible for the other three APIs. Therefore, the choice of PLX affords the type of the experimental system needed to focus on the solubilizing effect of OS-DLB.

EXPERIMENTAL

Materials

PHT was obtained from Spectrum (Gardena, CA), GSF from Hawkins (Minneapolis, MN), IBU from BASF (Bishop, TX), and LOR from Mallinckrodt (St. Louis, MO). All drug substances were used as received. PLX was obtained from BASF (North Mount Olive, NJ) and was gently ground with mortar and pestle and screened through a US 100 mesh sieve (aperture size of 150 μm) before use. OS-DLB was prepared by Professor Yuan Yao's laboratory as described elsewhere (16). All solvents were of HPLC grade and were obtained from Fisher Chemical (Fair Lawn, NJ).

Methods

Quantification of Drug Association

The amount of API associated with OS-DLB in solution was quantified following a 3-step procedure. First, in order to extract the drug molecules from the colloidal OS-DLB particles, 500 μL of dimethyl sulfoxide was added to an equal volume of aqueous solution of API, OS-DLB, and PLX and agitated at room temperature for 30 min. Following the extraction of the API from the OS-DLB, 500 μL of 20% (w/w) sodium chloride solution was added to the mixture and agitated at room temperature for 30 min in order to precipitate the OS-DLB nanoparticles. Finally, the mixture was centrifuged at 12,000 rpm for 20 min, and the amount of drugs in the supernatant was quantified by HPLC assay, using

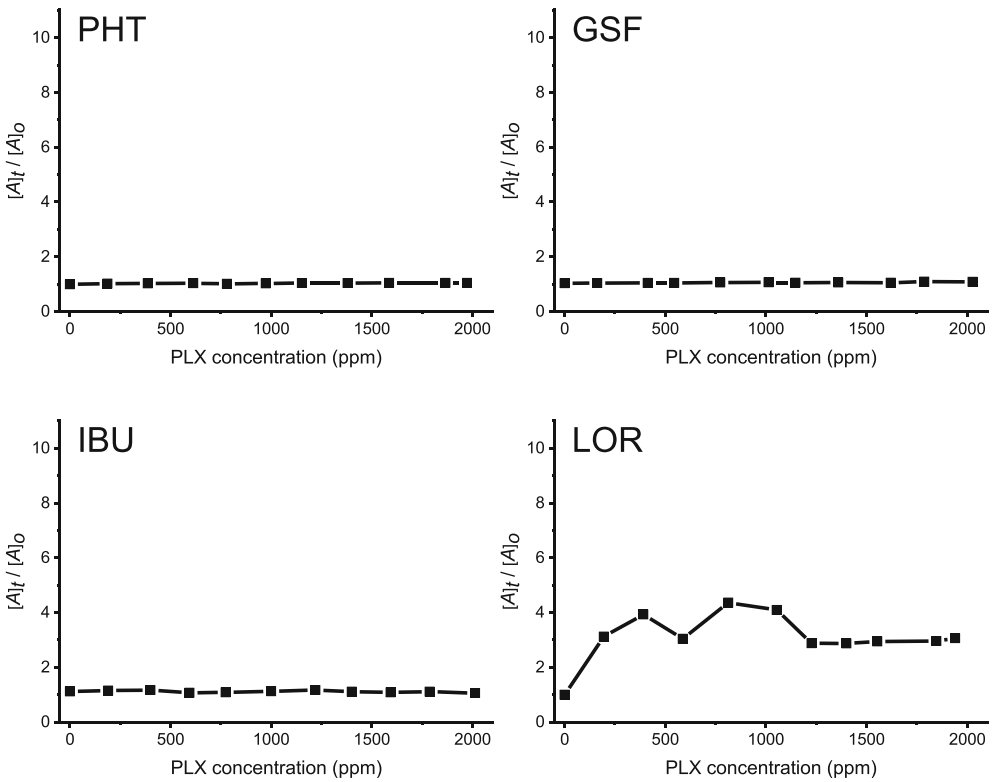


Fig. 1. Solubility enhancement of the model drugs in aqueous PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of the drug in the presence of PLX in solution and the solubility in plain water, respectively

a Shimadzu SCL-10AVP HPLC system (Kyoto, Japan), equipped with an Applied Biosystems 783A UV detector (Foster City, CA) and an Agilent Zorbax SB-C18 column (Santa Clara, CA). The mobile phase flow rate was set at 1 mL/min and the injection volume was 20 μL. Key parameters of the HPLC analysis method pertaining to the model drugs are summarized in Table I. A control study was performed (data not shown) to determine the efficiency of removal of the drug associated with the OS-DLB particles. The efficiency of extraction of OS-DLB-associated drug was at least 95%.

Phase Solubility Measurements

Solubility measurements were carried out according to the method described by Connors and Higuchi (17), whereby excess amounts of API were added to aqueous solutions containing either OS-DLB or PLX, as well as combinations of OS-DLB and PLX, at concentrations ranging from 0 to 2000 ppm. The samples were subjected to continuous agitation at 25 °C for 24 h in order to reach equilibrium. These conditions have been shown to lead to equilibrium solubility for particularly slowly dissolving solutes (18). An aliquot from each sample was then removed and filtered through a 0.45-μm surfactant-free cellulose acetate membrane. Filter adsorption effects, if present, become increasingly important with decreasing solute concentration. Since the solutions were all saturated with the API, there is always excess solid solute such that potential adsorption of the drug to the filter, if any, would have no effect on the actual equilibrium saturation concentration. The samples were then treated and analyzed as described in the preceding section. The OS-DLB is an investigational material available in short supply. Consequently, tests were done in duplicate, reporting average values. Microsoft Excel (2013) Solver was used to perform nonlinear least squares curve fitting of the experimental data.

RESULTS

Figure 2 shows the solubilization enhancement of the model APIs as a function of the concentration of OS-DLB dispersed in water at 25 ± 0.5 °C, with different concentrations of PLX. The term $[A]_t$ represents the total equilibrium solubility of the drug in the aqueous mixture containing OS-DLB and PLX, and $[A]_o$ represents the solubility in plain water, used as reference. The solubilization profiles in Fig. 2 have some similarity to the type of solubility curves obtained when the solubilizing agent is a complexing agent (19). However, while solubilization by complexation is typically separated into two profile types, type A and type B, solubilization by OS-DLB gives three profile types, which we term type I, type II, and type III. Figure 3 depicts the two types of solubilization profiles obtainable by complexation (top) and three profile types obtained for solubilization by means of OS-DLB (bottom). We should point out that in the classical description of solubilization by complexation (19), there is no fundamental difference between type A and type B profiles, as type A is in fact a subset of type B. The different designation is thus based on practical considerations regarding the particular system under study. In this report, we employ an analogously practical designation for the solubilization profiles obtained. As demonstrated below, type I, II, and III profiles can all be described by one general equation. Therefore, whether an experimental solubilization profile is designated as type I, type II or type III for example depends on the domain/value of the different parameters involved. In other words, each of the type I, II, and III profiles represents a specific set of conditions under the solubilization model described below.

Table I. Key Parameters of the HPLC Method for the Analysis of the Model Compounds

Compound	Mobile phase (acetonitrile:water)	Wavelength (nm)
Phenytoin	38:62	220
Griseofulvin	35:60:5 tetrahydrofuran	295
Ibuprofen	60:40, 0.01% trifluoroacetic acid	220
Loratadine	68:32	248

Solubilization Model

The solubilization profiles produced by the effect of OS-DLB on the solubility of the API can be described by considering up to three solution phase equilibria operating simultaneously. The first equilibrium, which is common to every solid solute, is that existing between the API in the solid (A_{solid}) and solution (A_{liq}) phases,

$$A_{solid} \rightleftharpoons A_{liq} \quad \text{Equilibrium 1}$$

Equilibrium 1 is the fundamental solubility equilibrium of the API in plain water, resulting in the saturation concentration of the solute (aqueous solubility), denoted as $[A]_o$. This is the reference point, common to all solubilization profiles in Fig. 3, and corresponds to the intercept on the vertical axis on the solubilization plots.

Type I Profile—Partition-Association Equilibrium Effect

The presence of covalently linked octenylsuccinate (C_8) groups on the OS-DLB dendrimer provides a nonpolar microenvironment that favors the uptake of hydrophobic drugs. Such uptake involves a simultaneous secondary equilibrium, Equilibrium 2 (11). This is a liquid-liquid partitioning equilibrium, involving the distribution of the API between the aqueous phase (A_{aq}) and the organic phase of the OS-DLB environment (A_{ADAS}), *i.e.*, the API in the API-DLB associated species (ADAS)

$$A_{aq} \overset{K_p}{\rightleftharpoons} A_{ADAS} \quad \text{Equilibrium 2}$$

The partitioning constant (K_p) of Equilibrium 2 is given by

$$K_p = \frac{[A]_{ADAS}}{[A]_{aq}} \tag{1}$$

where $[A]_{aq}$ is the API concentration in the aqueous phase and $[A]_{ADAS}$ is the API concentration in the organic OS-DLB phase. In the liquid mixture, the total amount of API per unit volume, $[A]_t$, corresponds to the sum of $[A]_{aq}$ plus the amount of API, in the form of A_{ADAS}, present in the same volume, *i.e.*,

$$[A]_t = [A]_{aq} + [D][A]_{ADAS} \tag{2}$$

where $[D]$ is the OS-DLB content present in the mixture, per unit volume (concentration). Equation 2 applies to any type

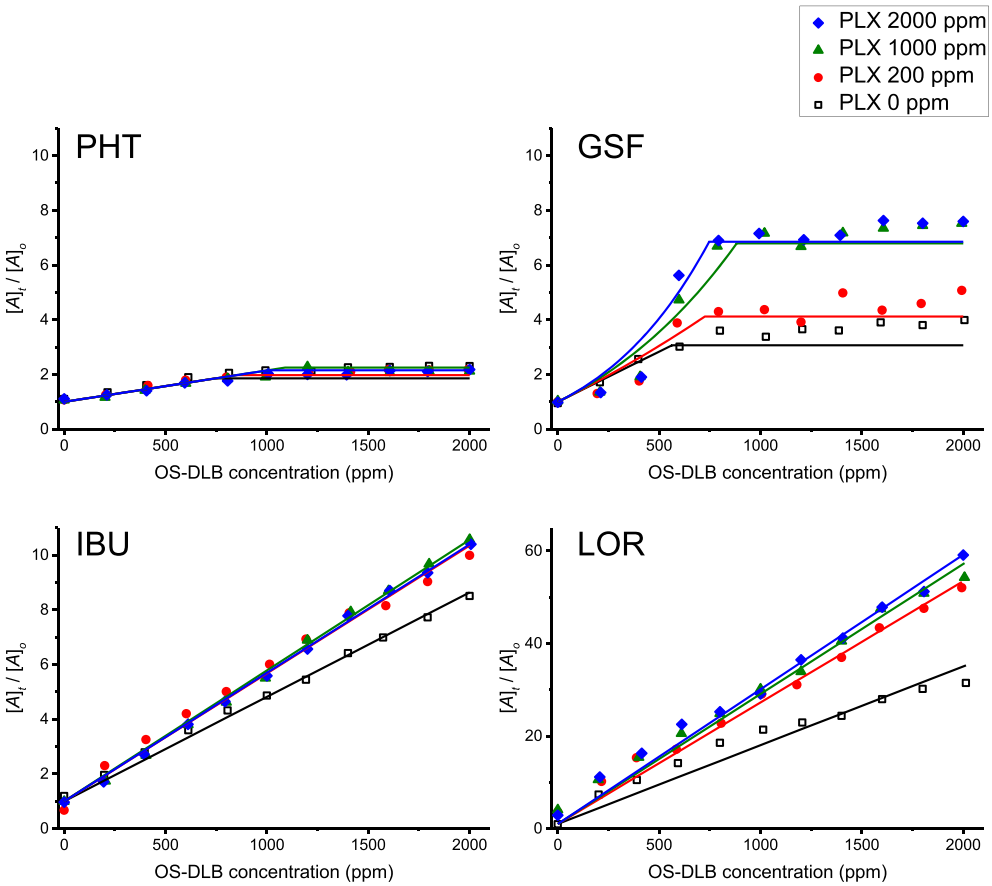


Fig. 2. Graphic summary of the solubility enhancement of the model APIs in aqueous solutions of OS-DLB and PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of the drug in the presence of OS-DLB and PLX in the solution and the solubility in plain water, respectively. The symbols and solid curves represent the observed and predicted solubility values, respectively. Detailed information provided in Figs. 4, 5, 6, and 7

of solution, whether or not it is saturated with the API. In a saturated solution, the value of $[A]_{aq}$ is fixed, *i.e.*, $[A]_{aq} = [A]_o$. From Eq. 1, substituting into Eq. 2 and rearranging, we have

$$\frac{[A]_t}{[A]_o} = 1 + K_p[D] \tag{3}$$

which is the expression for the type I solubilization profile depicted in Fig. 3.

Figure 2 shows that the rank order in the solubilizing effect of OS-DLB matches the rank order in hydrophobicity of the drugs. The more hydrophobic the drug molecule, the greater the solubilizing effect of OS-DLB. As such, LOR and IBU exhibit the greatest relative increase in solubility in the presence of OS-DLB. This effect is attributable to the hydrophobic C_8 chains of the OS groups, covalently bonded to the polysaccharide chains of the DLB dendrimers. The hydrophobic chains of the OS groups create a nonpolar microenvironment on the OS-DLB, favoring the partitioning uptake of hydrophobic drugs. Figures 4 and 5 show the solubilizing effect of OS-DLB on IBU and LOR, respectively, as a function of OS-DLB concentration. The solubilization curves for these two APIs correspond to the type I profile depicted in Fig. 3, indicating that the solubilizing effect is the result of the partitioning uptake equilibrium, described by Eq. 3. The top left plot in each of Figs. 4 and 5 shows the solubilizing effect of OS-DLB, free from any PLX, while the remaining three plots show the effect of different concentration of PLX mixed with the OS-DLB. As stated above, PLX is used at concentrations below its CMC and is therefore not expected to have any appreciable solubilizing. It is noteworthy that even though PLX in plain water has a slight solubilizing effect on LOR (see Fig. 1), there is a minimal solubilizing effect by PLX when OS-DLB is present.

Type II Profile—Solubility Limit of the Partition-Association Species

Figure 6 shows that the effect of OS-DLB on the solubility of PHT results in a type II profile. This profile type is analogous to type B_S solubilization profile produced by complexation (see Fig. 3). It should be pointed out that there is no fundamental difference between type A_L and type B_S complexation profiles. The difference reflects the properties of the system and experimental conditions, rather than a phenomenological difference in the underlying phenomena. In fact, the type A_L profile can be regarded as a subset of type B_S. That is, the initial segment of the type B_S profile corresponds to type A_L. Alternatively, if the ligand concentration of a type A_L system is progressively increased, at some point, the solubility limit of the complex is expected to be reached and the type A_L profile will take the shape of B_S profile. A similar situation is observed with OS-DLB. The type I profile can

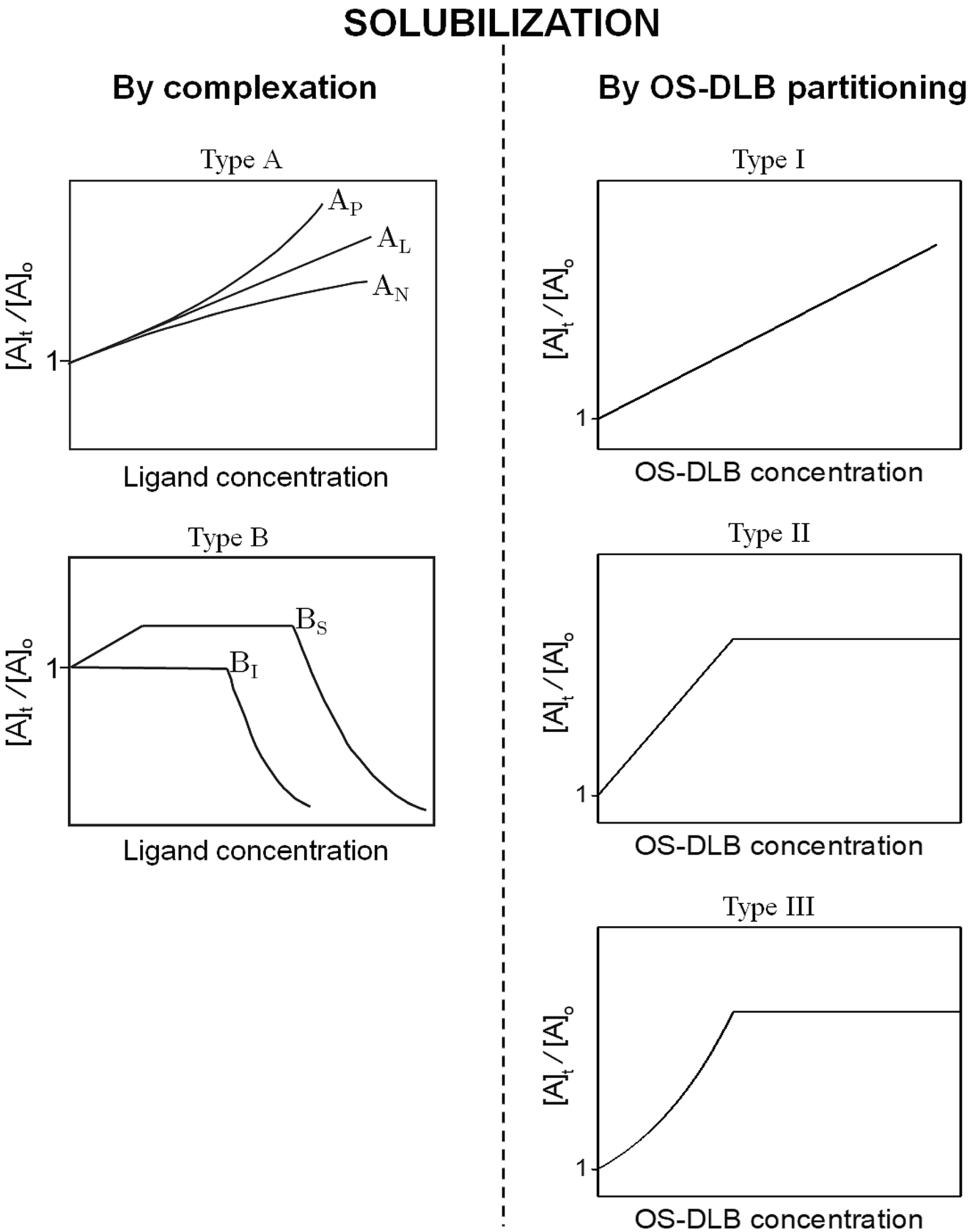


Fig. 3. General solubilization curves for complexation (top) and partitioning/association by OS-DLB (bottom)

be regarded as a subset of type II. The OS-DLB raw material is a solid powder. Consequently, there is an upper limit to how much of it can be dispersed per unit volume of aqueous solvent. The API-OS-DLB association species, ADAS, is therefore expected to

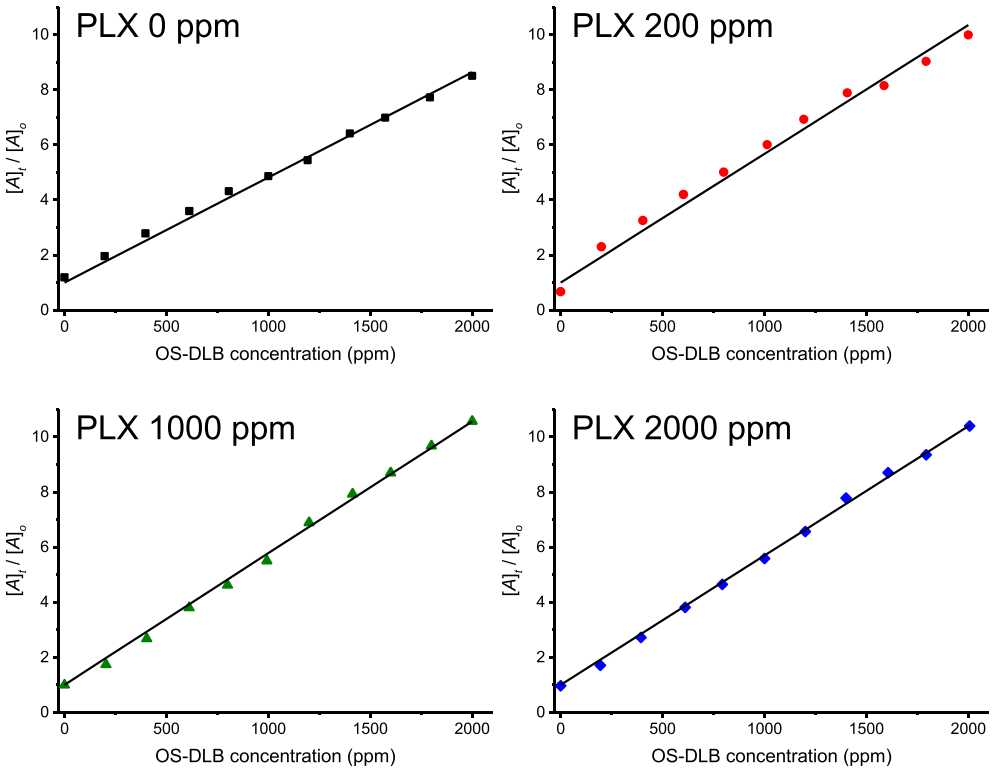


Fig. 4. Solubility enhancement of IBU in aqueous solutions of OS-DLB and PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of IBU with OS-DLB and PLX present in solution and the solubility in plain water, respectively. The symbols and solid curves represent the observed and predicted solubility values, respectively

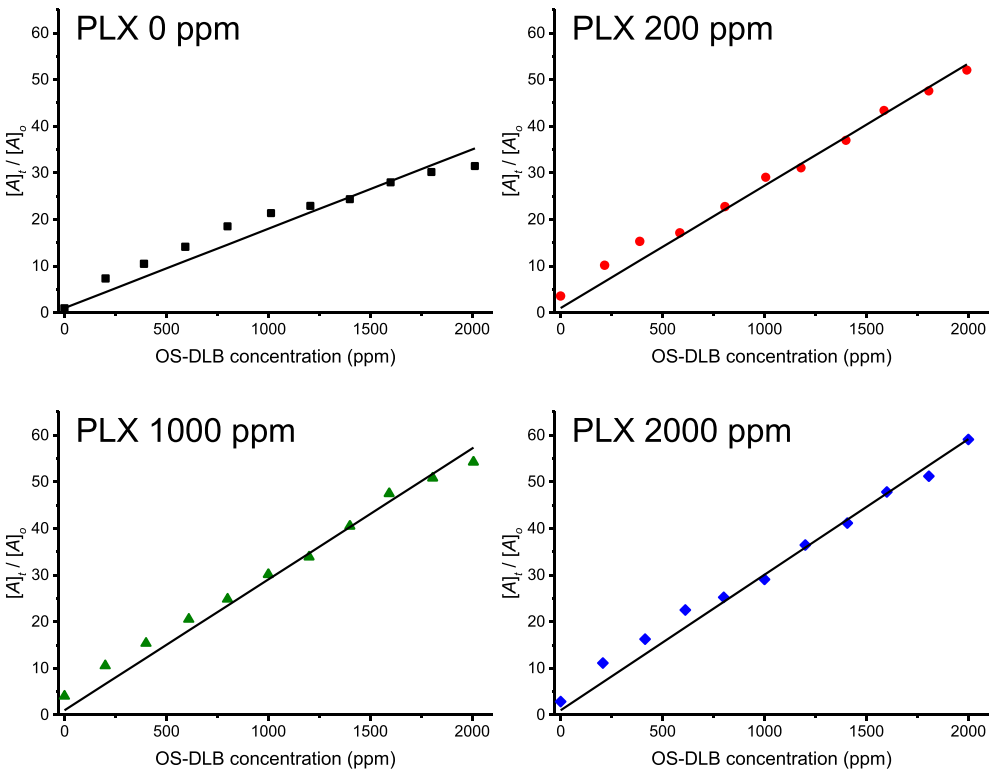


Fig. 5. Solubility enhancement of LOR in aqueous solutions of OS-DLB and PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of LOR with OS-DLB and PLX present in solution and the solubility in plain water, respectively. The symbols and solid curves represent the observed and predicted solubility values, respectively

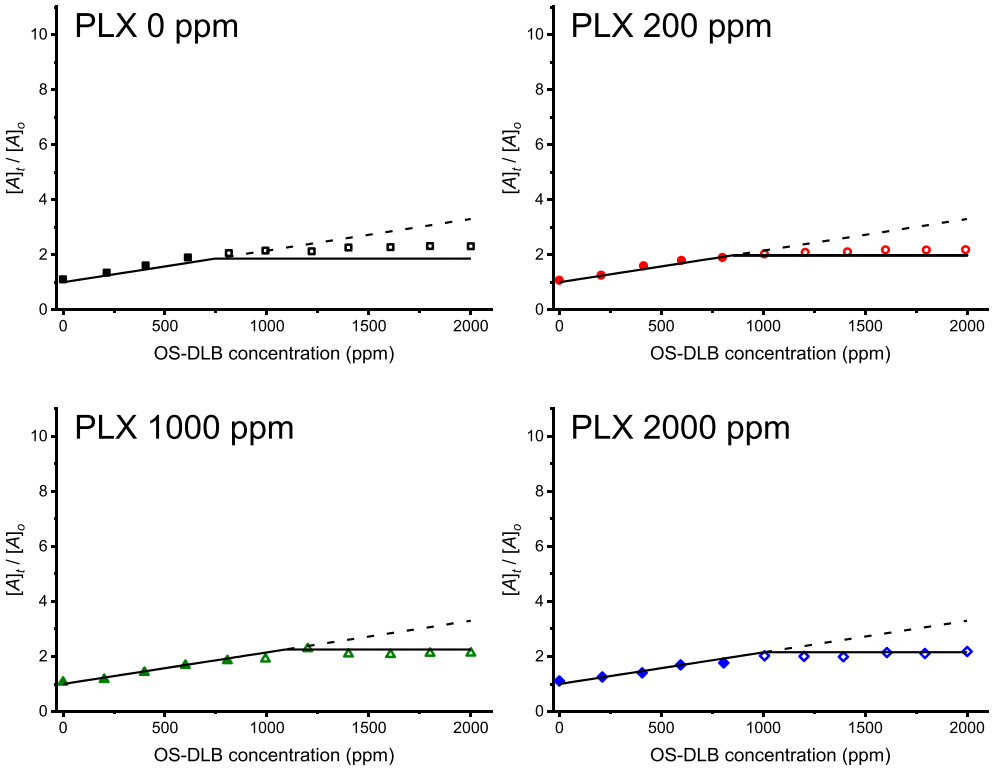


Fig. 6. Solubility enhancement of PHT in aqueous solutions of OS-DLB and PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of PHT with OS-DLB and PLX present in solution and the solubility in plain water, respectively. The symbols and solid curves represent the observed and predicted solubility values, respectively. The open symbols show the region where $[A]_t$ plateaus as a result of reaching the solubility limit of the ADAS. The broken lines represent the hypothetical solubilization profile of PHT obtained if the solubility product of the dendrimer complex had not been reached

exhibit a solubility limit. It is clear that the particular API in the ADAS influences its solubility limit of the latter. Comparison of the solubilization profiles of PHT on the one hand, with those of IBU and LOR on the other, shows that within the same range of OS-DLB concentration, the PHT-ADAS reaches the solubility limit, whereas IBU-ADAS and LOR-ADAS do not. This means that in addition to Equilibrium 2 (partitioning), Equilibrium 3 is also an underlying process in the type II profile.

$$A_{aq} + ADAS_{aq} \overset{K_{sp}}{\rightleftharpoons} ADAS_{ppt} \quad \text{Equilibrium 3}$$

where $ADAS_{aq}$ and $ADAS_{ppt}$ represent the ADAS in the aqueous phase and that precipitated as a solid, respectively. For each API, the corresponding ADAS is expected to have its own characteristic solubility limit. Such limit may or may not be reached, depending on the experimental conditions. Quantitatively, the solubility limit of ADAS (Equilibrium 3) can be expressed in terms of a solubility product

$$K_{sp} = [A]_{aq}[ADAS]_{aq} \tag{4}$$

where K_{sp} is the solubility product constant. Equation 4 is a general equilibrium expression. For API-saturated systems, as is the case in this investigation, the right hand side of Eq. 4 has one fixed term and one control variable. Again, in a drug-saturated solution, the value of $[A]_{aq}$ is fixed, so $[A]_{aq} = [A]_o$. On the other hand, as long as concentration of added OS-DLB does not exceed its own solubility limit, the value of $[ADAS]_{aq}$ is equivalent to the concentration of OS-DLB added to the system, $[D]$; that is, it follows that Eq. 4 can be expressed in the alternative form

$$K_{sp} = [A]_o[D] \tag{5}$$

In a type II profile, the saturation concentration of ADAS, $[ADAS]_{sat}$, can be alternatively expressed in terms of the control variable, $[D]$, according to the definition $[ADAS]_{sat} = [D]_{\max}$, which corresponds to the concentration of added OS-DLB, $[D]_{\max}$, at which $[A]_t$ plateaus (see Fig. 6).

The type II profile is therefore a composite, whereby the ascending portion of the profile is described by Eq. 3, and the plateau portion corresponds to the limit imposed by Eq. 5. These two domains are given by Eq. 3 and by incorporating Eq. 5 into Eq. 3, respectively,

$$\frac{[A]_t}{[A]_o} = \begin{cases} 1 + K_p[D] & [A]_o[D] < K_{sp} \\ 1 + \dfrac{K_p K_{sp}}{[A]_o} & [A]_o[D] \geq K_{sp} \end{cases} \tag{6}$$

Type III Profile—Extrinsic Effect of PLX

Figure 7 shows the solubility effect of OS-DLB on GSF. In the absence of PLX, GSF exhibits a type II

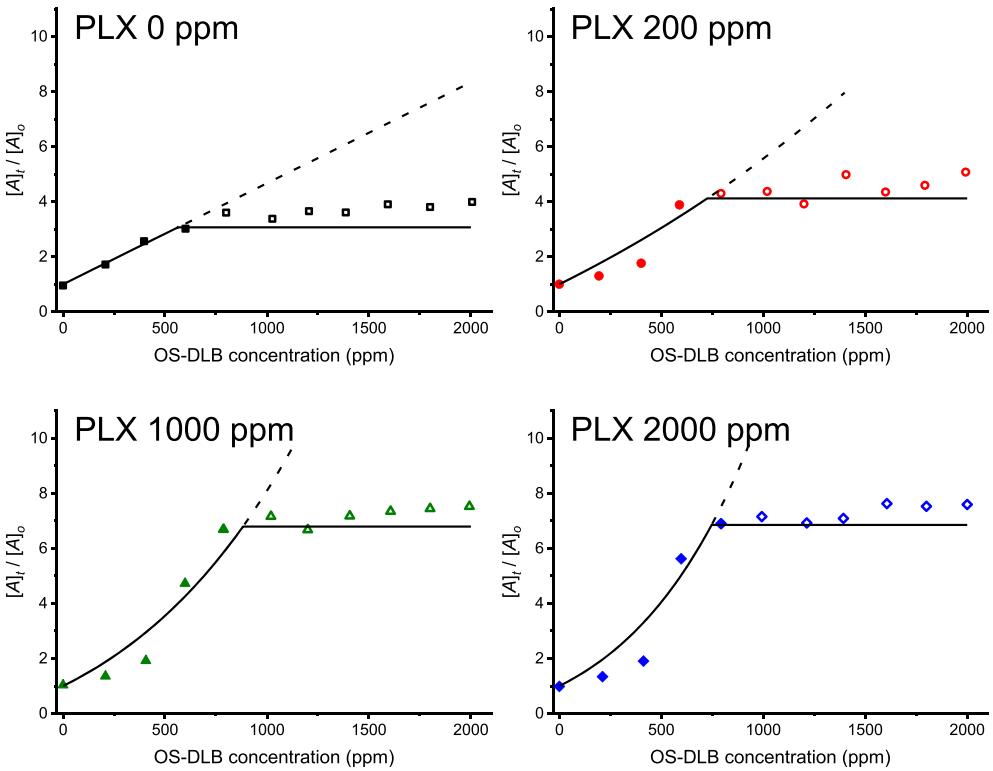
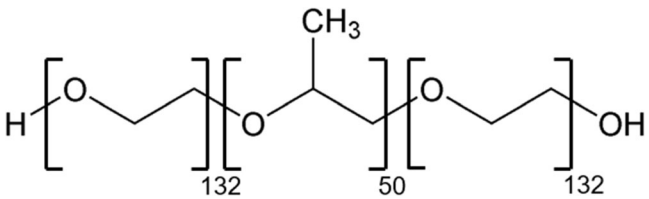


Fig. 7. Solubility enhancement of GSF in aqueous solutions of OS-DLB and PLX solutions of different concentrations at 25 ± 0.5 °C. $[A]_t$ and $[A]_o$ represent the equilibrium solubility of GSF with OS-DLB and PLX present in solution and the solubility in plain water, respectively. The symbols and solid curves represent the observed and predicted solubility values, respectively. The open symbols show the region where $[A]_t$ plateaus as a result of reaching the solubility limit for the ADAS. The broken lines represent the hypothetical solubilization profile of PHT obtained if the solubility product of the dendrimer complex had not been reached

profile. However, in the presence of PLX, the solubilization of GSF exhibits the type III profile depicted in Fig. 3. Even though PLX by itself does not solubilize GSF, the results in Fig. 7 indicate that PLX has the ability to modify the solubilizing microenvironment in the OS-DLB. The ascending portion of the solubilization profile of GSF shows a continuously steeper solubilization profile with increasing OS-DLB. Furthermore, the positive deviation from linearity (increasing steepness) in relation to the prediction from Eq. 6 becomes more pronounced as with increasing PLX concentration. It is noteworthy that the curvature of ascending portion of the solubilization profile conforms to an exponential profile. The results in Fig. 1 demonstrate that when the solvating environment consists exclusively of water molecules, PLX is unable to solubilize GSF. On the other hand, the results in Fig. 7 show that when the solvating environment includes the hydrophobic OS-DLB, PLX becomes capable of enhancing the solubilizing effect of OS-DLB.

Poloxamer 338 (PLX) is a block copolymer consisting of a linear chain block polyoxyethylene, followed by a linear block of polyoxypropylene, and then followed by another linear block of polyoxyethylene. That is, a linear chain consisting of PEG-PPG-PEG (polyethylene glycol-polypropylene glycol-polyethylene glycol) segments. The molecular structure of PLX is



It is important to point out that both PEG and PPG are organic solvents. PEG is an excipient commonly used to solubilize drugs in pharmaceutical formulations. Both PEG and PPG are miscible with water. This means mixing neither PEG nor PPG form micelles in water. The reason PLX is able to form micelles and has a measurable CMC value is that the middle PPG segment in its chain is more hydrophobic than the PEG segments on either side. Therefore, the surfactant-like properties of PLX notwithstanding, its molecular structure consists of three concatenated segments, each consisting of the molecular structure of an organic solvent. In a hydrophobic environment like the C_8 of the OS-DLB, the PEG and PPG segments of PLX will not have the same ability to form micellar aggregates as when in water. This notion is relevant to describe and model the effect of PLX on the type III profile.

Table II. Type of Solubilization Profile Based on System Conditions, Based on the Model of Eq. 7

Intrinsic effect	Extrinsic effect	Profile type
$[A]_o[D] < K_{sp}$	$\sigma = 0$	Type I
$[A]_o[D] \geq K_{sp}$	$\sigma = 0$	Type II
$[A]_o[D] \geq K_{sp}$	$\sigma > 0$	Type III

In view of the lack of curvature in Fig. 1, the curvature of the ascending portion of the solubilization profiles in Fig. 7 indicates that PLX acts as a solubilization modifier (cosolubilizer) within the microenvironment of OS-DLB. The exponential cosolubilizing effect is most frequently observed with cosolvents. The (co)solubilization power in these cases is quantitatively represented by the factor σ (20):

$$\log\frac{S_t}{S_o} = \sigma f_c \tag{7}$$

where S_t and S_o, are the solubilities in the water-cosolvent mixture and in pure water, respectively, σ therefore is a measure of the solubilizing power of the cosolvent (cosolubilizer), relative to that of water, and f_c is the concentration of the cosolvent (expressed as volume fraction). The above expression can be alternatively expressed in the form

$$\frac{S_t}{S_o} = 10^{\sigma f_c} \tag{8}$$

In order to model the curvature shown in Fig. 7, we adopt the same general type of σ factor as that in Eq. 8, to quantitatively describe the solvent-modifying effect that PLX exerts on Equilibrium 2, leading to the type III profile. The solvent modifier (PLX) has a solubilizing power, σ, such that increasing concentrations of PLX result in increasingly large (exponential) positive deviations from linearity, relative to the solubilizing ability of OS-DLB alone. Based on these considerations, the type III profile can be described as a modification on the type II profile, as follows

$$\frac{[A]_t}{[A]_o} = \begin{cases} 1 + 10^{\sigma[D]}K_p[D] & [A]_o[D] < K_{sp} \\ 1 + \dfrac{10^{\sigma[D]_{\max}}K_pK_{sp}}{[A]_o} & [A]_o[D] \geq K_{sp} \end{cases} \tag{9}$$

which reduces to Eq. 6 (type II profile) as $\sigma \rightarrow 0$, *i.e.*, when PLX has no ability to act as a solvent modifier or cosolubilizer. Equation 9 describes the type III profile obtained for the solubility of GSF.

DISCUSSION

The solubilizing effect of OS-DLB on drug solutes can be briefly described as follows. The aliphatic C_8 chains of the OS groups covalently linked to the polysaccharide chains of the DLB nanoparticles create a hydrophobic microenvironment in the OS-DLB. The hydrophobic microenvironment favors the uptake of hydrophobic solutes. Hydrophobic solutes are "picked up" by the OS-DLB colloidal particles *via* a partitioning-based association mechanism, between the C_8 microenvironment and the surrounding aqueous phase. Under these circumstances, the total concentration of solubilized solute increases in proportion to the concentration of OS-DLB, giving place to the type I profile. As the concentration of OS-DLB continues to increase, the solubility limit of the drug-loaded OS-DLB will be reached. At this point, the concentration of the free drug in aqueous solution, as well as that of the drug associated with the dispersed OS-DLB, will remain constant upon the continued addition of OS-DLB,

Table III. Solubilization Parameters of the Model Drugs under the Combined Effect of OS-DLB and PLX. The Partition/Association Constants of PHT and GSF Are Obtained by Fitting Eq. 3 to the Initial Linear Portions of the Data

Model drug	$[A]_o$	Solubilization parameter	Concentration of PLX (ppm)			
	(mg/mL)		0	200	1000	2000
Phenytoin	17.91	K_p (L/g)	1.39	1.23	1.00	1.03
		K_{sp} (10^4 ppm^2)	1.34	1.52	1.95	1.80
		$[D]_{max}$ (ppm)	750	851	1091	1007
		σ	0	0	0	0
Griseofulvin	9.86	K_p (L/g)	3.38	3.38	3.38	3.38
		K_{sp} (10^4 ppm^2)	7.10	6.95	8.70	7.37
		$[D]_{max}$ (ppm)	719	705	882	747
		σ	0	0.16	0.33	0.49
Ibuprofen	55.12	K_p (L/g)	3.82	4.67	4.78	4.69
		K_{sp} (10^4 ppm^2)	(b)	(b)	(b)	(b)
		$[D]_{max}$ (ppm)	(a)	(a)	(a)	(a)
		σ	0	0	0	0
Loratadine	0.592	K_p (L/g)	17.02	26.23	28.08	29.08
		K_{sp} (10^4 ppm^2)	(b)	(b)	(b)	(b)
		$[D]_{max}$ (ppm)	(a)	(a)	(a)	(a)
		σ	0	0	0	0

(a) > 2000 ppm
(b) > 2000 × $[A]_o$. See Table II

giving place to the type II profile. The type I and type II profiles reflect the intrinsic solubilizing properties of OS-DLB. The type III profile on the other hand is the result of an extrinsic factor, *i.e.*, the effect a cosolubilizer such as PLX. Equation 9 is the most general one in the sense that it captures both the intrinsic and extrinsic solubilization effects observed with the different model APIs of this study. Table II gives a summary of the conditions under which the model expressed by Eq. 9 would give the different types of profiles observed.

By itself, PLX has no solubilization power for the APIs of this study, as shown in Fig. 1. The (lack of) solubilization power of PLX is unaffected by OS-DLB, as shown in the type I and type II profiles in Figs. 4, 5, and 6. However, the type III profile in Fig. 7 shows that PLX acquires some cosolubilizing power in the presence of OS-DLB. All four APIs included in the study exhibit different degrees of hydrophobicity. The solubility results show that the solubilizing ability of OS-DLB increases with increasing solute hydrophobicity; the rank order in relative increase in solubility follows the increasing rank order in hydrophobicity of the drugs. The relative solubility increase observed ranges from over sixty-fold to about two-fold, depending on the hydrophobicity of the drug. Another consideration is that the four model APIs can be separated into two subgroups. On the one hand, LOR and IBU represent compounds whose aqueous solubility is mostly limited by their hydrophobic character. While GSF and PHT on the other hand represent compounds whose solubility is primarily limited by their crystal properties. It is noteworthy that within the same range of OS-DLB concentration, LOR and IBU give a type I profile while GSF and PHT give a type II. The precise mechanism of precipitation of the ADAS is beyond the scope of the present study. However, the experimental results suggest that the inherent tendency toward crystallization of drugs like GSF and PHT contributes toward the precipitation tendency of the ADAS. Even though the maximal degree of solubilization and the type of solubilization profile observed for PHT and GSF are different, the OS-DLB concentration at which the plateau is observed is similar for the two compounds. These observations suggest that in addition to the inherent tendency of the drug to precipitate, the overall concentration of the ADAS colloidal particles also plays a role. Although further studies would be required to explore this notion, there is a common concentration range of OS-DLB at which the plateau in solubility is observed for both GSF and PHT. The calculated average distance among the ADAS particles in such range is between 350 and 400 nm, which corresponds to roughly 5 times the OS-DLB particle diameter.

The type III profile reflects extrinsic solubilization effects, that is, solubility-related effects that are separate from the actual solubilizing ability of OS-DLB. However, these extrinsic phenomena are of great significance to formulation scientists. Even though PLX by itself is not an effective solubilizer of the drugs, it can act, in some instances, as a solubility modifier, in combination with OS-DLB. Table III lists the values of the parameters from Eq. 9, obtained for the different systems included in the study. Poloxamers are nonionic surface active agents commonly used as solubilizing and emulsifying agents. However, poloxamer surfactants can also behave as cosolvents (1). Although most cosolvents are liquids, solids that are highly soluble in the main solvent can also function as cosolvents. Examples of solid materials that can act as cosolvents in aqueous solutions are sorbitol (21), polyvinylpyrrolidone (22), urea (23), and high molecular weight hydrophilic polymers such as polyethylene glycol (24).

The cosolubilizing effect of PLX becomes smaller in both the low and high ends of drug hydrophobicity. PHT is the drug with the lowest hydrophobicity of the group, for which OS-DLB has a minimum solubilizing effect, and the presence of PLX makes no significant difference. For LOR and IBU on the other hand, which occupy the high end of hydrophobicity, the presence of PLX produces a modest increase in the slope of their solubility profile. For the solute of intermediate hydrophobicity, GSF, PLX exerted the most significant modifying effect on solubility. These results indicate that PLX modifies the polarity of the C_8 microenvironment of OS-DLB, with different overall effect, depending on the hydrophobicity of the drug solute. By this account, PLX modifies the overall polarity of the microenvironment, increasing its compatibility with GSF (intermediate polarity). Such a change in polarity is insufficient to closely match the polarity of PHT (higher polarity), while having only a small effect on LOR and IBU (low polarity). These results have important practical implications to formulation development, as they suggest, in turn, that the overall solubilizing properties of BDSDs can be refined/optimized by selecting an appropriate processing aid material, based on the polarity of the drug of interest, without limitation to PLX.

It is important to stress the fact that PLX is by no means the only processing aid suitable for making BDSDs. Materials such as PEG, polyvinylpyrrolidone and its derivatives, and excipients such as Soluplus to name a few, would serve as processing aids. A processing aid somewhat less hydrophilic than PLX could be expected to further enhance the solubilization of drugs like LOR and IBU. On the other end, a processing aid material more polar than PLX could help enhance the solubilization of less hydrophobic drugs such as PHT. Alternatively, the aliphatic chain covalently linked to the DLB could also be varied in order to make the substituted DLB a strong solubilizer for drugs of different degrees of hydrophobicity. Several studies (25,26) have demonstrated that the polarity of the hydrocarbon chain can be increased by incorporating a double bond, an ether group, a hydroxyl group, or a carbonyl group into the hydrocarbon chain of a surfactant. However, the use of long alkyl chains risks reducing the aqueous solubility of DLB. Elworthy and Patel (27) have shown that the solubilization ability of surfactants with alkyl chains more than 16 carbons decreased due to their lower solubility in water. One important consideration is that the OS chemistry has been designated as generally recognized as safe (GRAS) by the FDA. Therefore, while modifications to the aliphatic chain may have improved physicochemical properties, they will come with a heavy cost in terms of regulatory approval for use as a pharmaceutical excipient.

CONCLUSIONS

The effect of OS-DLB and PLX on the solubilization of poorly water-soluble compounds is influenced by the hydrophobicity of the solute in two ways. On the one hand, the solubilizing power of OS-DLB increases as the hydrophobicity of the drug increases. On the other hand, the presence of another component in solution, such as PLX, can enhance the solubilizing effect of OS-DLB, for a drug of intermediate hydrophobicity such as

GSF. Experimentally, the solubility enhancement of the model drugs in aqueous solutions of OS-DLB and PLX is observed to fall into 3 main scenarios or types of solubilization profiles. However, each solubilization profile corresponds to different domain of a single general equation.

In this research, it is shown that even though PLX is not a solubilizer of the model drugs used, under certain cirmcustances it can actually modify the microenvironment created by the OS groups, with measurable effects on the solubilizing ability of OS-DLB. A sensible approach would be to explore already-approved excipients, other than PLX, as modifiers of the OS microenvironment, in order to further understand and exploit the solubilizing ability of OS-DLB. Jansook and Loftsson (28) have shown that common pharmaceutical excipients, such as edetate disodium, benzalkonium chloride, and hydroxypropylmethylcellulose, can influence the affinity of cyclodextrins for various poorly water-soluble drugs by modifying the polarity of cyclodextrin cavity. Such findings demonstrate that common pharmaceutical excipients can also have a significant effect on the polarity of the microenvironment surrounding cyclodextrin and consequently its complexation ability (solubilization power) for poorly soluble drugs. Taking this notion one step further, solubility screening studies covering common pharmaceutical excipients, can be performed to ascertain the influence of such excipients on the solubilization of drugs by OS-DLB. From a "developability" point of view, such solubilization screening studies will help facilitate future drug development efforts by enabling formulation scientists to establish, early in the process, the best combination of excipients and OS-DLB for a new chemical entity, based on its hydrophobicity.

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