Continental J. Applied Sciences 8 (2): 48 - 54, 2013 ISSN: 1597 – 9928
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Printed in Nigeria doi:10.5707/cjapplsci.2013.8.2.48.54

SIMULATING SOLVENT-MEDIATED PHASE TRANSFORMATIONS WITH THE AID OF MATHEMATICAL SOFTWARE THAT RUNS ON MATLAB

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ABSTRACT
Predict phase transformations models are generated and modified via comparison with experimental data. These models are obtained by putting physical insight into mathematical equations using MATLAB mathematical software to provide information necessary to understand phenomena of polymorphism in more detail.In this article a solvent-mediated phase transformation, which is one out of the two routes of transformation, is simulated and the equations which describe the transformation are modified in order to solve them using MATLAB. The result obtained showed that is possible to determine a plateau supersaturation where the supersaturation does not change, and this plateau is due to faster progress of the dissolution and growth progress.

KEYWORDS: Models, MATLAB, Polymorphism, Predict phase, pharmaceuticals, dyestuffs and pesticides.

Received for Publication: 22/12/12 Accepted for Publication: 28/02/13
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INTRODUCTION

German Baltic chemist Wilhelm Ostwald in 1899 suggested the theory that solids of nearly every substance can occur in different forms (Cardew and Davey, 1985). Today we know that these forms can be amorphous solids, ampholytes, and many more. When a substance can occur in more than one crystal from, the substance is called polymorph. Polymorphism occurs in a very wide range of materials (Cardew and Davey, 1985) and industrial products such as pharmaceuticals, dyestuffs and pesticides. Therefore this issue needs to be investigated carefully to predict, which crystal form appears under certain conditions and in production processes and how stable the form is. However, this is very important for several reasons. For example, in many cases it is necessary to avoid phase transformation during storage, since this can cause product degradation or change the appearance of the product and make it, hence, inalienable. A far more important aspect for pharmaceutical companies is settled in the field of law. Patents do only apply for crystal forms of a product, which are stated in the patent itself. If a competing company is able to produce the same product in a new, unknown crystal form the original patent does not apply and, hence, the competing company is allowed to fabricate and sell it. Since developing pharmaceutical costs huge amounts of money, this would cause an immense loss for the company which has designed it (Davey, 2003).

To predict phase transformations, models must be generated and modified via comparison with experimental data. These models are obtained by putting physical insight into mathematical equations. These equations can then be conveniently and quickly progressed by using mathematical software such as

MATLAB. In this study, solvent-mediated phase transformation, which is one out of two routes of transformation, can be simulated using MATLAB mathematical software. Therefore the equations, which describe the transformation are adopted from literature (Cardew and Davey, 1985) and modified in order to solve them by using MATLAB. Also, fundamental information on solvent-mediated phase transformation through equations in order to show the kinetic expressions is provided, which is necessary to understand the phenomena of polymorphism in detail.

Polymorphism

Polymophrism is the characteristic of substances to occur in different crystal forms in which the molecules are arranged and/or are conformed differently within the crystal lattice (Gu*et al*, 2001). An example is the appearance of α-glycine, β-glycine and γ-glycine, in which β-glycine is the most unstable form, whereas the transformation from α-glycine to γ-glycine occurs under room temperature and pressure (Sakai, *et al*, 1993). The different shapes of α-glycine and γ-glycine are shown in Figure 1.

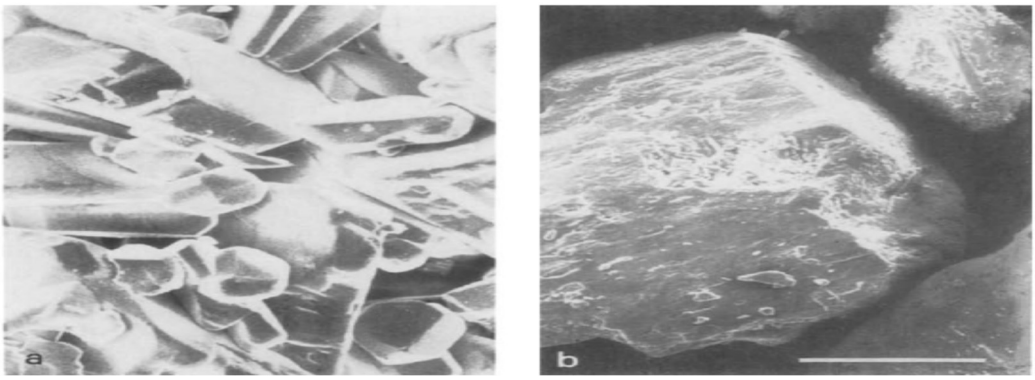

Figure 1: Scanning electron microscopy photographs of glycine polymorphs: (a) α-glycine and (b) γ-glycine. The marker represents a length of 200 µm. (MÜller, 1913)

Generally, it can be said that there is a stable crystal and one or more instable forms under any conditions, when the substance appears as a crystal. An essential parameter, which influences whether a crystal is stable or metastable, is very often the temperature (Muller, 1913). However, the stable form is not always present, since the transformation from an instable to a stable state can be extremely slow. The appearance of instable crystals over a long time scale is called metastability. An example for metastability is diamante, which is metastable with respect to graphite (Cardew and Davey, 1985).

There are two different routes of phase transformations from an instable to a stable crystal, the solid-state and the solvent-mediated transformation. Both have in common that their thermodynamic driving force is the minimisation of the free energy of the system (Cardew and Davey, 1985). The characteristic feature of a solid-state transformation is the complete internal rearrangement of molecules or atoms in the solid state. In the solvent-mediated transformation the metastable solid dissolves in a solvent where crystals of the stable phase nucleate and grow independently (Cardew and Davey, 1985).

Solvent-mediated phase transformation

The kinetics of solvent-mediated phase transformation were investigated and described first in 1985 by P. T. Cardew and R. J. Davey. Solvent-mediated transformations employs solubility diagrams where the mole fractions are plotted against the temperature. The curves for phase 1 and 2 denote the solubility as shown in figure 2. A solution, which contains a higher concentration of a substance than the solubility concentration, is called supersaturated. Only in supersaturated solutions crystal nucleation and grow can take place.

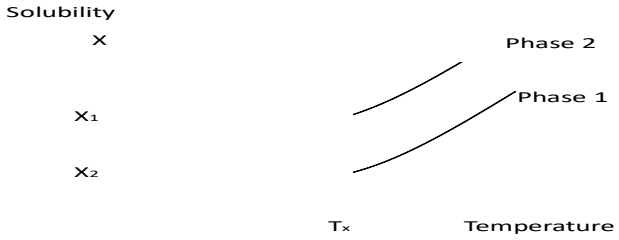

Figure 2: Solubility curves of a monotropic system. Phase 1 is the metastable phase while Phase 2 is the stable phase. (Davey *et al*, 1986)

A supersaturated solution with the initial concentration x at temperature $T_x$considered. Obviously precipitation can yield both the metastable phase 1 as well as the stable phase 2, but according to Ostwald's empirical observations, the nucleation and grow of phase 1 takes place at first till the solution drops down to the solubility of this phase, x_1 (Davey *et al*, 1986). These observations were proposed as Ostwald's Law of Stages. However this rule is only valid when $J_2k_2^3 << J_1k_1^3$, where J_1 and J_2 are the nucleation rates of phase 1 and phase 2, respectively, and where k_1 and k_2 are the first order growth constants of phase 1 and phase 2, respectively [Davey et al, 1986]. The starting point for the actual transformation is slurry of mono-sized crystal of phase 1 in contact with some nuclei of phase 2, which were also formed in small scales (Cardew and Davey, 1985). During the growth of phase 2 nuclei, crystals of phase 1 are dissolved and keep the concentration within the solvent supersaturated with respect to phase 2. The formation of stable crystals is finished, when all crystals of phase 1 were dissolved and the concentration within the solution is in equilibrium with the solubility of phase 2. System in which the solvent mediated phase transformations occur, are for example shown in Table 1.

Table 1: Examples of systems where solvent-mediated phase transformations occur

System	Solvent	Temp. [°C]	Reference
Zeolite A ⟶ Zeolite P	H_2O	82	Subotic et al, 1986
Vaterite ⟶ Aragonite	H_2O	94	Bischoff, 1968
α-glycine ⟶ γ-glycine	H_2O	40	MÜller, 1913
Stearic acid C ⟶ Stearic acid B	$C2H_5OH$, n-hexane, benzene	20 – 30	Wellner et al, 1981

MATLAB

Matrix Laboratory (MATLAB) which is a commercial software product available from the Mathworks (http://www.mathworks.com/). It is a software package is widely used for the analysis and visualization of data. It is originally designed to facilitate linear algebra and numerical calculations, with the basic module of a matrix with not explicitly defined dimensions (Teschl, 2001, MATLAB Guild).

MATLAB IS used in this study to solve the differential equations and to visualize the results. A major advantage of MATLAB® is that several methods to solve differential equations, such as e.g. a method based on explicit Runge-Kutta formula and an implementation of the trapezoidal rule, are already included. It is very easy to switch between those methods, since only one command may be changed. Additionally,

changes regarding the step-width, the initial conditions as well as numerical values can also be executed easily. Also the convenient display of the results, with a few commands such as the *plot*-command the visualization of the results can be implemented and instantly compared with the results in original experimental data.

METHODOLOGY

The methodology employed in this work is to model the kinetics of solvent-mediated phase transformation.The kinetics of solvent-phase transformation mathematical differential equations is adopted from literature (Davey, 1982). This study investigates a polymorphic system with a solvent-mediated phase transformation, which the system obeys Ostwald's Law Davey, (1982) and that two mono-dispersed crystals can be formed, a stable form and a metastable form. It is assumed that the conditions are not changed and that no mass is added or removed in the transformation.

In the model the present supersaturation σ_{II}, the intialsupersaturation σ_i and the supersaturation in solution saturated with the metastable phase σ_x are defined:

$$\sigma_{II} = (x - x_{II}) / x_{II} \quad (1)$$

$$\sigma_i = (x_i - x_{II}) / x_{II} \quad (2)$$

$$\sigma_x = (x_I - x_{II}) / x_{II} \quad (3)$$

x denotes the actual mole fraction of solute within the system, x_{II} the solubility of phase 2 and x_I the solubility of phase 1.All of the supersaturations are with respect to the stable phase, which is per definition phase 2 and phase 1 denotes the metastable phase. Since the total numbers of moles are constant, a mass balance can be written:

$$\sigma_I = \sigma_{II} + (x_{I,s} + x_{II,s}) / x_{II} \quad (4)$$

$x_{I,s}$ and $x_{II,s}$ denote the mole fractions of precipitated phase 1 and 2, respectively, at any time. Using the boundary conditions it is possible to modify this mass balance for t=0, it is known that:

- the supersaturation σ_{II} is equal to the supersaturation in solution saturated with the metastable phase σ_x,
- there is a negligible amount of precipitated phase 2
- the amount of precipitated phase 1 is equal to the initial amount of precipitated phas1.

This can be mathematically expressed as followed:

At t=0:

$$\sigma_{II} = \sigma_x \quad (5)$$

$$x_{II,s} \approx 0 \quad (6)$$

$$x_{I,s} = x_{I,I} \quad (7)$$

Accordingly, the final conditions the following are considered:

- the supersaturation with respect to phase 2 is zero
- the precipitated phase 2 reaches its final value
- the amount of precipitated phase 1 is zero

This can be mathematically expressed as followed:

At $t \rightarrow \infty$

$$\sigma_{II} = 0 \quad (8)$$

$$x_{II,} = x_{II,f} \quad (9)$$

$$x_{I,s} = 0 \quad (10)$$

After substituting the boundary conditions into the mass balance and after some additional transformations, the expression becomes:

$$\sigma_{II}/\sigma_i = 1 - Z_{ii}^3 - [1- (\sigma_{II} /\sigma_i)] \text{ x } Z_I^3 \quad (11)$$

In which Z_{II} is the ratio of the actual radius r_{II} of phase 2 crystals and its final value $r_{II,f}$ and in which Z_I is the ratio of the actual radius of phase 1 r_{II} vs. the initial value $r_{I,I}$.

Furthermore, the time dependence of Z_I and Z_{II} can be expressed by applying growth and dissolution kinetics.

$$dZ_I / dt = (k_d / r_{I,i}) (x_{ii} / x_I) (\sigma_{II} / \sigma_x) \quad (12)$$

$$dZ_{II} / dt = k_{II}\sigma_{II} / r_{II,f} \quad (13)$$

Assuming that linear growth kinetics and the size dependence of the mass transfer coefficient k_d is neglected, it is possible to solve the equations 11, 12 and 13 simultaneously as a function of the parameter τ which is called the transformation time. This parameter is defined as followed:

$$\tau = (K_D / K_{II}) (\sigma_x / \sigma_i) t \quad (14)$$

Where, t is the time, and where the following expressions apply:

$$K_D = (x_{II} / x_I) (k_D\sigma_i / r_{I,i}) \quad (15)$$

$$K_{II} = (k_{II}\sigma_i / r_{II,f}) \quad (16)$$

Differentiating equation 14 with respect to t obtaining following expression:

$$d\tau / dt = (K_D / K_{II}) (\sigma_x / \sigma_i) \quad (17)$$

Substituting equation 17 into equation 12 and 13, respectively to obtain the following expressions:

(17) → (12) $dZ_I / d\tau = K_{II} [(\sigma_{II} - \sigma_x) / \sigma_x]$ (18)

(17) → (13) $dZ_{II} / d\tau = [(K_{II}^2 K_D) / (\sigma_{II} / \sigma_x)]$ (19)

An m-file, *deq2x.m,* which contains equation 11, 18 and 19, was then implemented to solve the differential equations in order to receive values for Z_I and Z_{II} using MATLAB®-integrated solvers (MATLAB User Guide). Then, function, *sigx.m* is applied to calculate σ_{II}on the basis of the solutions for Z_I and Z_{II}. The two codes were automatically accessed by applying the main function, *final.m*, which then plot the result and displayed as shown in Figure 3 and 4.

However, in order to calculate σ_{II}, correlations and numerical values of $\sigma_x = 1$, $\sigma_I = 10$ x σ_x, $K_{II} = 0.25$ were assumed. In order to examine the effect of a rapid dissolution of the metastable phase and a rapid growth of the stable phase, respectively, two different solutions with the following parameters were adopted: $K_D = 10$ x K_{II} and$K_D = 0.1$ x K_{II}.

Solving the equations stated in methodology, to obtain a plot of the supersaturation against the transformation time τ. The MATLAB is used to solve these equations in order to achieve the supersaturation against the transformation time τ and to visualize the results.

RESULTS AND DISCUSSIONS

The supersaturationσ_{II} plotted against the transformation time τ for a dissolution-controlled transformation (K_D= 10 x K_{II}) is show in the graph thus:

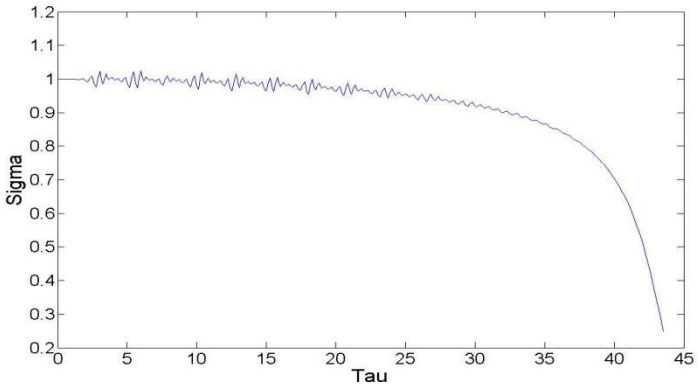

Figure 3: The supersaturationσ_{II} plotted against the transformation time τ for a dissolution-controlled transformation (K_D= 10 x K_{II}).

The supersaturationσ_{II} plotted against the transformation time τ for a growth-controlled transformation (K_D= 0.1 x K_{II}) is show in the graph thus:

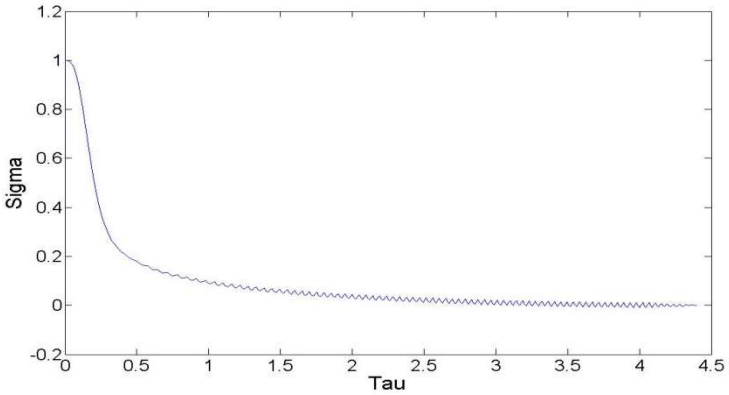

Figure 4: The supersaturationσ_{II} plotted against the transformation time τ for a growth-controlled transformation (K_D= 0.1 x K_{II}).

The results obtained are in agreement with the ones obtained by Cardew and Davey (1985), but the transformation time scale appears to differ, which is probably due to K_D values differences. As in the literature it is possible to determine a plateau supersaturation where the supersaturation σ_{II} does not change. This plateau is due to faster progress of the dissolution and growth process, respectively (Cardew and Davey (1985). In the case of K_D = 10 x K_{II}, the dissolution progress of phase 1 is faster than the growth of phase 2 and hence, the supersaturation maintains at values close to 1 for a relatively long time scale. In the case of K_D = 0.1 x K_{II}, the growth of stable crystals controls the process and, hence, the supersaturation plateau can be found at a supersaturation values close to 0.

The simulation can be used to predict polymorph phase transformations, If σ_x, σ_I, $K_{II}$and K_D is known. The MATLAB® programme code can be extended to the application of seeds of the stable phase to enhance the phase transformation and predicting seeding affect transformations in investigating the effect and magnitude of seeding in different systems.

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