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Research Paper

A novel approach for predicting the dissolution profiles of pharmaceutical tablets

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ABSTRACT

In this paper, the intrinsic dissolution profiles of naproxen (NAP) at pH values of 1.5 and 3.0 and of trimethoprim (TMP) at pH values of 1.5, 3.0, 5.0, 6.5 and 7.2 were measured. Meanwhile, the dissolution profiles of NAP and TMP from cylindrical tablets were measured at different temperatures (298.15 K, 305.15 K, 301.15 K and 310.15 K) and stirring speeds (50 rpm, 100 rpm and 150 rpm) as well as at different pH values (1.5, 3.0, 5.0, 6.5 and 7.2). Additionally the pH-dependent solubilities of both APIs were measured and modeled. The chemical-potential-gradient model combined with the perturbed-chain statistical associating fluid theory (PC-SAFT) was applied to predict the dissolution profiles of the cylindrical tablets of NAP and TMP under different conditions based on the analysis of their intrinsic dissolution profiles as well as on the determination of the surface-area reduction of the API tablets during dissolution. It was shown that the predicted dissolution profiles of the tablets under different conditions were in a good accordance with the experimental findings.

1. Introduction

Poorly-soluble active pharmaceutical ingredients (APIs) often show complex dissolution characteristics. The analysis of the dissolution mechanisms and the prediction of API dissolution profiles from intrinsic dissolution as well as from actual tablets are challenging topics in pharmaceutical development. In the last decades, several empirical, semi-empirical and mechanistic mathematical models have been proposed to describe the API dissolution profiles from a variety of solid pharmaceutical dosage forms, e.g. matrix systems [1–3], erodible tablets [4,5], microspheres [6], hydrogels [7], powders [8] and immediate release tablets [9–12]. Siepmann and Siepmann [13] gave a detailed review of the empirical, semi-empirical and mechanistic mathematical models that have been applied to describe the API dissolution profiles from solid pharmaceutical dosage forms. In their review, they pointed out, that currently the predictive capability of empirical and semi-empirical models is often quite low and the application of mechanistic mathematical models that offer a deeper understanding of API dissolution mechanism on a molecular scale is usually difficult to apply due to their complexity [5]. In addition to that, more and more new APIs are poorly soluble in water [14–16] which makes it rather difficult to apply theoretical models to describe their dissolution profiles as several steps are involved in the complex dissolution process [8,17–19]. Thus, the development of a theoretical model that enables a deep insight into the dissolution mechanism of these kinds of APIs, a sufficient applicability and a high predictive capability is still challenging in pharmaceutical science and development.

In previous works, on the basis of the work of Ji et al. and Lu et al. [20,21], a two-step chemical-potential-gradient model was developed to analyze the dissolution mechanism of several crystalline APIs and their formulations under various conditions based on their intrinsic dissolution profiles [22–24]. According to the theory of this model, two consecutive steps, namely the surface reaction and diffusion, were considered and expressed in terms of the chemical-potential gradient of the API (the thermodynamic driving force) and the corresponding surface-reaction and diffusion rate constants (from kinetic aspect) [20,22–24]. Within this model, the perturbed-chain statistical associating fluid theory (PC-SAFT) [25] was applied to determine the solubilities and activity coefficients of the APIs in the solution. Furthermore, this model was also used to predict the intrinsic dissolution profiles of APIs and their formulations as function of stirring speed, temperature and pH value of the media with a high accuracy compared to the experimental data [22–24,26]. For modeling the API intrinsic dissolution profiles, it was assumed that the effective surface area of the dissolving API which contacted the media was a constant during the API dissolution. However, in case of oral administered APIs, the

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surface area of the cylindrical tablet (or capsule) changes during the dissolution process and thus it is clear that this assumption for the API tablet dissolution does not hold. Katzhendler et al. [27] developed a general mathematical approach based on the Hopfenberg equation [28] to describe the API dissolution profile from erodible tablets which underwent surface erosion. Although the model could be used to well represent the tablet dissolution profiles, the rate constants of tablet erosion had to be fitted to experimental dissolution data [27]. Therefore, in this work, an extension of the chemical-potential-gradient model was developed to fully predict the dissolution profiles of the actual cylindrical tablets only based on the analysis of the API intrinsic dissolution profiles as well as on the determination of the surface-area reduction of the API tablets during dissolution.

Naproxen (NAP), a weak acid, and trimethoprim (TMP), a weak base, were selected as model APIs as they are both poorly soluble in water and show different physicochemical properties. The chemical structures of these APIs are shown in Fig. 1.

The intrinsic dissolution profiles of NAP at pH values of 1.5 and 3.0 and of TMP at pH values of 1.5, 3.0, 5.0, 6.5 and 7.2 were measured. The dissolution profiles of NAP and TMP from cylindrical tablets were measured at different temperatures (298.15 K, 305.15 K, 310.15 K and 315.15 K) and stirring speed (50 rpm, 100 rpm and 150 rpm) as well as at different pH values (1.5, 3.0, 5.0, 6.5 and 7.2). Meanwhile, the dissolution mechanisms of NAP and TMP for their intrinsic dissolution at the selected pH values were analyzed. Furthermore, the dissolution profiles of the cylindrical tablets of NAP and TMP under different conditions were predicted and the predicted results were compared with the experimental findings, as schematically shown in Fig. 2.

2. Theory

2.1. Chemical-potential-gradient model

The API dissolution process contains two main consecutive steps [20,22,23]. Firstly, the disintegration of API from the crystal lattice and the hydration of the API take place, which is the so-called surface reaction step. Meanwhile, the solid–liquid interface is formed. Secondly, the diffusion of the API molecules from the solid–liquid interface into the bulk phase of the medium takes place. As detailed introduced in previous works, the chemical-potential-gradient model describes the dissolution rate of an API in a medium in terms of the chemical-potential gradient of the API (thermodynamic driving force) and the rate constants (from the kinetic aspect) [22–24]. Within this model, the API dissolution rate is determined by Eq. (1).

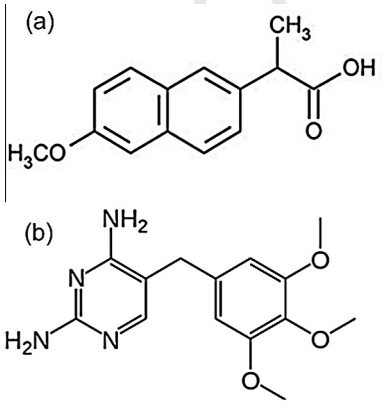

Fig. 1. Chemical structures of NAP (a) and TMP (b) used in this work.

$$J_{API} = V \cdot \frac{dc^B_{API}}{dt} \cdot \frac{1}{A} \quad (1)$$

In Eq. (1), J_{API} is the dissolution rate of the API in mol/(m^2 s), V is the volume of the dissolution medium in m^3; c^B_{API} is the concentration of the API in the bulk phase of the medium in mol/m^3; t is the time in s; A is the surface area of the dissolving API in contact with the dissolution medium in m^2.

As detailed introduced in our previous work [22–24], the surface reaction rate and the diffusion rate are described by Eqs. (2) and (3), respectively.

$$J_{API} = k_S\left(\frac{\mu^S_{API}}{RT} - \frac{\mu^I_{API}}{RT}\right) = k_S(\ln a^I_{API} - \ln a^I_{API}) \quad (2)$$

$$J_{API} = k_d\left(\frac{\mu^I_{API}}{RT} - \frac{\mu^B_{API}}{RT}\right) = k_d(\ln a^I_{API} - \ln a^B_{API}) \quad (3)$$

In Eqs. (2) and (3), μ^S_{API}, μ^I_{API} and μ^B_{API} are the chemical potentials of the API in the solid phase, at the solid–liquid interface and in the bulk phase, respectively, in J/mol. k_S and k_d are the surface-reaction rate constant and the diffusion rate constant in mol/(m^2 s). R is the ideal gas constant in J/(mol K), T is the temperature in K. a^I_{API}, a^I_{API} and a^B_{API} are the API activity in the saturated solution, at the solid–liquid interface and in the bulk phase, respectively.

The instantaneous API transport rate across the solid–liquid interface can be described by the Statistical Rate Theory established by Dejmek and Ward [29,30], as expressed in Eq. (4).

$$\begin{aligned} J_{API} &= \left(x^L_{API}\alpha_1 a_f\sqrt{T} + x^L_{API}\alpha_2\emptyset a_f 0.51\sqrt{\frac{\omega^3}{v}}\delta^2\right) \\ &\quad \times \left\{\exp\left(\frac{\mu^S_{API} - \mu^I_{API}}{RT}\right) - \exp\left(\frac{\mu^I_{API} - \mu^S_{API}}{RT}\right)\right\} \\ &= \left(x^L_{API}\alpha_1 a_f\sqrt{T} + x^L_{API}\alpha_2\emptyset a_f 0.51\sqrt{\frac{\omega^3}{v}}\delta^2\right)\left(\frac{a^I_{API}}{a^I_{API}} - \frac{a^I_{API}}{a^I_{API}}\right) \end{aligned} \quad (4)$$

x^L_{API} is the API solubility in the media in mole fraction, α_1 and α_2 are the proportionality constants, $\emptyset$ is a constant fraction of molecules that strike the solid surface, α_f describes the fraction of the area of the solid–liquid interface which is available for the transport of molecules from the medium, ω is the stirring speed in round/s, δ is the thickness of the diffusion layer in m [22,23,29,30], v is the kinematic viscosity of the medium in m^2/s. In this work, the temperature-dependent kinematic viscosities of water were taken from the literature [31] and were correlated by: $v/(\mathrm{m}^2/\mathrm{s}) = 2.248 \cdot 10^{-10} \cdot (T/°\mathrm{C})^2 - 3.195 \cdot 10^{-8} \cdot (T/°\mathrm{C}) + 1.572 \cdot 10^{-6}$.

In Eqs. (2)–(4), the API activity can be calculated according to Eq. (5).

$$a_{API} = x_{API}\gamma_{API} \quad (5)$$

In Eq. (5), x_{API} is the concentration of the API in the solution in mole fraction and γ_{API} the corresponding API activity coefficient. As PC-SAFT has been successfully applied to describe the thermodynamic properties of the API/solvent systems [32–36], in this work, the PC-SAFT [25] was applied to estimate the API activity coefficient in the aqueous solution.

The rate constants k_s and k_d as well as the parameters K_1 ($K_1 = \alpha_1 a_f$) and K_2 ($K_2 = \alpha_2\emptyset a_f\delta^2$) (see Eq. (4)), were fitted to the experimental API dissolution profiles in the solution based on Eqs. (2)–(4).

Based on the magnitude of the determined rate constants k_s and k_d, the rate-controlling step of the API dissolution can be analyzed. Generally, the following three cases are included in the API dissolution process.