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Evaluation of the versatile character of a nanoemulsion formulation

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ABSTRACT

The formulate-ability of six model active pharmaceutical ingredients (API), with different physico-chemical profiles, in a nanoemulsion designed to be intraveinously administrable was explored. Nanoemulsions were spontaneously generated at room temperature by pouring a phosphate buffer in an anhydrous mixture containing pharmaceutically acceptable triglycerides and non-ionic surfactants. After determination of the apparent solubility of each API in excipients and characterization of mixtures by DSC, API-loaded nanoemulsions were formulated and characterized in terms of granulometric properties, surface potential, drug recovery efficiency, pH, osmolarity, *in vitro* drug release, and stability.

Except ciprofloxacin, a BCS class IV drug, all studied APIs were soluble in at least one excipient used, *i.e.* Labrasol®. At 2 wt% API, all drug-loaded nanoemulsions present properties compatible with i.v. administration. The formulation should permit to increase apparent solubility of poorly water-soluble APIs, and also to prolong delivery of hydrophobic as well of more hydrophilic compounds. Herein, the relative affinity of the API for nanodroplets and the release medium would directly influence drug release profiles. Nanoemulsions were stable for 7 days. They could also been extemporaneously reconstituted before use. Such a versatile nanoemulsion would provide a valuable option as formulation strategy for improvement of drug properties.

1. Introduction

About half of new chemical entities entering drug development pipelines are poorly water soluble. As solubility is, with permeability, a fundamental prerequisite to absorption in the gastrointestinal tract, many of drug candidates present low oral bioavailability (Amidon et al., 1995). To overcome this serious hurdle and to limit the number of lead compounds or drug candidates to be eliminated from discovery pipelines, formulation strategies can be envisaged as soon as possible in drug discovery to enhance the solubility, and *in fine* the bioavailability of compounds (Chen et al., 2012; Li and Zhao, 2007; Strickley, 2004). Various solubilization approaches may be considered as the development of drug-cyclodextrin inclusion complexes (Kurkov and Loftsson, 2013) or mesoporous systems (Xu et al., 2013), solid dispersions (Gue et al., 2013; Van den Mooter, 2012), and lipid-based drug delivery systems (DDS) (Mu et al., 2013; Porter et al., 2013; Pouton, 2000). Lipid-based DDS not only improve active pharmaceutical ingredient (API) solubilization but also prevent API precipitation upon dilution in the gastrointestinal (GI) tract, protect labile APIs, and control their release rates (Rane and Anderson, 2008). Moreover, thanks to the use of judiciously chosen excipients, they can also increase API membrane permeability, inhibit efflux transporters, and enhance lymphatic transport (Fricker et al., 2010; O'driscoll and Griffin, 2008).

Lipid-based drug delivery systems include in particular lipid nanoparticles (Malzert-Fréon et al., 2010, 2006) and nanoemulsions (Constantinides et al., 2008; de Villiers et al., 2009). Lipid nanoparticles refer to solid colloidal particles ranging in size from 10 nm to 1 μm (Kreuter, 1994), and are mainly formulated through the generation of nanoemulsions acting as templates for nano-precipitation or lipid nano-crystallization (Anton et al., 2008). Nanoemulsions are highly biocompatible, and isotropic dispersed systems consisting of nanoscale oil droplets (typically, 20–300 nm), which may be formulated by various processes of high or low energy. Low energy approaches are very attractive since they are effective at producing fine droplets, require low equipment, are simple and low costly to use, and are easy to implement (Chang et al., 2013). The two commonly reported low-energy nanoemulsification methods are the phase inversion

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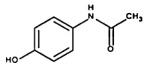
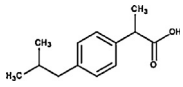
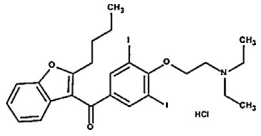
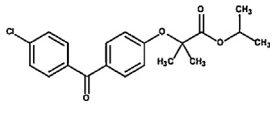
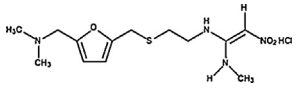
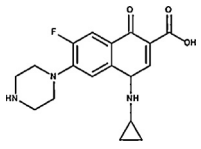
temperature method (PIT method) and the spontaneous emulsification method. The latter method allows generating nanoemulsions at room temperature without use of any organic solvent and heat. It only requires addition of an aqueous phase into an anhydrous solution made of natural or synthetic oils with surfactants and API to be encapsulated, with gentle stirring at constant temperature (Forgiarini et al., 2001). Even if nanoemulsions are nanocarriers particularly appealing for oral administration especially as Self Emulsifying Drug Delivery Systems (SEDDS) (Kotta et al., 2014; Neupane et al., 2014), they can be also envisaged for other administration routes like intranasal (Kumar et al., 2008), ophthalmic (Gallarate et al., 2013), pulmonary (Nasr et al., 2012), topical ways (Schwarz et al., 2012), and can be employed for intraveinous administration of drugs after adjustment of fundamental physico-chemical properties like droplets mean diameter, osmolarity, pH, and sterility (Kelmann et al., 2007; Mahmoud et al., 2014; Ragelle et al., 2012).

Usually, design of an effective nanoemulsion first implies assessment of the solubility of each lead compound or each drug candidate in various lipid excipients, cosolvents and surfactants to identify appropriate vehicles with satisfactory solubility as well as chemical and physical stability (Li and Zhao, 2007). Nevertheless, such a solubility screening is time-consuming, labor-intensive, and requires a large amount of compound. The *in silico* prediction of API solubility in excipients could be useful, but is difficult to develop because of the complex nature of the excipients, the dominance of interfacial effects, and the presence of complex interactions between compounds (Rane and Anderson, 2008). Even if parallel formulation screening approaches using miniaturized solvent-casting are proposed in the literature (Dai et al., 2007), the formulation of a versatile nanoemulsion able to optimize the delivery of structurally very diverse APIs, and suitable for different administration ways, and in particular by the most restricting one, *i.e.* the intraveinous way, is a poorly explored approach so far.

In a previous formulation work, by means of the low energy phase inversion temperature method, and thanks to the introduction of macrogolglyceride (Labrasol®) acting as a solubility enhancer, we developed lipid nanoparticles able to encapsulate drugs presenting limited solubility in both water and lipids, with high loading rates, and without using organic solvents (Malzert-Fréon et al., 2010). Then, considering that Labrasol® is also known as an interesting excipient to formulate self-emulsifying nanoemulsions, we attempted to upgrade our delivery systems towards lipid nanoemulsions produced by spontaneous emulsification. Furthermore, these nanoemulsions contain Kolliphor® HS15 which is known as a powerful solubilizer in injectable preparations (Li and Zhao, 2007).

In this article, we propose to render these nanoemulsions administrable by different routes and in particular by the intraveinous route. To evaluate the versatile character of these nanoemulsions, and *in fine* to propose an early formulation for numerous promising drugs, six model APIs with different physico-chemical properties (*i.e.* log *P*/log $D_{7.4}$, water solubility, molecular weight, pKa) were selected in order to gain better understanding of their formulate-ability in the designed nanoemulsion platform. The resulting API-loaded nanoemulsions were characterized in

Table 1
Physico-chemical properties of the studied APIs, from [a] (Avdeef, 2012); [b] (Kalantzi et al., 2006); [c] (Potthast et al., 2005); [d] (Lamprecht et al., 2002); [e] (Elgart et al., 2013); [f] (Vogt et al., 2008); [g] (Griffin et al., 2014); [h] (Kortejärvi et al., 2005); [i] (Botté et al., 2011); [j] (Olivera et al., 2011). Log $D_{7.4}$ values which were not referenced in [a] (Avdeef, 2012) were predicted by using ChemAxon software (noted * in this case). Log *P* of ciprofloxacin was found in [i] instead of [a].

Compound	Chemical structures	*Mw* (g/mol)	*Tm* (°C)	pKa[a]	Log P[a]/Log $D_{7.4}$*	Phosphate buffer pH 7.4 solubility (mg/mL)	BCS class
Paracetamol		151	171	9.63	0.34/0.34	14.3[b]	I
Ibuprofen		206	78	4.45	4.13/0.45	3.44[c]	II[c]
Amiodarone HCl		682	162	9.06	7.8/6.53*	0.001[d]	II[e]
Fenofibrate		361	84	-4.9	5.3/5.28*	0.0003[f]	II[g]
Ranitidine HCl		351	142	2.11 8.31	1.3/6.53*	>550[h]	III[h]
Ciprofloxacin		331	268	6.16 8.62	2.3[i]/−1.6*	0.07[j]	IV[j]