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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.