European Journal of Pharmaceutics and Biopharmaceutics 109 (2016) 43–48

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Extension of the dissolution-precipitation model for kinetic elucidation of solvent-mediated polymorphic transformations

Paulina Jakubiak, Franz Schuler, Rubén Alvarez-Sánchez *

Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Switzerland

ARTICLE INFO

Article history:
Received 25 July 2016
Accepted in revised form 29 August 2016
Available online 17 September 2016

Keywords:
Polymorphism
Crystallization
Crystal forms
Transformation
Kinetic model

ABSTRACT

Thorough understanding and control of the different crystal forms of a drug product is key for fine chemistry and materials science; it ultimately determines the product's physicochemical properties and performance. In this work, we extend the application of a mechanistic dissolution-precipitation model to solvent-mediated solid form transformations. To address the relevance of the model, various kinetic solvent-mediated polymorphic transition studies were retrieved from the literature. Our model succeeds in accurately describing the experimental data, shedding light on the molecular steps driving the polymorphic conversion. Given its simplicity and mechanistic character, the model can be viewed as a useful tool to monitor, predict and optimize the solvent-mediated transformations of solid forms.

1. Introduction

Solids can be present in nature in different forms. According to their degree of order, solids can be amorphous or crystalline. In addition, crystal arrangements can occur in different forms called polymorphs. Widespread in chemistry and pharmaceutical sciences, the phenomenon of polymorphism is defined as the ability of a compound to exist in various crystalline forms with the same chemical composition but different molecular arrangements. Depending on the structure of the crystal lattice, solid state materials exhibit distinct physicochemical characteristics which can impact the final product's properties and performance. Hence, it is particularly important to monitor the different polymorphs of a solid product and characterize their functional attributes [1].

Polymorphism is of key importance in the pharmaceutical industry. Differences in properties such as solubility, dissolution and melting points across polymorphs can lead to differences in oral bioavailability and thus affect the drug's efficacy-safety profile. Also, during drug manufacturing, control of the handling and stability properties of the polymorphs is essential to ensure a reproducible and high-quality production process. Similarly, polymorphic transformations can strongly affect a drug's shelf-life. Legally, the different polymorphs of an active molecule are subject to patent claims and can be patented as separate inventions [2].

For these reasons, it is essential to understand the thermodynamic and kinetic properties of a polymorphic system in order to select the most suitable, thermodynamically stable form for development and manufacture, and thereby ensure reliable drug products of consistent quality and performance [3].

As postulated by Ostwald in his step rule of stages, the solid state that nucleates in the first crystallization phase is thermodynamically unstable and close in free energy to the molecules in solution. Subsequently, this metastable form follows a conversion to a more stable polymorph [4]. Metastable solid forms display higher solubility compared to the stable polymorphs and this difference in free energy controls the solvent-mediated transformations from a metastable to stable polymorph [3,5,6]. Three key steps are involved, dissolution of the metastable form, followed by nucleation and growth of the stable crystals. The kinetics of these conversions is determined by their relative rates [7].

Different analytical tools can be combined to monitor dissolved drug concentration and solid-state over time within heterogenous mixtures. These techniques include, IR and Raman spectroscopy, solid-state NMR, differential scanning calorimetry, optical microscopy, thermogravimetric analysis and X-ray diffraction. Raman spectroscopy can be applied for *in situ* and *on-line* measurements of the solid-phase behavior and therefore has a significant advantage over the traditional *off-line* methods for polymorphic studies. This real-time monitoring provides straightforward tools to study the kinetics of solvent-mediated polymorphic transitions [8] and has led to the development of different mathematical models [9–11].

* Corresponding author at: F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4070 Basel, Switzerland.
E-mail address: ruben.alvarez_sanchez@roche.com (R. Alvarez-Sánchez).

http://dx.doi.org/10.1016/j.ejpb.2016.08.019
0939-6411/

We recently presented a unified dissolution and precipitation model that can describe supersaturation and precipitation kinetics of poorly soluble weakly basic compounds observed *in vitro* in biorelevant media [12]. Here we report on an extension of the model to describe solvent-mediated polymorphic transformations, and we demonstrate its applicability using examples of solvent-mediated polymorphic transformations reported in the literature. The mechanistic nature of the model along with its simplicity enables accurate evaluations of the transformation kinetics in a computationally convenient manner.

2. Materials and methods

2.1. Theory

As detailed in our previous work [12], the kinetics of a compound in solution and as solid can be explained in terms of three concomitant processes: dissolution, particle nucleation and particle growth. Assuming monodispersity, these three elementary steps can describe the concentration-time profile of the solute and amount of solid according to Eq. (1):

$$V \cdot \frac{dC}{dt} = -\frac{dA_s}{dt} = k_{diss} \cdot A_s - k_{growth} \cdot A_s \cdot C - V \cdot k_{nuc} \cdot C^{\alpha} \quad (1)$$

where C is the solute concentration, A_s denotes the amount of undissolved compound, V is the volume of solvent, k_{diss}, k_{growth} and k_{nuc} represent the dissolution, growth and nucleation rate constants, respectively, and α is the nucleation molecularity index.

At equilibrium in saturating conditions, the solute concentration reaches the solubility limit (C_{sol}) and the nucleation term can be neglected as demonstrated elsewhere in the Supplemental Information [12]. Under these conditions the following relationship can be derived from Eq. (1):

$$C_{sol} = \frac{k_{diss}}{k_{growth}} \quad (2)$$

The units for the different model parameters are determined by the time and concentration units stated in the description of the respective experiment.

By combining Eqs. (1) and (2), we obtain Eq. (3) describing the concentration-time profile of a dissolution-precipitation experiment:

$$\frac{dC}{dt} = \frac{k_{growth} \cdot A_s \cdot (C_{sol} - C)}{V} - k_{nuc} \cdot C^{\alpha} \quad (3)$$

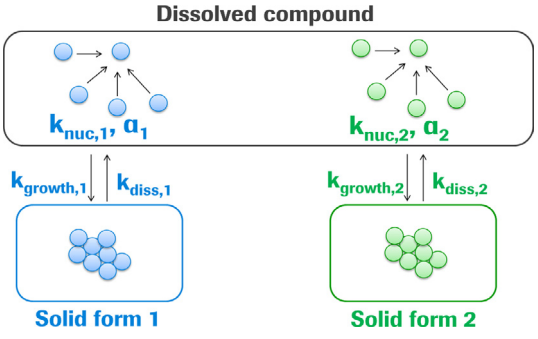

Fig. 1. A schematic drawing showing the main processes governing the interconversion of dissolved and solid material. In the depicted example, crystallization leads to the formation of two different solid forms. These solid forms can interconvert by means of dissolution and re-precipitation.

In such a model, the system is considered to be formed of a single solid type characterized by the four parameters k_{growth}, C_{sol}, k_{nuc} and α. However, as depicted in Fig. 1, it is possible to postulate that the solid pool is composed of two or more solid forms in which case the system can be described as follows:

$$\frac{dC}{dt} = \sum_{i=1}^{n} \frac{k_{growth,i} \cdot A_{s,i} \cdot (C_{sol,i} - C)}{V} - k_{nuc,i} \cdot C^{\alpha,i} \quad (4)$$

$$\frac{dA_{s,i}}{dt} = -\frac{k_{growth,i} \cdot A_{s,i} \cdot (C_{sol,i} - C)}{V} + k_{nuc,i} \cdot C^{\alpha,i} \quad (5)$$

where i designates the i^{th} solid form within the mixture.

2.2. Polymorphic transformation studies

We evaluated the model using published data retrieved for different compounds studied under various conditions of solvent, temperature, initial solid amounts and solute concentrations. Whenever available, studies showing kinetic data for all species involved were selected. Data were extracted from plots using Digitizeit version 2.0.6 (Bormisoft, Braunschweig, Germany).

2.3. Modeling methodology

The solvent-mediated conversion modeling was performed using Berkeley Madonna version 8.3.18 (University of California, Berkeley, CA). The model parameters were estimated using the curve-fitting procedure. The integration step size was fixed at 0.001 min and the Rosenbrock "stiff" method was used as the integration method in all the models tested. The profiles of the solid forms and solute were fitted simultaneously to provide a single set of parameters for the complete dataset.

3. Results and discussion

3.1. Model presentation and analysis

As described in the theoretical part in Section 2, we previously developed a model that explains the interconversion of dissolved and solid material in diverse conditions. The model has been successful in describing complex kinetic dissolution-precipitation behavior of various drugs in gastrointestinal biorelevant media [12]. With the aim of extending this framework we hypothesized that such a model could also be applied to more complex systems where different solid forms coexist and interconvert. This concept could apply to any solvent-dependent transformation such as amorphous to crystalline form, polymorphic transitions as well as solvate formations. The model can be defined as a set of differential equations that describe the kinetics of the solute as well as each individual solid form (Eqs. (4) and (5)), with each form being characterized by 4 different parameters. Thus, for a ternary system involving 2 solid forms and the solute, a set of 3 differential equations and 8 parameters is needed to appropriately describe the system. The proposed parameters (k_{diss}, k_{growth}, k_{nuc} and α) hold a clear physical meaning and relate to the different elementary steps that can occur, namely dissolution and growth of existing particles as well as formation of incipient nucleation particles out of dissolved compound.

Fig. 2 shows a hypothetical solvent-dependent transformation process between two solid forms described by the model where the system starts as a supersaturated solution above the solubility limit of both solid forms. In the first phase, the compound in solution precipitates to form the kinetically most favored solid form and finds the pseudo-equilibrium at the solubility of the kinetic solid form. During this phase, the thermodynamic solid form