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Modeling and predicting the influence of variable factors on dissolution of crystalline pharmaceuticals

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HIGHLIGHTS

- Solubilities of poorly-soluble and soluble APIs were modeled using PC-SAFT.
- Dissolution profiles of poorly-soluble and soluble APIs were measured.
- Dissolution mechanism of APIs was analyzed by a chemical-potential-gradient model.
- Dissolution mechanism of APIs can be changed dependent on their water solubilities.
- Dissolution profiles of APIs were predicted in accordance with experimental data.

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ABSTRACT

In this work, the dissolution profiles of different crystalline active pharmaceutical ingredients (APIs), which show a diverse water solubility (paracetamol > hydrochlorothiazide > trimethoprim > naproxen > indomethacin > cinnarizine) were measured in water at different temperatures and stirring speeds using a rotating disk system. Meanwhile, the dissolution mechanism of these APIs was analyzed by using a two-step chemical-potential-gradient model. The solubilities and activity coefficients of the investigated APIs were calculated by using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). It was found out, that the dissolution mechanism of different crystalline APIs in water can be different dependent on their water solubilities. Additionally, an increase in both, the surface reaction and diffusion rate constants for all investigated crystalline APIs was observed with an increase in temperature and stirring speed. By the use of linear correlations between the API surface reaction and diffusion rate constants with the temperature and stirring speed, the dissolution profiles of the selected APIs could be predicted as function of temperature and stirring speed with high accuracy compared to the experimental data.

1. Introduction

The dissolution characteristics of active pharmaceutical ingredients (APIs) play an important role in pharmaceutical development (Blagden et al., 2007; Garcia et al., 1999; Lawrence, 2008; Shefter and Higuchi, 1963). Within the last decades a huge effort has been made to design pharmaceuticals with optimal dissolution performance (Dash et al., 2010; Gibson, 2009; Lewis et al., 1998; Stella and Nti-Addae, 2007). As different factors, such as medium composition, pH, solid state of the API, API solubility, temperature and stirring speed often influence the API dissolution (Amidon et al., 1995; Dressman et al., 1998; Ei-Arini and Leuenberger, 1995; Kostewicz et al., 2004; Rao et al., 1990; Snyder and Doherty, 2007; Tsinman et al., 2009), it is important to identify the mechanisms of API dissolution. For API product development, more realistic factors (e.g. a number of excipients and realistic dissolution methods) should be considered and investigated. Intrinsic dissolution measurements of the APIs were often performed to investigate the influence of different factors on the API dissolution. As experimental measurements of API dissolution under different conditions are often cost- and time-consuming, the use of appropriate theoretical models to describe and predict the dissolution profiles of APIs is advantageous to reduce the experimental efforts and to increase the effectiveness of pharmaceutical product design. In previous works of different groups, several models (e.g. the Noyes-Whitney equation (Noyes and Whitney, 1897), the Nernst and Brunner film theory (Brunner, 1903; Nernst, 1904), the Higuchi

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model (Higuchi, 1961), the Weibull model, the Hixon-Crowell model, the Korsmeyer-Peppas model (Korsmeyer et al., 1983), the Hopfenberg model (Hopfenberg, 1976), the Baker-Lonsdale model (Baker and Lonsdale, 1974) and the Gompertz model (Dash et al., 2010), etc.) were proposed to describe the dissolution profiles of pure crystalline pharmaceuticals and their formulations under various conditions. Recently, a two-step chemical-potential-gradient model combined with the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT (Gross and Sadowski, 2001)) was developed to analyze the API dissolution mechanism (Ji et al., 2015; Paus et al., 2015b, 2015d) based on the work of Ji et al. (2010) and Lu et al. (2011). In previous works, the influences of pH, media composition and amorphous formulation on the dissolution of pooly-soluble APIs were already investigated (Ji et al., 2015; Paus et al., 2015b, 2015d). In addition to that, the analysis of the influence of variable factors as API solubility, temperature and stirring speed on the API dissolution mechanism are of high importance to characterize the API performance in aqueous media. Here, the application of a mechanistic model that provides new insights into the API dissolution mechanism turns out to be advantageous. Thus, in this work, cinnarizine (CIN), indomethacin (IND), naproxen (NAP), hydrochlorothiazide (HCT), trimethoprim (TMP) and paracetamol (PARA) were selected as model APIs, as their solubilities cover a relatively wide range. The chemical structures of these APIs are presented in Fig. 1. The influences of the API solubility, temperature and stirring speed on the dissolution mechanism of these model crystalline APIs were analyzed by using the two-step chemical-potential-gradient model. Additionally, the dissolution profiles of these crystalline APIs were predicted as function of temperature and stirring speed.

2. Model description

2.1. Chemical-potential-gradient model

In the dissolution process of a crystalline API in a solution, two main steps are considered as depicted in Fig. 2. Within the first step, the disintegration of the API crystals and the hydration of the API molecules take place, which is called the assumed surface reaction. The thermodynamic driving force of the surface reaction is given by the chemical-potential gradient of the API between the solid phase μ^S_{API} and the solid–liquid interface μ^I_{API}. Within the second step, the hydrated API molecules diffuse from the solid–liquid interface into the solution bulk phase (see Fig. 2). The thermodynamic driving force of this diffusion step is given by the chemical-potential gradient of the API between the solid–liquid interface μ^I_{API} and the solution bulk phase μ^B_{API}.

The chemical potential of the API in the solid phase μ^S_{API} equals to that in its saturated solution μ^L_{API} based on the solid–liquid equilibrium (SLE) (Prausnitz et al., 1998), and it is calculated by Eq. (1).

$$\mu^S_{API} = \mu^L_{API} = \mu^L_{0API} + RT \ln (a^L_{API}) \quad (1)$$

In Eq. (1), μ^L_{0API} is the chemical potential of the API in the standard state (here the pure liquid API) in J/mol, R is the ideal gas constant in J/mol/K, T is the temperature in K and a^L_{API} is the activity of the API in the saturated solution.

The chemical potential of the API at the solid–liquid interface μ^I_{API} is calculated by Eq. (2).

$$\mu^I_{API} = \mu^L_{0API} + RT \ln (a^I_{API}) \quad (2)$$

In Eq. (2), a^I_{API} is the activity of the API at the solid–iquid interface, which can be determined by the Statistical Rate Theory

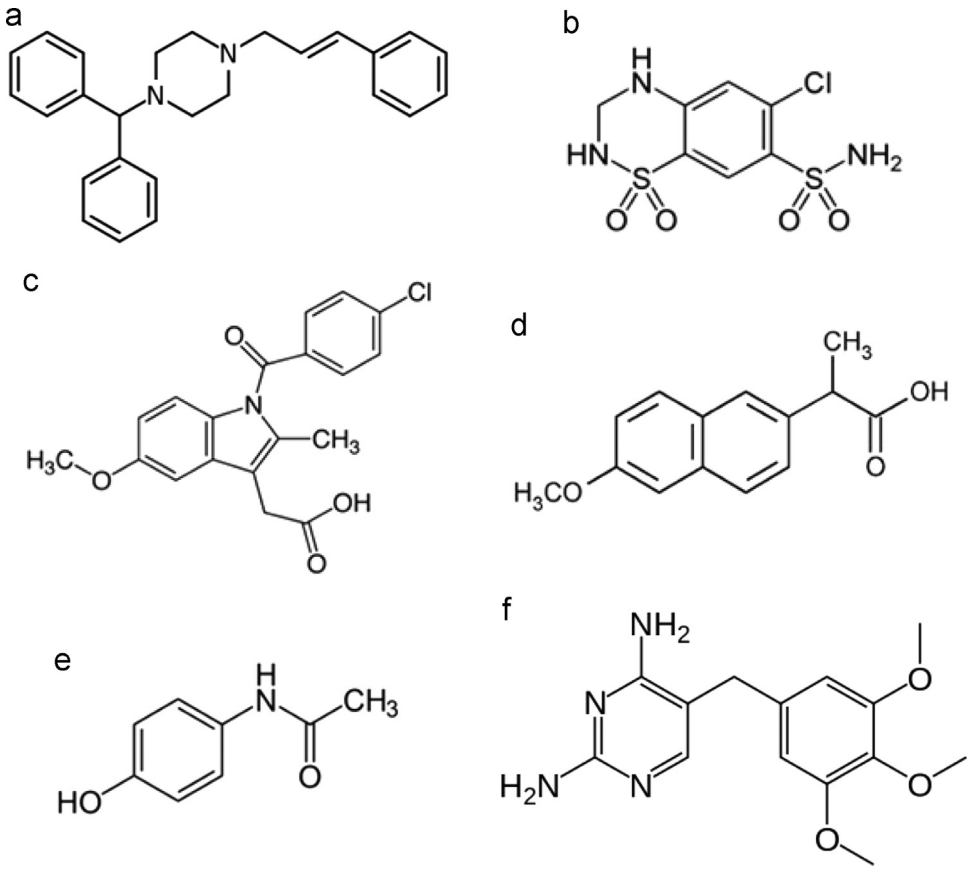

Fig. 1. Chemical structures of CIN (a), HCT (b), IND (c), NAP (d), PARA (e) and TMP (f).