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Solubility of Ketoprofen in colloidal PLGA

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ABSTRACT

The successful design and development of pharmaceutical drug–polymer composites requires detailed information about the phase behavior of the drug–polymer binary system. This study presents an extended investigation of the phase equilibrium established between the chiral anti-inflammatory drug Ketoprofen (KET) and the bio-compatible and biodegradable polymer poly(lactic-co-glycolic) acid 5050 (PLGA). Equilibration experiments were carried out in aqueous suspensions of KET crystals together with PLGA in the form of spherical amorphous nanoparticles obtained by supercritical fluid extraction of emulsions (SFEE). The influence of temperature was studied in the range between 0 °C and 50 °C, while the effect of KET chirality was investigated by using two different crystalline forms of KET, namely enantiopure S-KET and a racemic compound, RS-KET, in equilibration experiments. It was found that the level of KET established in PLGA at equilibrium increases with temperature, e.g. from 6.9 wt.% at 20 °C to 25.8 wt.% at 40 °C for the case of S-KET. At each temperature level, the solubility of KET in PLGA was lower for equilibration with RS-KET, significantly higher for equilibration with S-KET, and the highest for simultaneous equilibration with both crystalline species. Experimental solubility data of KET in PLGA were also described in a model based on the Sanchez–Lacombe equation of state. For experiments carried out at 10 °C or below, an equilibrium state could not be reached even after a prolonged equilibration period, presumably because the polymer phase had undergone a transition into the glassy state. For this temperature range, where an experimental equilibration is not any more possible, the model may be used to estimate the solubility of KET in PLGA by extrapolation.

1. Introduction

The microencapsulation of active pharmaceutical ingredients into polymeric drug delivery systems is a promising and widely used method in drug formulation technology, enabling a number of interesting novel pharmaceutical delivery concepts. For instance, in controlled drug release applications, encapsulation enhances and prolongs the effectiveness of active ingredients, while in drug targeting, polymeric particles are used as carrier vehicles for the targeted delivery of the drug to a specific site of action.

The entrapping of an active ingredient into polymeric microparticles may be achieved by different techniques. Among the conventional processes, the most prominent and widely applied are spray drying, emulsion processes with subsequent solvent extraction or evaporation, and anti-solvent processes such as coacervation. A number of new manufacturing methods are based on the application of supercritical fluids, i.e. mostly $scCO_2$, as anti-solvent, aerosol propellant and solvent-extracting agent (Yeo and Kiran, 2005). In this context, the process called supercritical fluid extraction of emulsions (SFEE) is a relatively new technique that has been particularly successful in the formulation of micro- and nanoparticles of water-insoluble pharmaceutical polymers such as poly(lactic-co-glycolic) acid (PLGA) (Kluge et al., 2009a).

In many cases, the co-formulation of drug and polymer aims at producing a solid solution where the drug is dispersed in the amorphous polymer matrix at a molecular level. However, the entrapment of the active ingredient into the polymeric material may be thermodynamically unfavorable, especially if high drug loadings are desired, or if the mutual affinity between drug and polymer is low. Such co-formulations would bear the risk of reduced long-term stability and shelf-life, representing a major hurdle with respect to potential applications (Vasanthavada et al., 2005). Hence, the design and development of such co-formulations could strongly benefit from a priori information about the compatibility of drug and polymer, in order to select a promising polymer excipient forming stable co-formulations and allowing for maximal drug load. However, there is still a lack of such data, as well

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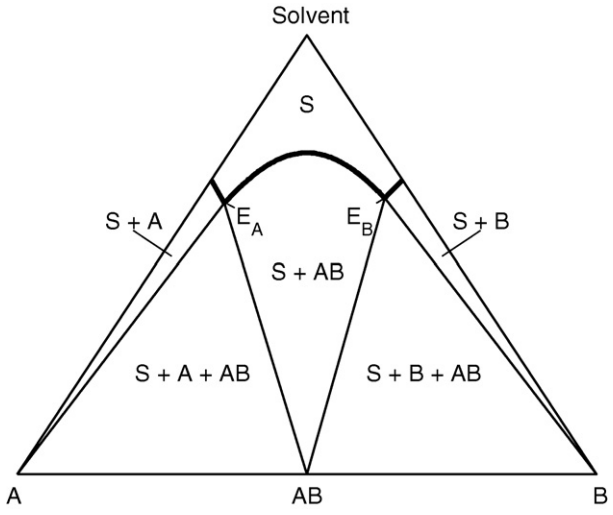

Fig. 1. Scheme of a ternary phase diagram for the solution of a compound-forming chiral system such as KET. (A) S-KET, (B) R-KET, (AB) the crystalline compound RS-KET and (S) the solution. The bold line represents the solubility of the relevant solid form of KET in PLGA. Eutectic points are designated as E_A and E_B, respectively.

as of robust and reliable experimental methods to generate such information in an accurate and efficient manner.

A crucial step in this direction is the determination of the level of drug present in the polymer phase if the latter is fully equilibrated with the pharmaceutical compound in the crystalline state, i.e. the solubility of the drug in the polymeric matrix, which in this case represents the solvent. In practice, equilibration is hardly achieved in short times since it is based on the slow diffusion of molecules inside the polymer phase. However, the equilibration process may be facilitated by using polymeric nanoparticles, where diffusion distances are short, and consequently, equilibration is fast. In this context, a previous study has successfully demonstrated that solvent-free PLGA nanoparticles as obtained by SFEE processing may be used to investigate the equilibration of PLGA with crystalline Ketoprofen (KET), a chiral molecule belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs) (Kluge et al., 2009b).

In order to further underline the potential that arises from SFEE as a viable manufacturing technique and in order to highlight a novel application of and opportunity for this process, this work presents the results of an extended study, investigating the temperature dependence of the phase equilibrium between KET and PLGA in the range between 0 °C and 50 °C, as well as the effect of KET chirality. While it may be anticipated that the solubility of KET in PLGA increases with the temperature, the expected effect of chirality on equilibrium needs to be elaborated in more detail. As a chiral molecule, KET exists in nature as two mirror-symmetric enantiomers, S-KET and R-KET. In the solid state KET forms a racemic compound, i.e. a crystal structure with a one to one ratio of S-KET and R-KET, which is crystallographically different from the enantiopure crystals of S-KET and R-KET (Lu et al., 2009). The characteristic symmetric behavior of such a system in solution is shown qualitatively in Fig. 1. At temperatures below the melting point, there are three thermodynamically stable solids of KET, namely crystalline S-KET (A), crystalline R-KET (B), and the racemic crystalline compound further referred to as RS-KET (AB). Depending on the ratio of the two enantiomers in the solution, equilibrium is always established with the relevant solid. Only in the transition from one domain to the other, the solution is simultaneously in equilibrium with two solids, i.e. with one of the enantiopure crystals and with the racemic compound. The fixed composition of the solution in these transition points is referred to as the eutectic composition, and is designated with E_A and E_B in Fig. 1.

Racemic RS-KET as well as enantiopure S-KET are commercially available, and have been used for the preparation of seed crystals. Hence, if PLGA is equilibrated with crystals of S-KET or RS-KET, solutions of enantiopure or racemic composition, respectively, are obtained. If PLGA is equilibrated with both crystalline forms simultaneously, a solution with eutectic composition is attained.

2. Experimental

2.1. Materials

Carbon dioxide (CO_2; 99.9%, from PanGas, Schlieren, Switzerland), poly(lactic-co-glycolic) acid 5050 DLG 5A (PLGA; Lakeshore Biomaterials, Birmingham, AL, United States), poly(vinyl alcohol) 4-88 (PVA), racemic Ketoprofen (RS-KET), enantiopure S-Ketoprofen (S-KET), dimethylsulfoxide (DMSO), trifluoroacetic acid (TFA), ethyl acetate (all from Sigma–Aldrich, Buchs, Switzerland), ethanol (analytical grade, Scharlau, Sentmenat, Spain), and n-hexane (Merck KGaA, Darmstadt, Germany) were used as received.

2.2. Emulsion preparation and SFEE processing

The organic solutes, i.e. PLGA, RS-KET or S-KET, or specified mixtures thereof, were dissolved at 10 wt.% in ethyl acetate saturated with water. A 1 wt.% solution of PVA was prepared in water saturated with ethyl acetate. The organic and aqueous solutions were used at a weight ratio of 1:4 to form an oil-in-water (o/w) emulsion upon ultrasonication with a Branson Sonifier 450 (Skan AG, Basel, Switzerland). Using 100 ml of emulsion, a sonication time of 2 min was applied at maximal power output while cooling the emulsion on ice.

Directly after emulsion preparation, the organic solvent was extracted from the dispersed micelles using $scCO_2$ as extracting agent in the supercritical fluid extraction of emulsions (SFEE) process. A scheme of the experimental setup used for the SFEE experiments as well as a detailed description of the process can be found in a previous study (Kluge et al., 2009a).

When only PLGA was used for the preparation of the emulsion and for SFEE processing, the procedure led to the formation of pure PLGA nanoparticles, which were then used for the impregnation experiments described in Section 2.4. Otherwise, if KET was directly dissolved in the organic micelles together with PLGA, SFEE processing led to KET–PLGA composite particles, as they were used for the de-supersaturation experiments described in Section 2.5.

2.3. Preparation of Ketoprofen crystals

Crystals of the racemic compound RS-KET and of enantiopure S-KET were prepared as follows. In a first step, either RS-KET or S-KET was used for the preparation of an emulsion and subsequent SFEE processing as described above. In all cases, this step led to a suspension of solvent-free amorphous precursor particles, and these product suspensions were stored in 40 ml aliquots that were allowed to recrystallize for 2 days. After recrystallization, each aliquot contained approximately 1 g of crystals, i.e. either the compound, RS-KET, or enantiopure crystals of S-KET. In order to remove all crystal fragments too small for sedimentation, the crystals were repeatedly centrifuged at 4000 rpm (Eppendorf Centrifuge 5810R) and resuspended in pure water until the supernatant was clear to the eye and considered free of suspended solids. The obtained fraction of large crystals of either RS-KET or S-KET was resuspended in water and used for equilibration experiments. Fig. 2 allows for a comparison of seed crystal morphology as compared to the corresponding raw material. It can be seen that the recrystallized