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Research Paper

Drug solubility in lipid nanocarriers: Influence of lipid matrix and available interfacial area

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ABSTRACT

Amongst other strategies for the formulation of poorly water-soluble drugs, solubilization of these drugs in lipid-based formulations is a promising option. Most screening methods for the identification of a suitable lipid-based formulation fail to elucidate the role interfacial effects play for drug solubility in disperse systems. In a novel screening approach called passive drug loading, different preformed lipid nanocarrier dispersions are incubated with drug powder. Afterwards, undissolved drug is filtered off and the amount of solubilized drug is determined. The aim of this study was to identify parameters for drug solubility in pure lipids as well as for drug loading to the lipid-water interface of lipid nanoparticles. Using passive loading, the solubility of eight poorly water-soluble drugs in seven lipid nanocarriers varying in particle size or lipid matrix was investigated. Drug solubility in the nanocarriers did not follow any apparent trend and different drugs dissolved best in different carriers. Drugs with a melting point below approximately 150 °C displayed distinctly better solubility than higher melting drugs. Additionally, relating the specific lipid nanocarrier surface area to the drug solubility allowed drawing conclusions on the drug localization. Fenofibrate, dibucaine and, less distinctly also clotrimazole, which all melt below 150 °C, were predominantly located in the lipid droplet core of the nanoparticles. In contrast, the five remaining drugs (betamethasone valerate, flufenamic acid, itraconazole, ketoconazole, mefenamic acid) were also located at the lipid-water interface to different, but substantial degrees. The ability to account for drug loading to the lipid-water interface is thus a major advantage of passive loading.

1. Introduction

Lipid-based drug delivery systems are amongst the most promising formulation approaches for poorly water-soluble drugs. Identification of more lipophilic and larger new drug candidates by modern drug discovery methods (Leeson, 2016) will further increase the demand for formulations that overcome poor water solubility. There is a broad variety of lipid-based formulations, both for parenteral and oral administration to (pre)dissolve poorly soluble lipophilic drugs. For parenteral administration of poorly soluble drugs, lipid nanoparticles are frequently used as drug delivery systems. A wide range of such lipid particle-based systems exists, both commercially available ones like drug-loaded nanoemulsions or liposomes (Allen and Cullis, 2013; Bunjes, 2010), and systems which are still in the research stage like solid lipid nanoparticles (Mehnert and Mäder, 2001), supercooled smectic nanoparticles (Kuntsche et al., 2004) or cubic phase nanoparticles (Tiberg and Johnsson, 2011). What all systems have in common is a particle size in the nanometer range and that they are stable upon dilution, *e.g.* upon administration to the bloodstream. For oral drug delivery, water-free mixtures of lipids and surfactants are employed which form emulsions or microemulsions upon dilution with water in the GI tract. These formulations are currently categorized by the lipid formulation classification system, which is based on the formulation's composition (lipids, surfactants, hydrophilic cosolvents) and the system that forms upon dilution with water in the GI-tract (Pouton, 2000, 2006).

Irrespective of the intended route of administration, drug candidates are usually first screened for solubility in numerous excipients (Chen et al., 2012; Wyttenbach et al., 2007) which is both time- and material consuming since there are many lipids and mixtures of oils with surfactants to choose from. More importantly, neither potential drug association at the lipid-water interface of colloidal carriers nor drug redistribution or precipitation in the lipid-based formulations upon dilution with water is accounted for in this approach. Also, such conventional screening approaches do

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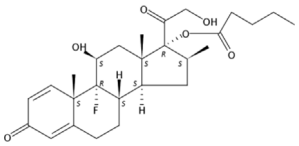
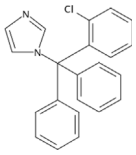
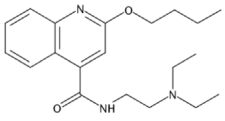
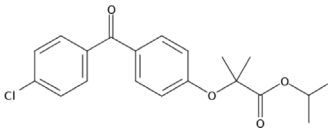
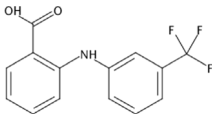
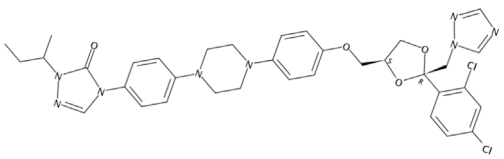
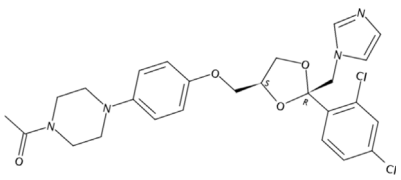
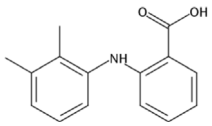
not help to develop an understanding of drug-excipient interactions. To accelerate and rationalize screening for excipients, promising models have been developed to predict drug solubility in pure lipid excipients (Alskär et al., 2016; Persson et al., 2013; Rane and Anderson, 2008). In a recent study, Alskär et al. identified not only drug characteristics that lead to high drug solubility in lipids, they also showed that the loading capacity of complex formulations could be accurately predicted from calculated descriptors and thermal properties of the drug (Alskär et al., 2016). Other authors used molecular dynamics to investigate how

Table 1
Physicochemical properties of the investigated drugs and buffers used for incubation.

Structure	Name	logP MW[g/mol]	Solubility in water [μg/ml]	T_m[°C]	pKa	Buffer	pH of dispersion
	Betamethasone valerate	4.13 477	1.1	183	–	none	7.3–7.6
	Clotrimazole	4.92 345	3	147	6.12	Tris pH 9	9.1
	Dibucaine	4.76 343	48	64	9.07; 12.9	Phosphate pH 11	10.9/10.5[b]
	Fenofibrate	5.8 361	0.131[a]	82	–	none	7.2–7.7
	Flufenamic acid	5.22 281	5.9	134	3.67	HCl pH 0.7	0.5–0.9
	Itraconazole	4.99 706	0.099	166	6.47	Tris pH 9	9.1
	Ketoconazole	4.04 531	26	150	6.88	Tris pH 9	9.1
	Mefenamic acid	4.83 241	13	230	3.73	HCl pH 0.7	0.5 – 0.8

LogP, solubility and pK_a are calculated values extracted from Scifinder; data were calculated for 20 °C and for the pH of the respective buffer, *i.e.* for neutral molecules.
[a] Experimental value from [Göke and Bunjes, 2017b].
[b] In the liposome dispersion prepared with 10 mM phosphate buffer pH 7.4.