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The quest for exceptional drug solubilization in diluted surfactant solutions and consideration of residual solid state

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ABSTRACT

Solubility screening in different surfactant solutions is an important part of pharmaceutical profiling. A particular interest is in low surfactant concentrations that mimic the dilution of an oral dosage form. Despite of intensive previous research on solubilization in micelles, there is only limited data available at low surfactant concentrations and generally missing is a physical state analysis of the residual solid. The present work therefore studied 13 model drugs in 6 different oral surfactant solutions (0.5%, *w*/w) by concomitant X-ray diffraction (XRPD) analysis to consider effects on solvent-mediated phase transformations. A particular aspect was potential occurrence of exceptionally high drug solubilization. As a result, general solubilization correlations were observed especially between surfactants that share chemical similarity. Exceptional solubility enhancement of several hundred-fold was evidenced in case of sodium dodecyl sulfate solutions with dipyridamole and progesterone. Furthermore, carbamazepine and testosterone showed surfactant-type dependent hydrate formation. The present results are of practical relevance for an optimization of surfactant screenings in preformulation and early development and provide a basis for mechanistic modeling of surfactant effects on solubilization and solid state modifications.

1. Introduction

A central task of pharmaceutical profiling is to screen solubility of drug candidates in various solvents and excipient solutions that should include different surfactants. These surfactant solutions are typically used for preclinical formulations or they may serve as intermediate bulk solutions for preparation of a final dosage form that should enable oral delivery of poorly soluble compound (Buckley et al., 2013; Kuentz et al., 2016). While most of these colloidal test solutions contain several percent of surfactant, it is further of interest to extend the solubility screening to diluted surfactant solutions. Such rather low surfactant concentrations of about 1% and less are for example relevant with respect to concentrations in the gastro-intestinal (GI) tract. A recent review article discussed the various effects of surfactants in oral formulations from a biopharmaceutical perspective (Wilson et al., 2016). Key is here to which extent surfactants can solubilize drugs at rather low surfactant concentration. Although the science of drug solubilization in micelles has a long tradition (Attwood and Florence, 1983; Christian and Scamehorn, 1995), it is currently not possible to reliably predict solubilization of new compounds. There are trends known for given surfactant types, for example that an increase of polysorbate alkyl chain from C12 to C18 provided increasing solubilization capacity for barbiturates (Ismail et al., 1970). Similar effects of varying hydrophobic chain length were also observed with another surfactant series of polyoxyethylene stearates (Gouda et al., 1970). As for the solubilized compound, there were further trends observed for example that the partition coefficient of steroid hormones into polyoxyethylene lauryl ether micelles was correlated with the partition coefficient between an aqueous solution and octanol (log*P*) (Tomida et al., 1978). There are certainly more studies in the literature that report solubilization trends for compounds and surfactants but this begs the practical question if such findings can be generalized to similar drugs in, for example, a given class of surfactants.

It has also been tried to quantitatively predict surfactant solubilization based on measured predictors such as the surface pressure at the critical micelle concentration (CMC) and a reference value of surface tension reduction (Liu et al., 2000). However, this interesting approach was only applied to aromatic model compounds and the model validity is unclear in case of more complex molecules that may have various functional groups as with typical poorly soluble drugs. Even in case of a

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rather broad applicability of the approach, there is still experimental input data required. More recently, a molecular dynamics simulation approach has been tried to model micellar partitioning and solubilization (Storm et al., 2013). This is a very interesting approach but like all molecular dynamics simulations, it is very challenging to obtain reliable simulations on a mesoscopic scale such as with micelles. It will likely take several further years until such an in silico approach can be implemented in the practice of pharmaceutical profiling.

A first step towards any future theoretical approach is to have sufficient experimental data for model validation. However, reliable and comparable solubilization data of drugs are hard to find in the literature at low surfactant concentrations. Solubility data depend on many factors such as pH-value, temperature or exact composition of the media so existing study results can often not be combined to a larger dataset and therefore, a need to experimentally evaluate a broader set of drugs and surfactants under the same conditions. It is further desirable to check the residual solid in solubility experiments (Wyttenbach et al., 2007) to account for potential solid phase changes. In general, data of solid state analysis are not available in solubilization studies of surfactants systems. However, this can be a relevant experimental point since recent studies demonstrated that kinetics of a pseudo-polymorphic transition (i.e. hydrate formation of piroxicam) and was influenced by the presence of 0.5% (w/w) sodium dodecyl sulfate (SDS) or polysorbate 80 (P80), respectively. (Kirchmeyer et al., 2016) The pseudo-polymorphic transformation of piroxicam was shown to effect remarkably the solubilized concentrations in the bulk phase. Lehto et al. (2009) studied pseudo-polymorphic transformation of carbamazepine in biorelevant media with concentration measurements in parallel. They also showed that the intrinsic dissolution rate was affected by the solid state transformation and it is therefore important to study solid state and dissolution or solubility in parallel.

The outlined need for solubilization data of diluted surfactant solutions in conjunction with characterization of the residual solid state provided the aim of the current research. A particular objective was to find correlations between different surfactants used and to look for outliers with exceptional drug solubilization. Finally, some guidance for pharmaceutical profiling was targeted based on the obtained findings.

2. Materials and methods

2.1. Materials

In total, 13 different pharmaceutical compounds were arbitrarily selected to span a typical chemical space of drugs. These compounds were used as model to study solubility and solid state changes in diluted surfactant solutions. Acetylsalicylic acid, carbamazepine, diflunisal, dipyridamole, estradiol, flurbiprofen, haloperidol, naproxen, pindolol, progesterone, dioctyl sulfosuccinate (DOSS) and cremophor EL (CEL, synonymous name is Kolliphor EL) were obtained from Sigma Aldrich (St. Louis, USA). Furosemide was purchased from Molekula GmbH (München, Germany), while ibuprofen was from Satwik Drugs Ltd. (Bidar, India). Testosterone was from TCI Europe N.V. (Zwijndrecht, Belgium), hydrochloric acid (0.1 M), and sodium hydroxide solution (0.1 M) were supplied by Merck KGaA (Darmstadt, Germany). Polysorbate 80 (P80) was from Croda Europe Ltd. (Cowick, United Kingdom), while sodium dodecyl sulfate (SDS) was from Stepan Company (Northfield, USA), solutol (SOLU, synonymous name is Kolliphor HS 15) was from BASF SE (Ludwigshafen, Germany) and sucrose monolaurate (SUCM) was obtained from Selectchemie AG (Zürich, Switzerland).

2.2. Methods

2.2.1. Sample preparation

Surfactant solutions were prepared by dissolving individually P80, solutol, cremophor EL, sucrose monolaurate, SDS, and DOSS (0.5% (w/w)) in deionized water and adjusting the pH of the solutions to pH 6.0 with hydrochloric acid or sodium hydroxide solution at 25 °C.

2.2.2. Solubility and residual solid analysis

Solubility of compounds in surfactant solutions was determined using a slightly modified 96-well SOlubility and REsidual SOlid Screening (SORESOS) assay, which measures both equilibrium solubility and solid form of the residual solid. (Wyttenbach et al., 2007) In brief, APIs were dispensed using the powder-picking-method (Alsenz, 2011) in 96-well flat bottom plates (Corning Inc., Durham, USA), single use stirring bars (product number VP711-1, 1.67 × 2.01 × 4.80 mm, parylene coated, V & P Scientific Inc., San Diego, CA) and excipient vehicles (150 µL) were added. The plate was sealed with pre-slit silicon caps. To ensure sufficient mixing of vehicles and compounds, the mixtures were agitated by head-over-head rotation for 24 h at room temperature. After equilibration, the suspensions were carefully transferred into 96-well filter plates and liquid was separated from residual solid by centrifugation. Collected filtrates were diluted with *N*-methyl-2-pyrrolidone and drug content was determined using a Waters Acquity Ultra Performance Liquid Chromatographic (UPLC) system equipped with a 2996 Photodiode Array Detector and an Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 µm particle size) from Waters (Milford, USA). Chromatograms were carefully checked for absence of any degradation products of the compounds in *N*-methyl-2-pyrrolidone. Degradation of the model drugs in NMP was checked before performing the experiments and during the UPLC analyses. Table 1 summarizes the experimental conditions (solvents, composition of mobile phase, detection wave length) used for the drugs. An isocratic flow of a mixture of solvent A and solvent B was applied for 0.3 min at a flow rate of 0.75 mL/min. Subsequently, the concentration of solvent B was linearly increased to 100% within 0.5 min. Solid state analysis of residual solid was performed by X-ray powder diffraction (XRPD) as described before by Wyttenbach et al. (2007) and Kirchmeyer et al. (2015). A STOE Stadi P Combi diffractometer with a primary Ge-monochromator (Cu Kα radiation), imaging plate position sensitive detector (IP-PSD), and a 96-well sample stage. The IP-PSD allowed simultaneous recording of the diffraction pattern on both sides of the primary beam which were summed up by the software STOE WinXPOW to reduce effects related to poor crystal orientation statistics. Samples were analyzed directly in the 96-well filter plate with an exposure time of 5 min per well.

2.2.3. Correlation and regression analysis

The program STATGRAPHICS Centurion XVI ed. Professional (V. 16.1.15) from Statpoint Technologies Inc. (Warrenton, USA) was used for statistical correlation as well as regression analysis.

Table 1
Experimental conditions used for UPLC analysis.

Compound	Composition (A:B)[a] [%]	Detection wavelength [nm]	Retention time [min]
Acetylsalicylic acid	80:20	276	0.64
Carbamazepine	70:30	285	0.65
Diflunisal	50:50	314	0.61
Dipyridamole	81:20	284	0.69
Estradiol	60:40	280	0.62
Flurbiprofen	50:50	255	0.62
Furosemide	75:25	274	0.71
Haloperidol	70:30	244	0.62
Ibuprofen	50:50	232	0.71
Naproxen	55:45	272	0.54
Pindolol	90:10	264	0.64
Progesterone	40:60	243	0.56
Testosterone	60:40	244	0.65

[a] Mobile phase A: deionized water with 0.1% (v/v) triethylamine adjusted to pH 2.2 with methanesulfonic acid, mobile phase B: acetonitrile.

Table 2
List of model drugs and selected physicochemical properties.

Compound	Mw [g/mol]	pK_a [a]	Category	Log$D$ [b] (pH 6.0)
Acetylsalicylic acid	180.2	3.7*	Acid	−1.3
Carbamazepine	236.3	–	Neutral	2.8
Diflunisal	250.2	2.7*	Acid	0.8
Dipyridamole	504.6	6.2	Base	1.8
Estradiol	272.4	–	Neutral	3.7
Flurbiprofen	244.3	4.2*	Acid	2.4
Furosemide	330.7	3.5	Acid	0.0
Haloperidol	375.9	8.4*	Base	1.6
Ibuprofen	206.3	4.4*	Acid	2.7
Naproxen	230.3	4.4*	Acid	1.2
Pindolol	248.3	9.2*	Base	−1.4
Progesterone	314.5	–	Neutral	4.1
Testosterone	288.4	–	Neutral	3.4

[a] Measured pK_a-values via photometric titration.
[b] Values calculated by the Marvin program suite (V.16.5.30) (ChemAxon Ltd., Cambridge, USA).
* Calculated pK_a-values by the MoKa-software (V2.6.6) (Molecular Discovery, Hertfortshire, UK).

3. Results and discussion

3.1. Drug solubilization screening at low surfactant concentration and analysis of residual solid

In preformulation, solubility screening in surfactant solutions typically includes several percent of surfactant in order to use it directly as a potential vehicle in preclinical formulation or as an intermediate drug product solution. In this work, a concentration of 0.5% (w/w) surfactant at pH 6 was used which may represent the surfactant concentration of a dissolved orally administered dosage form in the GI tract. A constant mass concentration was selected as it represents a diluted formulation. However, this practical approach comes with slightly varying molar concentrations. The chosen mass concentration was generally higher than the critical micelle concentrations (CMC) of the different surfactants that were reported in the literature (Dawson et al., 1986; Khan and Shah, 2008; Ong and Manoukian, 1988; BASF SE, 2012a, 2012b; Steffy et al., 2011). The extent of drug solubilization will certainly depend on their physicochemical properties (Table 2) as well as on physicochemical properties of the surfactants (Table 3). The 13 compounds comprised acids, bases as well as neutral compounds at the given reference pH. The lipophilicity as expressed by the calculated distribution coefficient (log$D$ at pH 6.0) exhibited a broad range of values from −1.4 (pindolol) to 4.1 (progesterone). More lipophilic compounds are more likely to partition into micellar cores, whereas hydrophilic compounds either are predominantly in the bulk phase or interact with the hydrophilic head groups (Fig. 1). It was shown in a study of electron resonance spectroscopy that not only lipophilicity was decisive for drug location in micelles but also acid/base properties play a role (Reis et al., 2007). The study concluded that the tested positively charged β-blockers were primarily located on the surface of SDS and bile salt micelles whereas neutral lipophilic benzodiazepines were in the deeper interior of the micelles. Such a location in the core of micelles can be further differentiated from drugs that are rather accommodated in the palisade region of micelles (Fig. 1). Amphiphilic compounds appear to prefer this location and a recent study with amlodipine hydrochloride and a nonionic surfactant evidenced formation of mixed micelles (Rub et al., 2016).

Solubility data for the various compounds and surfactants are shown in the supplementary data whereas the solubility enhancement factors are shown in Table 4. The comparatively hydrophilic compounds acetylsalicylic acid and pindolol did not display a pronounced solubilization in the micellar systems, except for a slight enhancement with the charged surfactants SDS and DOSS. As expected, the more lipophilic steroid drugs showed a clear solubilization in ionic surfactants compared to pure water. SDS increased the solubility of progesterone and of dipyridamole almost 200- and 400-times, respectively, compared to water. These results are exceptionally high compared to the other solubilization results. These highest values have in common with other rather high solubility enhancement results that aqueous drug solubility was in these cases comparatively low. The magnitude of achieved solubilization in such individual cases suggests that it is worthwhile in preformulation to screen for the best drug solubilizer by comparing various surfactant types.

Fig. 2 depicts a typical comparison of the different surfactants for selected drugs. The solubilization by SDS was here very pronounced compared to DOSS or the other non-ionic surfactants. Similar solubilization pattern was found for the majority of tested compounds despite of their log$D$ values and charges. However, care is needed with any generalization for non-ionic surfactant because even though naproxen showed also best solubilization in SDS as well, a previous work showed also excellent solubilization in non-ionic surfactants of the type Brij (Bhat et al., 2009). The comparative solubilization pattern among surfactants was also found to vary, as in the case of diflunical and flurbiprofen. Even though these acidic drugs differ in their log$D$ values, a similar pattern of preferred solubilization in pegylated non-ionic surfactants was evidenced for these fluorinated aryl acetic acid derivatives (Fig. 2).

In contrast to most other studies, micellar solubilization at low surfactant concentration was conducted in parallel to the characterization of the residual solid state. Solvent-mediated phase changes were only observed for carbamazepine and testosterone (Fig. 3 and Table 5), although also for flurbiprofen and diflunisal hydrate formation is reported in the literature (Grzesiak and Matzger, 2007; Hansen et al., 2001). Hydrate formation of carbamazepine was seen in all non-ionic surfactants and in pure water, while in SDS- and DOSS solutions, a mixture of anhydrate and hydrate was detected. Previous studies showed that carbamazepine hydrate was built in water and hydrate formation was even promoted by SDS (Boetker et al., 2016; Rodriguez-Hornedo and Murphy, 2004), which is in good agreement with the presented results. Additionally, measured solubility values of carbamazepine in water and SDS-solution (0.5%) were in good agreement with those reported earlier (Rodriguez-Hornedo and Murphy, 2004). In

Table 3
Molecular weight (Mw), hydrophilic-lipophilic balance (HLB), and critical micelle concentration (CMC) of surfactants.

Compound	Mw* [g/mol]	HLB	CMC [mM]	CMC [% w/w]
Polysorbate 80 (Constantinides and Scalart, 1997; Dawson et al., 1986)	1310	15	0.01	0.001
Solutol (BASF SE, 2012b)	345	14–16	0.37	0.01
Cremophor EL (BASF SE, 2012a)	2500*	12–14	0.20	0.02
Sucrose monolaurate (Ong and Manoukian, 1988)	525	13+	0.34	0.02
SDS (Housaindokht and Nakhaei Pour, 2012; Khan and Shah, 2008)	288	40	7.80	0.26
DOSS (Koos et al., 2012; Steffy et al., 2011)	445	11	2.92	0.13

* Mean molecular weight of pegylated surfactants based on description of excipients' composition.
+ Calculated with Molecular Modeling Pro, V.6.2.6 (Norgwyn Montgomery Software Inc., North Wales, USA).

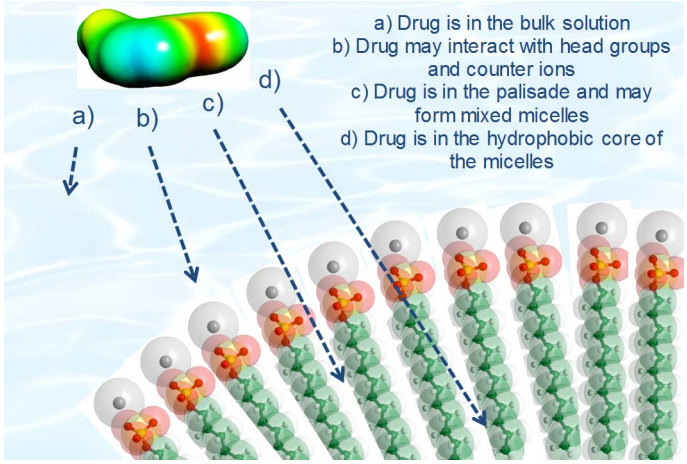

Fig. 1. Different possible locations and mechanisms of drug solubilization in presence of surfactant micelles (example of sodium dodecyl sulfate). One or several mechanisms are likely to dominate depending on the physical compound properties.

Table 4
Solubility enhancement factors of compounds in 0.5% (*w*/w) surfactant solutions at room temperature after 24 h.

	Solubility enhancement factor					
Compound	Polysorbate 80	Solutol	Cremophor EL	Sucrose monolaurate	SDS	DOSS
Acetylsalicylic acid	1.01	0.98	1.01	0.99	1.22	1.10
Carbamazepine	1.7	1.4	1.5	2.3	9.2	2.6
Diflunisal	9.5	8.6	9.0	5.2	6.4	3.8
Dipyridamole	21.4	16.3	16.2	23.3	404.0	1.3
Estradiol	19.9	22.3	20.9	17.0	58.0	5.6
Flurbiprofen	23.6	19.8	20.5	9.8	20.1	5.9
Furosemide	161.7	105.7	113.9	112.0	121.3	94.2
Haloperidol	1.5	1.5	1.8	3.4	13.8	0.8
Ibuprofen	3.7	3.1	3.5	2.2	4.8	1.7
Naproxen	6.4	4.8	5.4	3.7	9.6	2.5
Pindolol	1.8	1.6	1.5	2.5	6.1	3.1
Progesterone	9.7	10.3	11.5	27.7	189.1	12.6
Testosterone	2.8	2.8	2.6	6.6	36.4	4.8

case of testosterone, hydrates were formed in water, ionic surfactants and non-pegylated non-ionic surfactants. Adsorption of a specific surfactant onto particle surfaces plays an important role in a potential stabilization of anhydrates. Such surfactant effects have recently been studied with piroxicam (Kirchmeyer et al., 2015) where imaging showed that the kinetic hydrate transformation was suppressed by 0.5% (w/w) of polysorbate 80. This is in line with the present findings of pegylated surfactants. It can be argued that solubility values with anhydrate as residual solid are not representing true thermodynamic solubility but rather a metastable equilibrium for those compounds where hydrate formation is known. However, from a practical perspective, a pseudo-equilibrium for a certain time might be of interest since formulations are often prepared immediately before administration and not stored for a longer time. For the calculation of solubility enhancement factors (Table 4), solubility values after 24 h incubation time were used without adjusting solubility values from pseudo-equilibria. Although, this calculation is for hydrate-forming compounds not in line with the thermodynamic understanding of solubility enhancement, it is a practically oriented approach, which is biopharmaceutically meaningful and can be applied for solubility screening. However, present findings underline that proper solid state characterization is desirable at the end of solubility experiments.

3.2. Correlation and regression analysis of solubility enhancement

Similar patterns of drug solubilization among surfactants can be further studied by a correlation analysis. Correlation analysis helps also to look for outliers with exceptional drug solubilization. This can help to formulate some guidance for pharmaceutical profiling. We used for this purpose the logarithmic solubility enhancement, i.e. the surfactant-mediated solubilization divided by the solubility in pure water (Table 4). This normalization is helpful for a comparison among compounds with greatly varying aqueous solubility. Fig. 4 shows the results of a Pearson product moment correlation in a scatterplot matrix, which is a measure of the linear correlation between the log(solubility enhancement) values in two surfactants. Every pair of variables is plotted twice, once with the first variable on the X axis and one with that variable on the Y axis. In this plot, surfactant pairs that highly correlated can be easily identified. The correlation coefficients as well as *p*-values are listed in Table 6.

All correlations between surfactants reached the level of statistical significance but the quality of the correlation differed considerably. Some values were deviating from linearity as the overview of Fig. 4 displays. Exceptional solubility enhancement was shown for the different steroid compounds as well as for flurbiprofen and dipyridamole (Table 4). Such high values were expected for the compounds with rather high log*D* value and in case of dipyridamole is notable, that its pK_a value is close to the pH 6 of the solutions. It can be expected that slight perturbations would affect partitioning into the micelles. A quantitative measure for such partitioning can be inferred from log (solubility enhancement) values as it has been reported previously in the literature (Poole et al., 2009). It was hence of interest to compare log(solubility enhancement) with the distribution coefficient log*D*. As a result, these correlations were limited for the different surfactants and notable was mainly SDS that reached r of 0.638 (p = 0.014). It was expected that a single molecular property would not provide high correlation due to the complex physicochemistry of partitioning (Yang et al., 1996). We therefore focussed primarily on correlations between

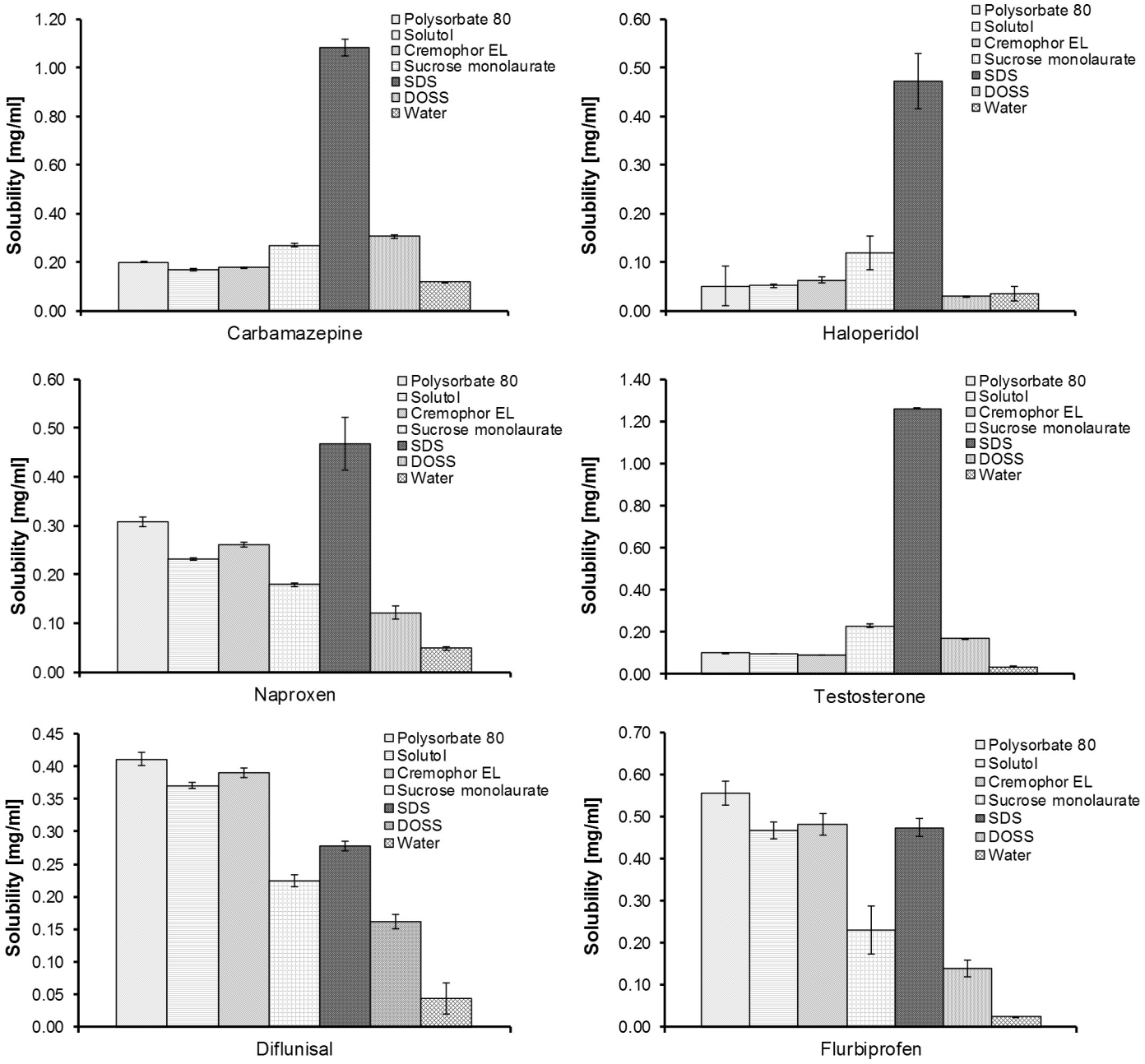

Fig. 2. Solubility of carbamazepine, haloperidol, naproxen, testosterone, diflunisal, and flurbiprofen in 0.5% (w/w) surfactant solutions at room temperature after 24 h incubation time.

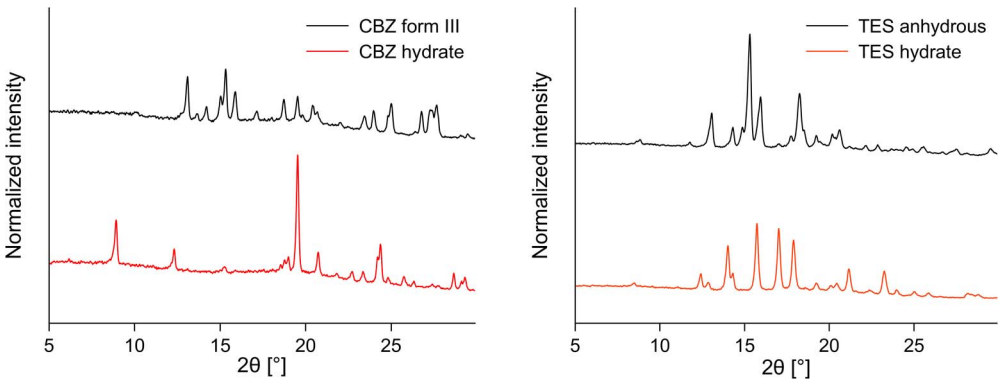

Fig. 3. XRPD pattern of anhydrous and hydrated forms of carbamazepine and testosterone obtained from the high-throughput assay.

Table 5
Solid state change of CBZ and TES in residual solids after incubation for 24 h in 0.5% (w/w) surfactant solutions at room temperature.

	Solid state characterized by XRPD analysis						
Compound	Polysorbate 80	Solutol	Cremophor EL	Sucrose monolaurate	SDS	DOSS	Water
Carbamazepine	H	H	H	H	AH/H	AH/H	H
Testosterone	AH	AH	AH	H	H	H	H
Other compounds*	AH	AH	AH	AH	AH	AH	AH

* For an overview of the other tested compounds, see Table 1; AH: anhydrous form of compound, H: hydrated form of compound, AH/H: mixture of both forms.

different surfactants rather than attempting further predicitons based on molecular drug properties.

Correlations were very high among pegylated surfactants, which form a good basis for regression. The surfactant solutol and cremophor EL are very similar since ricinoleic acid and hydroxystearic acid provide similar lipophilic surfactant tails. Fig. 5A shows the regression line with R^2 of 0.994. Persson et al. (2013) reported good correlation between pure excipients e.g. P80 and PEG 400. Although these findings in addition to our results indicate that some correlations hold true for pure excipients as well as for diluted systems, this cannot be generalized. The formation of colloids upon aqueous dilution requires that the diluted excipient solutions should be evaluated separately.

Log(solubility enhancement) CEL
= 0.02513 + 0.98930*Log(solubility enhancement) SOLU (1)

Eq. (1) describes a relationship that is close to the identity line. Fairly good model can also be formulated for the other relationships among pegylated surfactants as suggested by the *r*- values.

An example is shown by Fig. 5B where solubility enhancement in cremophor EL correlates well with the values obtained in polysorbate 80 solutions (R^2 = 0.981):

Log(solubility enhancement) CEL
= -0.01176 + 0.96648*Log(solubility enhancement) P80 (2)

The high correlations and adequate regression models allow predicting drug solubilization in one pegylated surfactant solution from another based on the results of our study. Thus, it seems to be justified to experimentally determine only one or two pegylated surfactant(s) to save resources in preformulation screening. Later in pharmaceutical development, the initially predicted values can be experimentally grounded when there is a special interest is for a given surfactant. Such an interest may, for example, origin from preformulation of lipid-based formulation if a particular surfactant is attractive because of its phase behavior. (Feeney et al., 2016) Moreover, solubilization may in vivo differ due to the presence of bile salts and phospholipids as well as by potential enzymatic hydrolysis of a given surfactant. (Arnold et al., 2012) There are also additional technical aspects that may lead to final excipient selection so that solubility enhancement values provide only one aspect albeit their biopharmaceutical importance for poorly soluble compounds. (Elder et al., 2016).

The correlation analysis (Fig. 4 and Table 6) indicates poorer correlations between sucrose monolaurate and anionic surfactants. A potential reason could be the comparatively short tail and sucrose head group which make sucrose monolaurate rather unique in the present

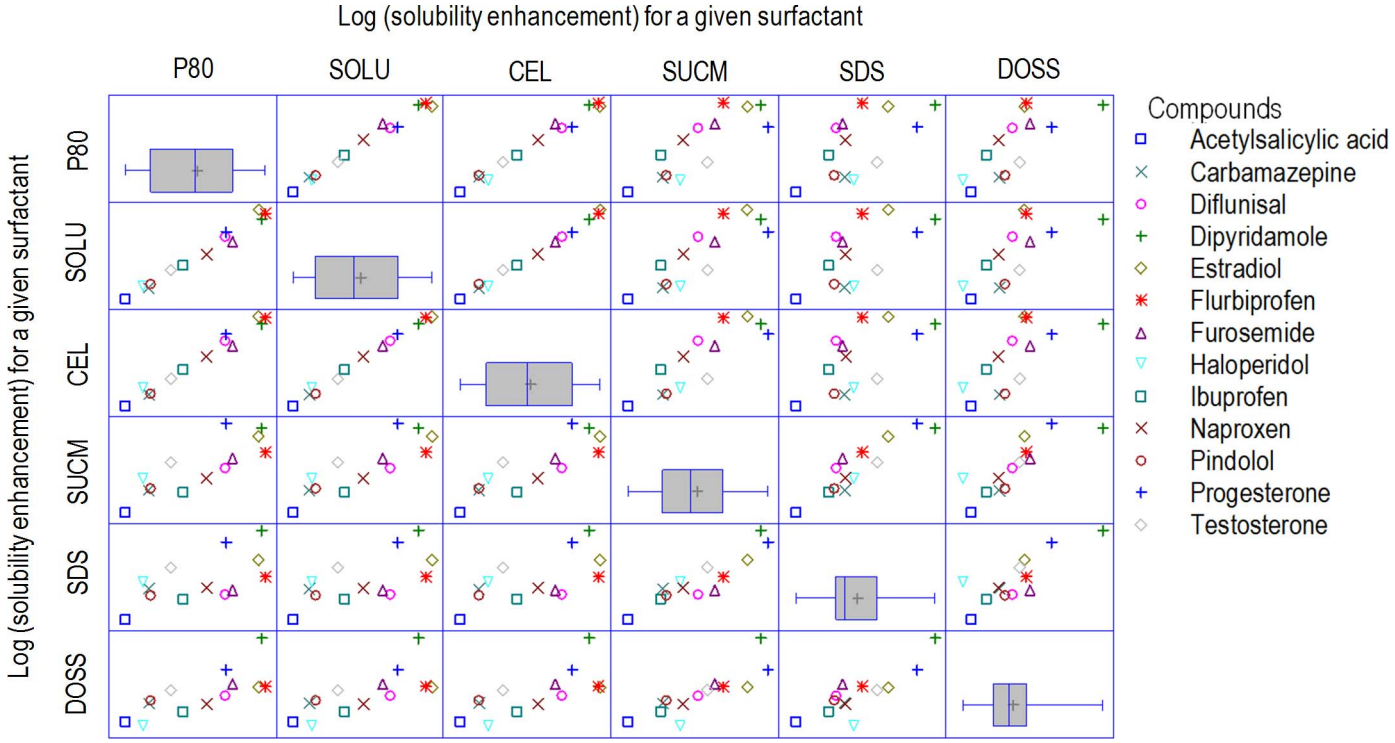

Fig. 4. Box-and scatter plots of the different solubility enhancements (SE) in 0.5% (w/w) surfactant solutions over water. Surfactants are polysorbate 80 (P80), solutol HS (SOLU), cremophor EL (CEL), sucrose monolaurate (SUCM), sodium dodecyl sulfate (SDS), and dioctyl sulfosuccinate (DOSS). Box plots from the lower to upper quartiles are shown for log(SE) of each surfactant with the median lines (and cross for the means). Correlation between any log(SE) values for a pair of surfactants is displayed by individual scatter plots. For color codes, please refer to the online version of the article.

Table 6
Correlation coefficients for the different 0.5% (w/w) surfactant solutions.

		Log(solubility enhancement) in a given surfactant solution					
		P80	SOLU	CEL	SUCM	SDS	DOSS
Log(solubility enhancement) in a given surfactant solution	P80		0.9912 (p = 0.0000)	0.9903 (p = 0.0000)	0.8414 (p = 0.0002)	0.6341 (p = 0.0149)	0.7525 (p = 0.0019)
	SOLU			0.9972 (p = 0.0000)	0.8682 (p = 0.0001)	0.6646 (p = 0.0095)	0.7368 (p = 0.0026)
	CEL				0.8660 (p = 0.0001)	0.6599 (p = 0.0102)	0.7174 (p = 0.0039)
	SUCM					0.9108 (p = 0.0000)	0.8422 (p = 0.0002)
	SDS						0.8373 (p = 0.0002)
	DOSS						

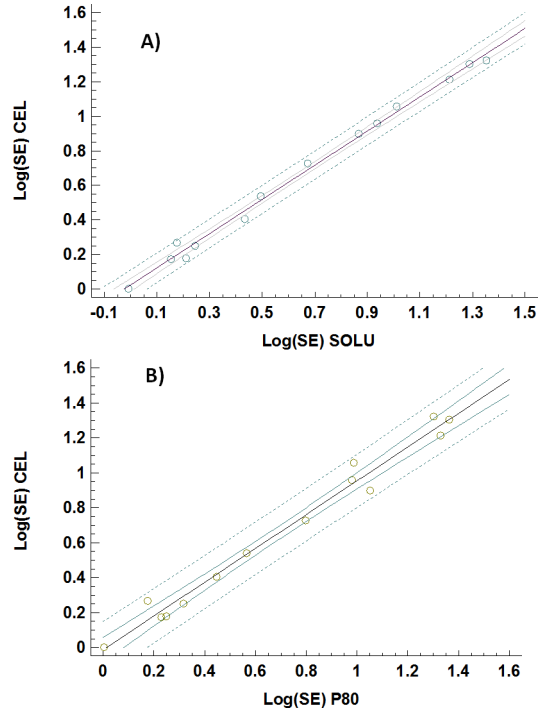

Fig. 5. Regression analysis of solubility enhancement (SE) in 0.5% surfactant solutions over water in case of A) cremophor EL versus log(SE) of solutol and B) cremophor EL versus log(SE) of polysorbate 80.

study of surfactants. Interestingly, although SDS and DOSS share a negatively charged head group, their correlation is rather limited regarding log(solubility enhancement) values. A potential reason could be the branched hydrophobic tail group of DOSS, which may in many cases be less effective in drug solubilization compared to SDS. Therefore, a predictive regression model for DOSS and SDS was not possible. The current lack of a predictive model for the log(solubility enhancement) may suggest that both anionic surfactants should be part of an early screening of surfactant solubilization. This inclusion of DOSS is also meaningful because apart from solubilization there is further surfactant performance in drug wettability and dispersion stabilization.

The current dataset shows that remarkable solubility enhancement can be achieved even at rather low surfactant concentrations, which may mimic a realistic range upon dilution of an oral dosage form.

4. Conclusions

A surfactant screening has to consider different excipient properties like, for example, tolerability, pharmaceutical quality, and especially its technical and biopharmaceutical performance. For the latter excipient performance, drug solubilization is of crucial importance. We therefore studied drug solubility enhancement at low surfactant concentrations that provide a model for diluted oral dosage forms. A broad screening of drug solubilization was conducted by consideration of optional solvent-mediated phase transformations. Findings suggest that especially charged surfactants like SDS may bear promise to achieve a solubility increase of several hundred-fold compared to water. High solubilization correlations were identified among pegylated surfactants of similar type. These correlations may be used to omit individual surfactants for a resource-saving solubilization testing in preformulation. Our results further stress the importance of solid state characterization of residual drug since surfactants may affect solvent-mediated phase transformations. Current findings may serve as basis to guide a surfactant screening in preformulation and data may in the future become part of a bigger database. Solubility values are also needed to estimate drug supersaturation upon aqueous formulation dispersion. The values will find additional use for in silico models of drug solubilization as well as more complex physiologically based pharmacokinetic modeling.

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