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Mathematical model to analyze the dissolution behavior of metastable crystals or amorphous drug accompanied with a solid-liquid interface reaction

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ABSTRACT

Metastable crystals and the amorphous state of poorly water-soluble drugs in solid dispersions (SDs), are subject to a solid-liquid interface reaction upon exposure to a solvent. The dissolution behavior during the solid-liquid interface reaction often shows that the concentration of drugs is supersaturated, with a high initial drug concentration compared with the solubility of stable crystals but finally approaching the latter solubility with time. However, a method for measuring the precipitation rate of stable crystals and/or the potential solubility of metastable crystals or amorphous drugs has not been established. In this study, a novel mathematical model that can represent the dissolution behavior of the solid-liquid interface reaction for metastable crystals or amorphous drug was developed and its validity was evaluated. The theory for this model was based on the Noyes-Whitney equation and assumes that the precipitation of stable crystals at the solid-liquid interface occurs through a first-order reaction. Moreover, two models were developed, one assuming that the surface area of the drug remains constant because of the presence of excess drug in the bulk and the other that the surface area changes in time-dependency because of agglomeration of the drug. SDs of Ibuprofen (IB)/polyvinylpyrrolidone (PVP) were prepared and their dissolution behaviors under non-sink conditions were fitted by the models to evaluate improvements in solubility. The model assuming time-dependent surface area showed good agreement with experimental values. Furthermore, by applying the model to the dissolution profile, parameters such as the precipitation rate and the potential solubility of the amorphous drug were successfully calculated. In addition, it was shown that the improvement in solubility with supersaturation was able to be evaluated quantitatively using this model. Therefore, this mathematical model would be a useful tool to quantitatively determine the supersaturation concentration of a metastable drug from solid dispersions.

1. Introduction

In past few decades, most pharmaceutical products and candidates have had poor water solubility (Kawabata et al., 2011), and various techniques have been used to solve this disadvantage, including formulation as polymorphs (Paaver et al., 2012), amorphous (Nielsen et al., 2015), co-crystals (Sanphui et al., 2015), nanosuspensions (Douroumis and Fahr, 2006), and lipid nanoparticles (Makwana et al., 2015). Of these, the solid dispersion (SD), which can maintain the metastable crystal and amorphous state of compounds through specific interactions with polymers (Mishra et al., 2015; Dukeck et al., 2013), is widely applied to various drugs to improve solubility and subsequently enhance oral absorption. In general, solubilized drugs are in a supersaturated state, with a high drug concentration compared with the solubility of stable crystals and the dissolution behavior of the drug in the supersaturated state tends to achieve a stable plateau with the precipitation of stable crystals (Wlodarski et al., 2015; Knopp et al., 2016a, 2016b; Sarode et al., 2013). The rate of precipitation to form stable crystals and/or the degree of maintenance in the supersaturation state depend on the interactions between the drugs and the polymers (Sarode et al., 2014; Jackson et al., 2016; Ozaki et al., 2013; Mah et al., 2016). Therefore, quantitative evaluation of these interactions would enable the development of formulations with improved solubility. However, it is extremely difficult to directly

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measure and determine the potential solubility of metastable crystals and amorphous forms during dissolution studies.

One approach to determining the dissolution behavior of a drug is through the use of a mathematical model that can describe physical phenomena such as dissolution processes. Such a mathematical model has the advantage of reducing the number of experiments required to determine the mechanism of drug dissolution from a formulation. The "Noyes-Whitney" dissolution rate equation is a formula that describes the dissolution behavior of a solid preparation (Noyes and Whitney, 1897). In addition, the simulation of the dissolution process and the prediction of oral absorption using mathematical models have also been attempted and is a useful tool for understanding mechanisms derived from internal changes in the drug (Sugano, 2011; Jakubiak et al., 2016; Chen et al., 2016; Tsume et al., 2015).

Recently, various models have been applied to the dissolution process of metastable crystals and amorphous drug at the solid-liquid interface. Laaksonen and Aaltonen attempted to develop a model that would express the change in drug crystal transition from the surface of a crystal in metastasis under the sink condition (Laaksonen and Aaltonen, 2013); however, use of the sink condition meant they were unable to analyze the dissolution profile of a supersaturated drug. Conversely, Sun and Lee modeled dissolution from the amorphous drug to a supersaturated state under a non-sink condition, and successfully determined the rate constant for reaching supersaturation, and the precipitation rate of stable crystals (Sun and Lee, 2013). However, the system of equations involved is too complex and predicted values over-estimated the time required for precipitation compared with experimental measurements. In addition, Gao described an integrated model of dissolution kinetics for a solute whose concentration at the solid-liquid interface changes with time, based on the Noyes-Whitney Equation (Gao, 2012). In Gao's model, it was assumed that the solvation or precipitation reaction could be approximated by a first-order reaction occurring at the solid-liquid interface, with the concentration gradient in the diffusion layer changing with time and the diffusional flux following Fick's law (i.e. proportional to the concentration gradient). It was also assumed that the surface area of the solute did not change so that the rate constant was treated as time-independent. As a result, the model suggested potential for the analysis of parameters related to the dissolution of the drug that trigger interfacial reactions such as the rate of precipitation of stable crystals. However, even in this model, it is difficult to analyze the potential solubility of a metastable crystal or amorphous form before precipitation of stable crystals and to quantitatively evaluate supersaturation. Because the concentration of a supersaturated drug is maintained at a high level for long periods, the blood concentration of the drug and the area under the concentration-time curve (AUC) might also become high (Childs et al., 2013; Knopp et al., 2016a, 2016b; Zhang et al., 2016). Therefore, comprehensive and quantitative evaluation of supersaturation can be useful *in vitro* for the predicting improvements in drug concentrations *in vivo*.

In this study, we focused on the diffusion process at the solid-liquid interface and attempted to derive and evaluate a novel macroscopic mathematical model that describes the dissolution process of a drug with an interface reaction such as between metastable crystals and the amorphous drug under non-sink conditions. To measure the dissolution profile of an amorphous drug, a SD of Ibuprofen (IB) and polyvinylpyrrolidone (PVP), which is a combination often used for solubilization studies, was prepared by the solvent method (Najib et al., 1986; Raimi-Abraham et al., 2015). We successfully developed two models with a constant surface area by adding excess drug and with a surface area that changed with time, and tried to evaluate their respective dissolution kinetics without using a rotating disk. In addition, using this model, the potential solubility of amorphous drugs in SD was quantitatively estimated and related to the preservation of supersaturation.

2. Theoretical basis

2.1. The case in which surface area is constant

The Noyes-Whitney equation is generally known to describe the diffusion process of a drug with a diffusion-controlling dissolution profile (Sarode et al., 2013). The dissolution model under this condition is shown in Fig. 1A and the equation used to describe the dissolution process is given by

$$\frac{dC_b}{dt} = \frac{kS}{V}(C_S - C_b), \tag{1}$$

where C_b represents the concentration of a drug in the system as a function of time t, S is the surface area of the drug, V is the volume of the medium, and C_S is the solubility of the drug. Furthermore, k represents the dissolution rate constant, defined as $k = D/h$, if D is the diffusion coefficient and h is the thickness of the diffusion layer. Solving Eq. (1) for C_b, gives

$$C_b = C_S\left\{1 - \exp\left(-\frac{kS}{V}t\right)\right\}. \tag{2}$$

Conversely, the dissolution model for a drug with a solid-liquid interface reaction is shown in Fig. 1B. Here, C_M denotes the solubility of metastable crystals or amorphous drug and C_S is the solubility of stable crystals. In this study, the change in concentration of the drug at the solid-liquid interface was modeled on the basis of the theory described by Gao (Gao, 2012), in which it is assumed that the concentration of the drug at the interface changes with time and can be approximated using a first-order reaction. The concentration of the drug at the solid-liquid interface is regarded as a function of time, $C_{SL}(t)$. At $t = 0$, the concentration of the drug at the solid-liquid interface equals the solubility of

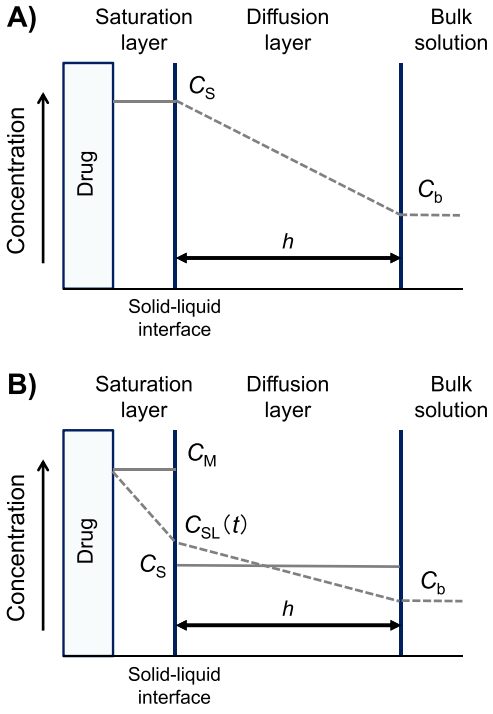

Fig. 1. Dissolution from solid drug: (A) the stable crystal; (B) the metastable crystal or amorphous drug with a reaction at the solid-liquid interface upon dissolution.