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Solubilization of active ingredients of different polarity in Pluronic® micellar solutions – Correlations between solubilizate polarity and solubilization site

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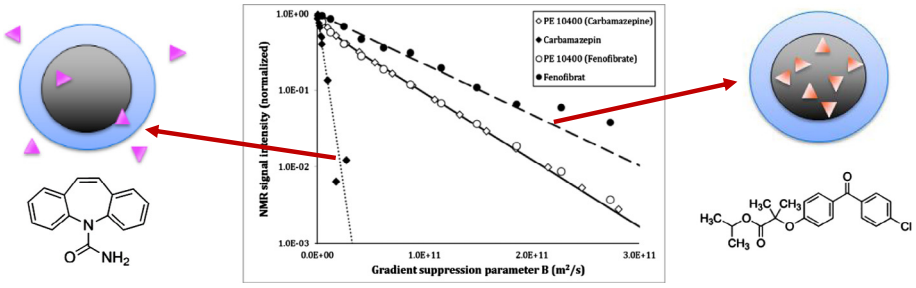
GRAPHICAL ABSTRACT



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ABSTRACT

The solubilization of two pharmaceutically active ingredients (AI) with significantly different water solubility, namely carbamazepine and fenofibrate (solubility of 150 ppm and 10 ppm, respectively), has been investigated using a series of Pluronics® (Poloxamers) containing different ethylene oxide and propylene oxide (EO/PO) units in the molecule. The results show largely enhanced solubilization of fenofibrate by Pluronic® micelles that increases with the PPO chain length provided the temperature is above the critical micelle temperature (cmt). In contrast the more water-soluble carbamazepine only shows a moderate increase in solubilization upon addition of Pluronics®. Small angle neutron scattering (SANS) and pulsed field gradient (PFG) NMR experiments show that the solubilization of fenofibrate occurs in the core of the micelles, whereas carbamazepine shows no direct association with the micelles. These clearly different solubilization mechanisms for the two AIs were confirmed by Nuclear Overhauser Enhancement Spectroscopy (NOESY) experiments, which show that fenofibrate interacts only with the PPO core of the micelle, whereas carbamazepine interacts with both PPO and PEO similarly. Accordingly, the large enhancement of the solubilization of fenofibrate is related to the fact that it is solubilized within the PPO core of the Pluronic® micelles, while the much more moderate increase of carbamazepine solubility is attributed to the change of solvent quality due to the presence of the amphiphilic copolymer and the interaction with the EO and PO units in solution.

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1. Introduction

The bioavailability of sparingly soluble pharmaceutical active ingredient (AI) molecules is often enhanced by micellar solubilization due to the presence of surfactants [1–4]. This is an important aspect as a sufficiently high content in aqueous solution and the transport through membranes etc. has to be facilitated in order to have efficiently working pharmaceutical formulations. However, this depends largely on the type of solubilizate that will have specific and individual interactions with a given surfactant [5]. Accordingly, one of the major challenges in pharmaceutical formulations is to develop effective surfactant solubilizer systems [6,7].

So far there has been little fundamental work published relating the effect of the molecular architecture of the solubilizer on its ability to solubilize a given hydrophobic compound and on how it influences their specific interaction with the solubilizate. In the pharmaceutical industry, solubilization is most commonly examined by 'trial and error' using high-throughput screening. That method helps to determine a suitable solubilizer without the need of knowledge in solubilization processes. However, an understanding of solubilization mechanisms at a molecular level and the specific interaction with the surfactant would allow the design of effective solubilizers in a more systematic and targeted manner. Here one also has to consider that the relevant solubilizates may differ largely with respect to their water solubility, polarity, and molecular architecture, i.e., one may not expect a general answer for enhanced solubilization but concepts that are adapted to the particular properties of the solubilizate.

Accordingly, the main objective of this work was to find a relationship between the surfactant structure and its solubilization capacity for different types of solubilizates. For this purpose we have used two different pharmaceutical AIs, namely fenofibrate and carbamazepine, which differ substantially both in their chemical structure and polarity, with carbamazepine being much more water-soluble than fenofibrate (150 ppm vs. 10 ppm). Several solubilization techniques and surfactants have been applied to solubilize carbamazepine [8–11] and fenofibrate [12–14] in order to enhance their bioavailability and to determine the behavior of these systems at different temperatures and salinities. Such experiments showed that carbamazepine becomes solubilized by the micelles of alkyltrimethylammonium and alkylsulfates in a similar fashion and the molar solubilization capacity increases with increasing alkyl chain length of the surfactant [15]. Similar finding have also been reported for the solubilization capacity of fenofibrate in SDS solution [16]. For the case of SDS also the effect of surfactant purity and electrolyte content on the solubilization capacity and the dissolution rate has been investigated [17]. In general, the dissolution rate of carbamazepine was found to be directly proportional to the SDS concentration [14,18]. The solubilization of carbamazepine could be enhanced in a targeted manner by variation of the chain length of amphiphilic block copolymers and at higher temperatures, whereas the addition of salt had no effect. For the case of nonionic surfactants it was recently found that carbamazepine is typically located within the palisade layer of such nonionic micelles, i.e., it prefers the interaction with the EO groups [10] and also nonionic microemulsions are suitable to improve the solubilization of carbamazepine [19]. Fenofibrate showed good incorporation into microemulsions with a distinct dependence on the hydrophobic chain composition [20].

Prevalent solubilizers are Pluronics® (Poloxamers) consisting of various ethylene oxide/propylene oxide EO/PO blocks, whose properties can be varied in a wide range via the EO/PO ratio and their chain lengths [21,22]. In addition, Pluronics® are very suitable for such solubilization studies as they are basically approved for formulations in the fields of pharmacy or agriculture. Extensive studies on Pluronic® structures were carried out at different temperatures, concentrations and pH values showing a large influence of the molecular architecture on the phase behavior [23–28]. Pluronics® are widely applied to form thermodynamically stable micellar systems in water that are able to solubilize insoluble AIs [29,30] and oils [31]. These solubilized hydrophobic compounds can also influence the Pluronic® structure [32–34], e.g. by increasing the aggregation number, the micellar size and the fraction of polymer micellized. In drug delivery systems, Pluronics® are used to enhance bioavailability, metabolic stability and circulation time of the drug [35,36]. These properties also enable Pluronics® to act as a scavenger for cardiotoxic drugs [37]. It might also be noted that the presence of compounds which are well solubilized within the PPO core of Pluronic micelles (which typically applies to moderately polar oils) also have a tendency to stimulate the formation of micelles aggregates, so that they will be formed at much lower concentration or temperature [38–40].

We focused our investigation on the experimental determination of the solubilization capacity of various Pluronics® with fenofibrate and carbamazepine and to find correlations between the solubilization performance and the molecular structure of solubilizate and Pluronic®. For a further structural understanding we performed a structural characterization of these systems by means of small angle neutron scattering (SANS) to determine the size and structure of the Pluronic® micelles. Furthermore pulsed field gradient (PFG)-NMR and nuclear Overhauser effect (NOESY)-NMR were applied to determine the solubilization sites of the AIs. The results of such a comprehensive characterization then shall provide the basis for a thorough understanding of the details of the solubilization process that can be applied to develop more effective solubilization systems in the future.

2. Materials and methods

2.1. Materials

2.1.1. Active ingredients

Two pharmaceutical compounds, carbamazepine and fenofibrate (both ⩾99%), were used. Their structure is given in Fig. 1. Both AIs were supplied by Sigma-Aldrich.

2.1.2. Surfactants

Different Pluronics® were supplied by BASF SE, Ludwigshafen Germany. They are listed in Table 1 which gives the trade name, molecular structure, hydrophilic-lipophilic balance (HLB)-numbers and values for the critical micelle temperature (cmt) at different concentrations of some Pluronics®.

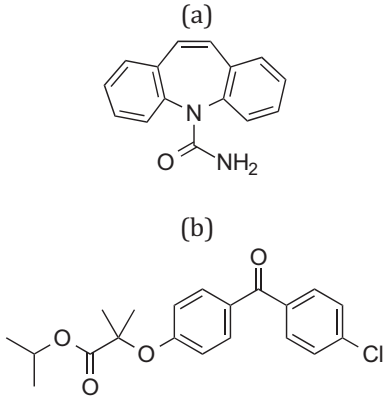

Fig. 1. (a) Carbamazepine and (b) fenofibrate.