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Evaluation of model solvent systems for assessing the accumulation of container extractables in drug formulations

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Abstract

The interaction between a medical device and a pharmaceutical solution it contacts may dictate solution safety and/or efficacy. Of specific concern is the ability of device components to leach into the contacting solution. As pharmaceutical solutions containing surfactants, co-solvents and solubilizing agents become more common, method's for assessing the extent of leaching are needed. In this manuscript, a model is developed which relates a solution's polarity to its ability to interact with a plastic material. The validity of the developed model is examined via direct analysis of several pharmaceutically relevant solutions. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Model solvent system; Container; Drug formulations

1. Introduction

Container systems and medical devices are often designed to be used in support of a large number of solution product types. In order for such systems and devices to be viable products in the pharmaceutical marketplace, they must be demonstrated to be safe and effective. An important aspect of the safety and efficacy of such systems and devices is the extent to which they interact with the product solutions they contact. Such contact may be long term, for example, storage of steam sterilized pre-mix formulations by plastic containers, or relatively short lived, for example, transport of medication-containing solutions through flexible plastic tubing. In any event, the process for the characterization of the interaction between a medical device and its contained solution product is termed a chemical compatibility assessment.

The chemical compatibility assessment considers two distinct yet complimentary mechanisms by which a device and its contacted solution can interact. These mechanisms include (1) the migration of a chemical component out of the device and into the contacted solution (leaching) and (2) the sorption of contained solution components by the device (binding). For leaching, the potential safety impact of the extracted compound(s) is of paramount concern, although leaching also can impact other product use conditions such as clar-

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ity, pH, color and the formation of particulates. For binding, product efficacy can be adversely impacted by loss of important product formulation components. Such a process may directly affect product potency (if the compound sorbed is the active ingredient) or product stability (if the compound sorbed is a solubility or stability enhancing additive).

Several means can be envisioned for assessing chemical compatibility. The direct approach is to measure the distribution of the compounds of interest (leachables and formulation components) during the course of product development studies (e.g. stability studies). However, there are practical limitations (such as cost and time to market) to the conduct of stability studies for each potential product application and it may not be practically possible to directly demonstrate the inertness of such systems and devices in each of their potential applications through the use of stability studies.

Alternatively, the product/device interaction can be modeled based on a rigorous scientific assessment of the physicochemical processes, which influence such an interaction. Over the past 15 years, pharmaceutical scientists have developed the theoretical basis for understanding and modeling the nature of container/solution interactions, applicable for water-based solution products. Such models are based on the linear correlation of polymer/solution interaction constants with solvent/water partition coefficients (Nasim et al., 1972; Illum and Bundgaard, 1982; Pitt et al., 1988; Hayward et al., 1990; Kenley and Jenke, 1990; Atkinson and Duffull, 1991; Roberts et al., 1991; Jenke, 1991; Jenke et al., 1991, 1992)

Within the past 10 years, an emerging and accelerating trend in pharmaceutical R&D has been the development and commercialization of new drugs that are formulated in aqueous systems that contain significant quantities of chemical agents (such as co-solvents and solubilizing agents) which can have a strong impact on the device/product interaction. In such cases, water-based methodologies are not applicable and new theoretical and analytical methodologies must be developed to support product development and registration.

The purpose of this study was to expand upon this previously published work and to examine the utility (i.e. applicability, sensitivity and reproducibility) of this relative partitioning (octanol/water) model to the assessment of additional solvent systems. This goal was achieved by studying the equilibrium distribution of model marker compounds between various container/solution systems.

2. Materials and methods

2.1. Test material

The test material was a plastic container system. This container system consists a non-poly vinylchloride (PVC) polyolefin container body and single plasticized PVC port and membrane tubes. The mean weight of these three components of the container system, representing a 250-ml product configuration, was container, 7.90 g; port tube, 0.62 g; and membrane port, 0.40 g.

2.2. Generation of the equilibrated test solutions

Tests systems consisting of the container system and donor solutions of interest to this study were prepared by equilibrating such systems under near ambient conditions. Equilibration conditions included relatively low contact temperatures (40 ± 2 °C), relatively short contact times (140 ± 2 h) and no agitation. The test system included one container system, cut into pieces to facilitate solution contact, and 75 ml of donor solution. Control samples, consisting of the donor solution only, were stored along side the test systems so that marker compound stability effects could be differentiated from solute adsorption behavior. Test and control articles were stored in Pyrex® glass bottles.

Marker compounds were added to the donor solutions of interest and their loss to the container was measured. The markers utilized included substituted phthalates (specifically dimethyl-, diethyl- and dipropyl phthalate) and benzoic acid. The markers were initially present in the donor solutions at levels of approximately 4–10 ppm. Addi-

tionally, di-2-ethylhexyl-phthalate (DEHP), arising from the PVC components in the container system, was measured in the donor solution after container/solution equilibration.

The solvent systems investigated included,

- water (buffer);
- binary water (buffer)/organic solvent (e.g. acetonitrile, ethanol) systems, and;
- surfactant systems (anion, neutral).

Specific solvent systems used in this study included.

- Water, pH 3.0 and 7.0.
- Ethanol/water mixtures, 10/90, pH 3.0; 10/90, pH 7.0; 50/50, pH 3.0.
- Acetonitrile/water mixtures, 10/90, pH 3.0; 10/90, pH 7.0; 5/95, pH 3.0; 15/85, pH 3.0.
- Cremophore EL (25% (w/v)), measured pH 5.29 (*).
- Lecithin (1.0% (w/v)), measured pH 3.45 (*).
- Tween (5%) 80, measured pH 4.07 (*).
- Sodium dodecylsulfate (0.2% (w/v)), measured pH 3.59 (*).

Solvent systems denoted with an * simulate matrices found in pharmaceutical products (Nema et al., 1997). Duplicate test articles were prepared for all the solvent systems used.

In order to assess the degree to which container/solution systems had equilibrated during storage, one set of test articles was tested after approximately 3 and 6 days of storage.

2.3. Analysis of the equilibrated test solutions

The equilibrated test solutions were analyzed for the marker solutes and target extractables by high performance liquid chromatography (HPLC) methods developed for this specific application. In general, the methods utilized a conventional reversed phase stationary phase [Alltech (Deerfield, IL) Adsorbosphere C18, 150 by 4.6 mm, 5 μm particles] and aqueous acetonitrile-based mobile phases [for example, 25/75 and 40/60 (v/v) acetonitrile/0.04 M phosphoric acid]. Analyte detection was by ultra violet (UV) absorption at an appropriate wavelength for the marker compounds (230 nm).

2.4. Calculations

The concentration of DEHP in the donor solutions was determined as follows. System response was correlated to DEHP concentration in standards via linear regression analysis of standard response versus standard concentration data. The level of DEHP in the donor solutions was determined by inputting sample system responses into the linear calibration model.

The change in the marker solute levels due to absorption by the container (percent of marker remaining in the donor solution) is calculated as follows:

$$\%\ \text{Remaining in the donor} = \left(\frac{A_s}{A_c}\right)100\%$$

where A_s is the measured peak response in the donor solution after storage (mean of two samples if appropriate) and A_c is the measured peak response in the control after storage.

Thus the closer the % remaining is to 100%, the less of the marker solute is bound by the container.

This calculation is valid if the analyte response is linearly related to a sample's analyte level with no constant bias. Response linearity for all marker solutes was evaluated over a relevant concentration range and found to support the validity of the calculation [regression models of standard solution's marker compound level and analytical response were determined to have near unit correlation coefficients (r^2) and low relative intercepts].

3. Results and discussion

3.1. Qualitative observations

3.1.1. General comments and properties of the model compounds

The intent of this portion of the study was to gain a qualitative understanding of the way in which changing solution properties impact the distribution of a chemical compound between a material (e.g. container) and the solution phase it contacts. A quantitative analysis of the data, specifically related to the development of a binding

Table 1
Effect of storage duration on the container/solution interaction

Donor solution	Percent of solute remaining in donor							
	Benzoic Acid		DMP		DEP		DPP	
	3 Days	6 Days	3 Days	6 Days	3 Days	6 Days	3 Days	6 Days
Water, pH 3	85.5	81.8	42.7	46.9	14.3	12.8	2.0	2.6
Water, pH 7	101	101	53.4	47.5	13.2	12.7	1.8	1.8
10/90 Ethanol/water, pH 3	86.2	85.0	63.9	61.7	24.1	21.8	3.3	3.3
10/90 Ethanol/water, pH 7	97.2	101	73.0	61.6	22.9	23.2	3.9	3.9
10/90 Acetonitrile/water, pH 3	89.6	88.5	83.3	71.5	24.8	22.5	3.6	3.4
10/90 Acetonitrile/water, pH 7	103	104	68.8	58.8	23.5	23.2	3.4	3.6
5/95 Acetonitrile/water, pH 3	86.0	86.1	64.3	53.4	16.1	15.4	2.1	1.7
15/85 Acetonitrile/water, pH 3	91.9	90.9	78.0	69.1	36.6	35.5	5.5	5.8

or interaction model, is presented in greater detail in Section 3.2.

Octanol/water partition coefficients ($\log P_{o/w}$) for the model solutes are as follows (Jenke, 1993; Sangster, 1994), benzoic acid, 1.68–1.85 (nominal value of 1.70 used throughout); dimethyl phthalate (DMP), 1.56; diethyl phthalate (DEP), 2.47; dipropyl phthalate (DPP), 3.27; DEHP, 7.3–8.9. Thus the model solutes studied span a wide range in terms of lipophilicity. The pK_a for benzoic acid is 4.20. Thus, the two pH's studied (7.0 and 3.0) allow one to consider benzoic acid in its ionized and neutral forms, respectively.

3.1.2. Impact of storage duration on donor solution composition

Eight of the test systems were analyzed after 3 and 6 days for storage to determine whether equilibrium had been established during the course of this study. As can be observed from Table 1, the % remaining for three of the model compounds (BA, DEP and DPP) and each donor solution is approximately the same at 3 and 6 days for many cases. Small differences are expected in the values due to analytical variation. Thus, one concludes that equilibrium was achieved with respect to the partitioning of these analytes between the plastic and solution phases.

Measured DMP levels in the binary solvent systems show a discernable decrease between the 3 and 6 day test intervals and thus the attainment of equilibrium at the 6 day interval is not unilaterally demonstrated. However, as shown in Fig. 1, the rate of change in DMP concentrations has significantly decreased at 6 days and thus the concentrations at 6 days are a adequate approximation of the equilibrium state.

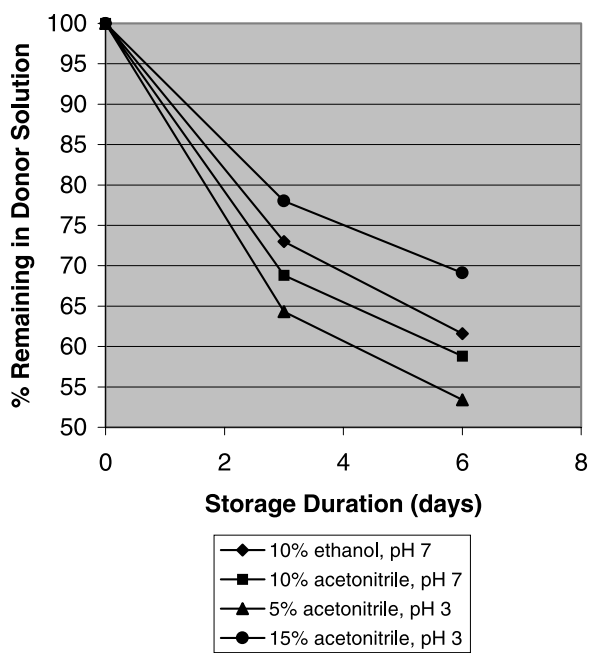

Fig. 1. Uptake of DMP as a function of storage time. While the concentration of DMP decreases between 3 and 6 days of storage, the rate of decrease has slowed at 6 days and the concentration at 6 days approximates the equilibrium concentration.

Table 2
Effect of solution pH on the donor solution composition at equilibrium: at constant solvent identification and solvent proportion.

Solution composition		Percent solute remaining in the donor				DEHP level in donor (ppm)
Solvent	pH	Benzoic acid	DMP	DEP	DPP	
Water	3	81.8	46.9	12.8	2.6	0.012
	7	101	47.5	12.7	1.8	0.010
Ethanol/water (10/90)	3	85.0	61.7	21.8	3.3	0.007
	7	101	61.6	23.2	3.9	0.006
Acetonitrile/water (10/90)	3	88.5	71.5	22.5	3.5	0.012
	7	104	58.8	23.2	3.6	0.020

The DEHP levels in the donor solutions were very small and did not appreciably change between 3 and 6 days.

One readily observes the impact of solute lipophilicity on the solute's distribution in a binary material/solution system. The % remaining increases with increasing solute lipophilicity (increasing solute log $P_{o/w}$), reflecting the binding of the higher lipophilicity solutes by the container.

3.1.3. Effect of solution pH (constant solvent ID and solvent proportion)

Solution pH is a primary factor in determining the material/solution interaction properties of acids and bases. This is because solution pH impacts the speciation (or chemical form) of the acidic or basic solute. In simple aqueous solutions, the impact of pH on the interaction is straightforward as the charged and uncharged form of an acid or base will partition differently. Oversimplifying somewhat, the charged form of an acid or base will partition unilaterally into an aqueous solvent while the neutral form will have some defined affinity for the material phase.

Since the pK_a of benzoic acid falls between the two pH values examined in this study, one expects its % remaining to be different at the two pH values. The difference should be similar in all three solvent systems in which pH was examined (water, ethanol/water and acetonitrile/water). The difference should be such that the % remaining should be lower at the lower pH (i.e. at the lower pH the neutral benzoic acid is bound to some extent by the container). One expects no significant difference to be observed for the neutral model solutes (substituted phthalates).

As shown in Table 2, the expected behavior is indeed exhibited in the test systems studied.

3.1.4. Effect of solvent proportion (constant solution pH and solvent ID)

It is expected that as the binary solvent phase becomes more lipophilic (i.e. the organic proportion in the binary aqueous phase increases), a solute's % remaining would increase (that is, that the solute would proportion more favorably into the binary solvent vs. the material phase). Such a trend is shown in Table 3, which summarizes the observed solute partitioning as a function of organic proportion in both an ethanol/water and acetonitrile/water system.

3.1.5. Effect of solvent ID [constant proportion (10/90) and pH]

At the 10/90 proportion, ethanol/water and acetonitrile/water binary mixtures have essentially equal polarities. However, as shown in Table 4, ethanol and acetonitrile are classified by Snyder in two different solvent groups, primarily due to differences in their ability to act as either proton donors or acceptors or in their dipole properties. One anticipates that these properties of a solvent would be impacted by solution pH and thus that solute binding in ethanol and acetonitrile could be effected in different manners by solution pH. Table 5 summarizes the impact of solution pH on the partitioning of the model solutes between the plastic and solutions phases. With the exception of DMP, the levels of the model solutes are not materially impacted by pH and thus the impact of such physio-chemical solvent properties is small.

3.1.6. Effect of organic solubilizing agents

The general nature of the container/solution equilibrium in the solutions containing variable levels of solubilizing agents that were examined in this study are summarized in Table 6. Analytical matrix effects contribute to some matrix-related bias in the data reported in Table 6, specifically for the early eluting compounds (e.g. BA and DMP) in the Chemophor matrix. For example, the % remaining for the early eluting analytes (benzoic acid and DMP) in the Chemophor matrix is greater than 100%. While the absolute value reported in Table 6 is subject to some uncertainty, the trends in behavior are relevant. Specifically, the ability of solubilizing agents to discernibly impact the container/solution equilibrium is clear. Additionally, the nature of the additive has a distinct impact on its effect. For example, con-

Table 3
Effect of solvent proportion on the donor solution composition at equilibrium

Solution composition			Percent solute remaining in the donor				DEHP level in donor (ppm)
Solvent	Ratio[a]	Polarity[b]	Benzoic acid	DMP	DEP	DPP	
Ethanol	0	25.52	81.8	46.9	12.8	2.6	0.012
	10/90	24.33	85.0	61.7	21.8	3.3	0.007
	50/50	19.59	105	103	91.6	67.2	60.2
Acetonitrile	0	25.52	81.8	46.9	12.8	2.6	0.012
	5/95	24.90	86.1	53.4	15.4	1.7	0.006
	10/90	24.28	88.5	71.5	22.5	3.5	0.012
	15/85	23.66	90.9	69.1	35.5	5.8	0.024

At constant pH (3.0) and constant solvent ID.

[a] Ratio of organic to water (v/v).

[b] Solvent polarity for water (25.52), ethanol (13.65) and acetonitrile (13.14) from Schoenmakers (1986a,b). For a mixture of two solvents with polarities of $P1$ and $P2$, the polarity of the mixture (P_m) becomes, $P_m = (\Phi \times P1) + [(1-\Phi)P2]$, where Φ is the proportion of solvent 1 in the mixture.

Table 4
Properties of the solvents used in this study per the Snyder classification

Solvent	Polarity	X_e	X_d	X_n	Solvent group
Water	10.2	0.37	0.37	0.25	VIII
Acetonitrile	5.8	0.31	0.27	0.42	VIb
Ethanol	4.3	0.52	0.19	0.29	II

From Schoenmakers (1986a). X_e is the proton acceptor parameter; X_d the proton donor parameter; X_n the strong dipole parameter.

Table 5
Effect of solvent ID on the donor solution composition at equilibrium

Solution composition			Percent solute remaining in the donor				DEHP level in donor (ppm)
pH	Solvent	Polarity	Benzoic acid	DMP	DEP	DPP	
3	Ethanol	24.33	85.0	61.7	21.8	3.3	0.007
	Acetonitrile	24.28	88.5	71.5	22.5	3.5	0.012
7	Ethanol	24.33	101	61.6	23.2	3.9	0.006
	Acetonitrile	24.28	104	58.8	23.2	3.6	0.020

At constant solvent proportion (10/90 acetonitrile/water or 10/90 ethanol/water) and pH.

Table 6
Effect of organic solubilizing agents on the donor solution composition at equilibrium

Solution composition			Percent solute remaining in the donor				DEHP level in donor (ppm)
Additive	Solution (%)	pH	Benzoic Acid	DMP	DEP	DPP	
None	0	3	81.8	46.9	12.8	2.6	0.012
Acetonitrile	15	3	90.9	69.1	35.5	5.8	0.024
Ethanol	50	3	105	103	91.6	67.2	60.2
Chemophor EL	25	5.3	112	123	91.4	92.5	1900[b]
Lecithin	1	3.5	28.0	26.0	19.5	16.5	23.0
Tween 80	5	4.1	93.4	74.3	52.7	38.5	808
SDS[a]	0.2	3.6	85.7	50.1	14.9	3.9	1.1

[a] SDS, sodium dodecylsulfate.
[b] Approximate value.

sider the behavior observed in the Lecithin versus Tween. In both cases, the % remaining changes proportionally with respect to the solute's log $P_{o/w}$. Thus in these solutions, partitioning theory could be used to reconcile the behavior observed. However, both the absolute magnitude of the % remaining and the change in % remaining as a function of model solute are quite different in the Lecithin matrix versus the Tween matrix. While such behavior may be readily reconciled considering the greatly different physio-chemical nature of these solvent systems, the delineation of such effects was beyond the scope of this investigation.

DEHP accumulates in several solubilizing solvent mixtures at relatively higher levels. However, all the values reported are less than the estimated total pool of DEHP in the plasticized PVC container components, which is approximately 4750 mg/l.

3.2. Modeling of the interaction process

3.2.1. Mathematical development

The equilibrium distribution of a chemical entity between two contacting phases (say a plastic material and a solution) can be expressed in terms of a partition or equilibrium interaction constant (E_b):

$$E_b = \frac{C_p}{C_s} \tag{1}$$

where C_p is the equilibrium concentration of the entity in the plastic and C_s is the equilibrium concentration of the entity in the solution phase.

For the plastic/solution system, this equation can be expressed as follows:

$$E_b = \left(\frac{m_p/W_p}{m_s/V_s}\right) \tag{2}$$

where m is the entity's mass in either phase at equilibrium, W_p the weight of plastic and V_s is the solution volume. One notes that if the units of V_s are in l and the units of W_p are in kg, then E_b is a dimensionless number if the units of the masses are the same and if the density of the solution is approximately 1 kg/l.

Now consider the nature of the experiment performed in this study. The donor solution initially contains a concentration C_i of the chemical entity. After equilibration, the concentration remaining in the donor is measured (C_m). Thus

$$C_m = \frac{m_s}{V_s} \quad \text{and} \quad m_p = (C_i - C_m)V_s \tag{3}$$

and the expression for E_b becomes:

$$E_b = \frac{[(C_i - C_m)V_s]}{(C_m W_p)} \tag{4}$$

Since all the variables in this equation are either known or measured, E_b can be calculated for all the entities and solvent systems examined in this study.

Table 7
log E_b dataset for the modeling of the plastic/solution interaction

Group #, P_m	1, 25.52	7, 24.90	3, 24.33	5, 24.28	8, 23.66	A, 19.59
BA[a]	0.226	0.130	0.113	0.00006	−0.108	−0.770
DMP	0.984	0.886	0.741	0.557	0.609	−0.240
DEP	1.78	1.69	1.52	1.48	1.20	−0.112
DPP	2.74	2.74	2.49	2.41	2.231	0.619

N/M, not measurable. In the experiments performed in this study, these analytes are not bound by the plastic to any great extent. The group numbers refer to the following solvent systems, 1, water; 7, 5/95 acetontirile/water; 3, 10/90 ethanol/water; 5, 10/90 acetonitrile/water; 8, 15/85 acetonitrile/water; and A, 50/50 ethanol/water.

[a] BA, benzoic acid.

It is anticipated that E_b would be related to some solvent property, with polarity (P_m) as a likely reference:

$$E_b = f(P_m) \quad (5)$$

The data generated in the water/ethanol and water/acetonitrile systems can be utilized to establish the nature of these relationships. This dataset is summarized in Table 7 and includes all the data obtained with a solution pH of 3.0.

3.2.2. Relationship between E_b and P_m

Various models were examined in order to establish the relationship between E_b and the polarity (P_m) of the solution phase. The best fit obtained for the models examined was for the following relationship.

$$\log E_b = \text{slope}(P_m) + \text{intercept}. \quad (6)$$

Curve fit data for such a relationship is shown in Table 8 and Fig. 2. For the homologous series of substituted phthalates examined in this study, the fit of the linear model is excellent. The fit is poorer for benzoic acid (only pH 3 data was used to avoid the complicating issue of effect of ionization on binding), owning in part to the small amount of binding observed for this solute in many of the solvent studies. Additionally, it is possible that this acidic model solute interacts with the container material via hydrogen bonding interactions which are not effectively reflected in the solvent's polarity.

Table 8
Curve fit parameters, linear relationship between log E_b and solvent polarity P_m

Model solute	Slope	Intercept	Correlation coefficient (r^2)
BA	0.1723	−4.155	0.884
DMP	0.2084	−4.326	0.991
DEP	0.3309	−6.586	0.995
DPP	0.3766	−6.726	0.989

Model is $\log E_b = \text{slope}(P_m) + \text{intercept}$.

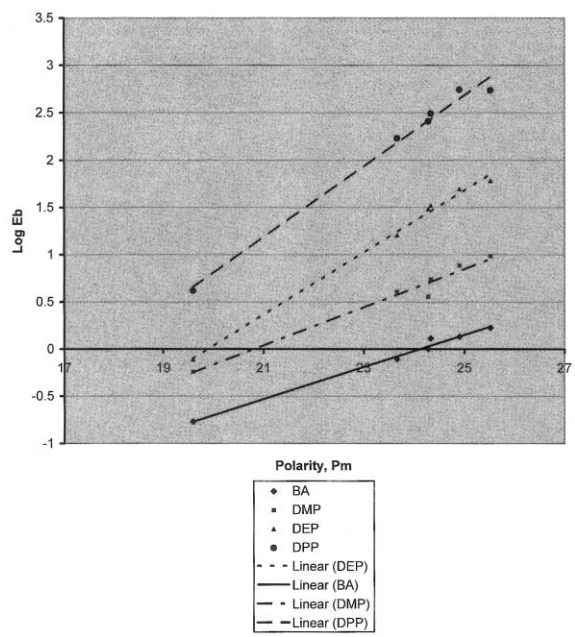

Fig. 2. Relationship between the equilibrium interaction constant (E_b) and the solvent system's polarity (P_m).

Table 9
Comparison of measured and calculated log E_b values for Tween 80 and SDS matrices

Matrix	Solute	log E_b	
		Measured	Calculated
Tween 80 (5%)[a]	BA	−0.217	−0.267
	DMP	0.467	0.378
	DPP	1.14	1.77
SDS (0.2%)[b]	BA	0.153	0.160
	DMP	0.926	0.894
	DPP	2.41	2.71

[a] Group D, calculated $P_m = 22.570$.
[b] Group E, calculated $P_m = 25.045$.

3.2.3. Application of the unified model to the secondary solvents examined in this study

An effective evaluation of the utility of the unified model is to examine its ability to account for the behavior observed in the secondary solvent systems examined in this study. Of these systems, the 5% Tween 80 and 0.2% sodium dodecylsulfate (SDS) are appropriate. The degree of binding in the 25% Cremophor EL was small and thus a quantitative analysis of system is inappropriate. The plastic/solution interaction in the 1% Lechithin system does not appear to be solely dependent on polarity- and lipophilicity-driven mechanisms and thus its behavior would be expected to fall outside the type of model investigated in this study.

This process for assessing the utility of the model was completed as follows. The measured log E_b was obtained for the four model solutes in both the Tween and SDS matrices. Slope and intercept values for the log E_b versus P_m models (Eq. (6)) were derived (e.g. Table 8). DEP, with its intermediate log $P_{o/w}$, was chosen to be the reference compound. This reference compound was used to obtain the P_m value for both Tween and SDS. Specifically, DEP's log $P_{o/w}$ was put into Eq. (6) which was then solved for P_m. The resulting P_m values were then used in Eq. (6) to obtain a calculated log E_b for the other marker compounds (BA, DMP, DPP) in both Tween and SDS. The effectiveness of the model is reflected in the agreement between these calculated log E_b values and their measured results.

The comparison between measured and calculated log E_b is highlighted in Table 9. For the SDS matrix, the agreement between calculated and measured log E_b is good and within the type of variation observed in the data used to generate the model (Eq. (6)). The agreement between the calculated and measured values of log E_b is not as good for the Tween matrix. For BA, the difference in pH of the Tween matrix (4.07) versus the model pH of 3.0 accounts for some of the difference observed. However, such a mechanism is not relevant for DMP and DPP and does not explain the behavior of these model compounds.

3.2.4. Concluding comments

The pharmaceutical formulations examined in this study represent solutions whose interaction characteristics are influenced by solution properties such as pH and additive concentration. While the physio-chemical characteristics of the additives and solutions used in this study (for example, the concentration-dependent ability to form micelles) most certainly provide insight into the trends reported in this study, few of the formulations were examined in sufficient depth or detail to allow for a quantitative discussion of such phenomenon.

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