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Influence of excipients on solubility and dissolution of pharmaceuticals

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ABSTRACT

In this work, solubilities and dissolution profiles of the active pharmaceutical ingredients (APIs) indomethacin and naproxen were measured in water in the presence of one excipient out of polyethylene glycol (PEG) 2000, 6000 and 12000, polyvinylpyrrolidone (PVP) K 25 and mannitol. It was found that the solubility of indomethacin and naproxen was increased with an addition of the selected excipients, which was also predicted by the perturbed-chain statistical associating fluid theory (PC-SAFT). The two-step chemical-potential-gradientty model was applied to investigate the dissolution mechanism of indomethacin and naproxen in water in the presence of the excipient. It was found that the dissolution mechanisms of indomethacin and naproxen were changed by the presence of excipients. Although the solubility of the API was increased by the addition of excipients, the dissolution rate of the API was decreased in some cases. This was mainly due to the combination of the molecular interactions between the API and the polymer with the influence of the excipients on the kinetic part (rate constant of the surface reaction or diffusion of the API or both) of API dissolution as function of PEG molar mass as well as of the API type. Based upon the determined rate constants, the dissolution profiles were modeled with a high accuracy compared with the experimental data.

1. Introduction

Many active pharmaceutical ingredients (APIs) show a low solubility and slow dissolution in aqueous solutions. As a result, the oral bioavailability of these poorly soluble APIs is often quite low. Therefore, several formulation strategies were developed to enhance the aqueous solubility and dissolution rate of these APIs. Within the formulation process, excipients are commonly used. Different polymers, e.g., polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP), were reported to be suitable formulation materials for many poorly soluble APIs (Caron et al., 2010; Joshi et al., 2004; Kochling et al., 2007; Lakshman et al., 2008; Papadimitriou et al., 2012; Windbergs et al., 2009). Moreover, sugars, e.g., mannitol, are often used for pharmaceutical formulations (Liao et al., 2005; Littringer et al., 2013). However, so far, the detailed influencing mechanism of these excipients on API solubility and dissolution is far from being well explained. As the dissolution process of many poorly soluble APIs often shows complex dynamic characteristics, an accurate description of their dissolution profiles and an appropriate analysis of their dissolution mechanism turn out to be difficult (DeAlmeida et al., 1997; Lu et al., 2011). Additionally, the presence of excipients, which might influence the dissolution mechanism of APIs, complicates the analysis and prediction of the specific API dissolution profile. Based on the approach proposed by Noyes and Whitney, (1897), several models, in most cases, empirical approaches (Costa et al., 2001; DeAlmeida et al., 1997; Gibaldi and Feldman, 1967; Higuchi, 1961, 1963; Higuchi et al., 1958; Hopfenberg, 1976; Korsmeyer et al., 1983; Mooney et al., 1981a,b) were developed to describe the dissolution profiles of APIs. Mooney et al. (1981a,b); Mooney et al. (1981a,b) investigated the dissolution of several weak acid APIs under unbuffered and buffered conditions from a rotating disk die and proposed a model for describing the initial steady-state dissolution rate of those APIs based on the Fick's second law of diffusion. In this model, a diffusion-controlled mass transport of the investigated APIs was assumed, in which simple, instantaneously established reaction equilibria were considered across a postulated diffusion layer (Mooney et al., 1981a,b). However, for the investigation on the influence of excipients on API dissolution, these models need to be combined with an appropriate thermodynamic model to take into account the molecular interactions between API and water, between API and the excipient

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as well as between the excipient and water. In previous works, based on the work of Ji et al. (2010) and Lu et al. (2011), a two-step chemical-potential-gradient model in which the molecular interactions of the systems were accounted for was developed to describe the dissolution profiles and to analyze the dissolution mechanism of poorly soluble crystalline APIs and their formulations under various conditions (Ji et al., 2015; Paus et al., 2015). Within 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 rate constants (from kinetic aspect). In this paper, the two-step chemical-potential-gradient model was used to analyze the influencing mechanism of excipients on the dissolution of APIs in water.

In this work, indomethacin and naproxen were selected as model APIs. PEG with different molar masses (PEG 2000, PEG 6000 and PEG 12000), PVP with a molecular weight of 25,000 g/mol (PVP K 25) and mannitol were selected as model excipients. The chemical structures of the APIs and excipients are shown in Fig. 1. In literature, PVP and PEG were reported to show a high influence on the aqueous solubility of poorly-soluble APIs (Afrasiabi Garekani et al., 2003; Bettinetti and Mura, 1994; Cadwallader and Madan, 1981; Mura et al., 1996). Mura et al. (1996) investigated the influence of PEGs with different molar masses on the aqueous solubility of naproxen. They found that by addition of 2 wt% of PEG 4000 in the solution, the solubility of naproxen was increased by more than two times. As during API dissolution, the amount of excipients is commonly quite small compared to the amount of solvent (intestinal fluid) and as a high influence of 2 wt% of PEG on API solubility was already reported in literature, in this work, the solubility and dissolution profiles of indomethacin and naproxen in water in the presence of 2 wt% of the model excipients were measured. As the perturbed-chain statistical associating fluid theory (PC-SAFT (Gross and Sadowski, 2001)) was already successfully applied to calculate the thermodynamic properties of APIs in polymers (Prudic et al., 2014a,b, 2015b), solvents and solvent mixtures (Ruether and Sadowski, 2009, 2011) under various conditions, it was applied to describe the influence of excipients on API solubility (thermodynamic aspect). The two-step chemical-potential-gradient model was applied to analyze the influencing mechanism of excipients on API dissolution (kinetic aspect) by accounting for the interactions between the API and the excipient, the API and water as well as the interactions between the excipient and water via PC-SAFT (Gross and Sadowski, 2001). Finally the dissolution profiles of the APIs were modeled and compared with the experimental findings.

2. Theory

2.1. Two-step chemical-potential-gradient model

As introduced in previous works (Ji et al., 2010, 2015; Paus et al., 2015), two main consecutive steps are involved in the API dissolution process. In the first step the disintegration of the API crystals and the hydration of the API molecules take place. This step is called surface reaction. For this step, the chemical potential gradient of the API between the solid phase μ^{S}_{API} and the solid–liquid interface μ^{I}_{API} is the thermodynamic driving force of the surface reaction. For the second step, the diffusion of the hydrated API molecules from the solid–liquid interface into the bulk phase of the medium takes place. Here the chemical potential gradient of the API between the solid–liquid interface μ^{I}_{API} and the bulk phase μ^{B}_{API}, is the thermodynamic driving force of diffusion. The rates of surface reaction and diffusion are described in Eqs. (1) and (2).

$$J_{API} = V \times \frac{dc^{B}_{API}}{dt} \times \frac{1}{A} = k_s \left(\frac{\mu^{S}_{API}}{RT} - \frac{\mu^{I}_{API}}{RT} \right) \quad (1)$$

$$J_{API} = k_d \left(\frac{\mu^{I}_{API}}{RT} - \frac{\mu^{B}_{API}}{RT} \right) \quad (2)$$

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; A is the surface area of the dissolving API in contact with the dissolution medium in m^2, c^{B}_{API} is the concentration of the API in the bulk phase of the medium in mol/m^3 and t is the time in s. In Eqs. (1) and (2), T is the temperature in K and R is the ideal gas constant in J/(mol K). 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 in J/mol, respectively. k_s and k_d are the rate constants of the surface reaction and diffusion in mol/(m^2 s), respectively.

Based on the values of k_s and k_d within Eqs. (1) and (2), the rate controlling step of API dissolution can be determined. The API dissolution is controlled by the surface reaction in the case of $k_s < k_d$ and it is controlled by diffusion if $k_d < k_s$. In the case of k_s equal to or similar to k_d both steps are important for API dissolution.

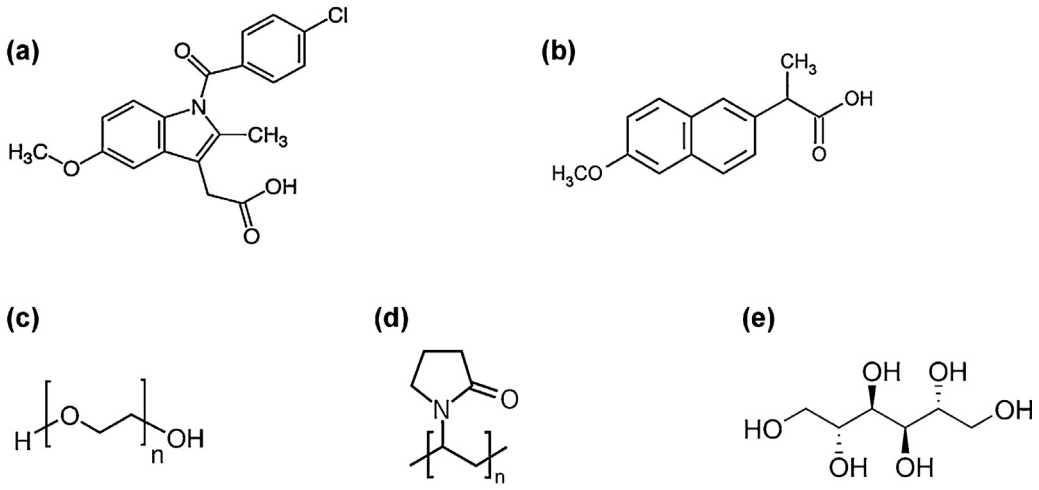

Fig. 1. Chemical structures of indomethacin (a), naproxen (b), PEG (c), PVP (d) and mannitol (e).