**Comparison of crystal growth kinetics of Piracetam, Fenofibrate, Acetaminophen, Phenylbutazone, Risperidone and Carbamazepine in methanol**

Rodrigo Soto1\*, Vivek Verma1, B. Kieran Hodnett1 and Åke C. Rasmuson1,2

*1 Synthesis and Solid State Pharmaceutical Centre (SSPC), Bernal Institute, Department of Chemical and Environmental Science, University of Limerick. Limerick V94 T9PX, Ireland; 2 Department of Chemical Engineering and Technology, KTH Royal Institute of Technology, SE-100 44 Stockholm, Sweden*

*\*Corresponding author: rodrigo.soto@ul.ie*

**Highlights**

* Crystal growth kinetics of six different API’s in methanol have been studied.
* Experimental desupersaturation data is modeled using empirical and mechanistic equations.
* Solid-liquid interfacial energies and mean diffusion distances have been estimated.
* The relevance of bulk diffusion study suggests surface integration as the limiting-step.

**1. Introduction**

Crystallization is the bottleneck unit operation in the separation of solids in the pharmaceutical industry and it can be envisaged as a two-step process: nucleation and crystal growth. Both steps contribute to the final particle size distribution of the crystallization outcome but are insufficiently understood. The nature of the solute-solvent intra and intermolecular interactions influences both nucleation and growth. It is hence expectable that molecules with a relative ease of nucleation in a given solvent will also show a growth facility. Very often, however, nucleation experiments do not allow for separating the effects of the steps of new particles formation from those of pure growth because the nucleation outcome can only be evaluated when the solids have grown to a certain size [1]. The process of crystal growth comprises the diffusion of molecules from the bulk phase to the crystal surface and their subsequent integration into the crystals lattice. There are several mechanisms that can describe the surface integration step, e.g. the Burton Cabrera Frank (BCF) or screw dislocations mechanism, and Birth and Spread (B+S) or two-dimensional nucleation mechanism [2]. Additionally, empirical power law equations are useful because they can be applied in a wider range of supersaturations. This study focuses the growth of six different active pharmaceutical ingredients (APIs) in the same solvent aiming to shed light to some fundamental physicochemical aspects influencing the crystal growth kinetics.

**2. Methods**

Isothermal seeded desupersaturation experiments in methanol were carried out in the range of temperature 288-303 K and supersaturations below 1.32, for Acetaminophen (AAP), Carbamazepine (CBMZ), Piracetam (PCM), Fenofifrate (FF), Phenylbutazone (PBZ) and Risperidone (RIS). The seed size was 100-180 μm and the stirring speed 250 rpm. The crystallizer (Easymax402, Mettler Toledo) was equipped with an *in-situ* IR probe (ReactIR15) to monitor the liquid concentration at any time and a FBRM probe (Particle track G400) to track the number of counts and their size distribution. After growth experiments, the crystals were harvested, dried and characterized by PXRD, SEM and in a particle size and shape analyzer (G3 morphology).

**3. Results and discussion**

The crystallographic habit of all the API studied is similar except for PBZ where a needle shape-like habit is distinguished. Experimental desupersaturation data was modeled using power law equations (Fig.1a), BCF and B+S theories. The fitting of power law equation was remarkably good and the involved parameters suggested that the growth is mainly surface integration controlled for the studied API’s within the explored experimental conditions. The BCF model provided faintly better fitting than the B+S one being therefore more likely this mechanism to govern. At the same supersaturation and temperature (Fig.1b) the crystal growth rates decreased in the order PCM>FF>AAP> PBZ>RIS>CBMZ. From the B+S model, the estimated solid-liquid interfacial energies (γsl) and mean surface diffusion distances ranged 0.82-1.55 mJ/m2 and 6.66‧10‑9-6.52‧10‑8 m, respectively. γsl values are comparable to those determined by nucleation experiments [3] but do not follow the relative growth order mentioned, suggesting that there are more factors at play. Interesting and coherent correlations between growth rates, solubility, molecular volume, mass transfer coefficients and crystal lattice energies have been found, which allows for rationalizing the crystal growth kinetic behavior observed.



**Figure 1.** (a) Example of the fitting provided by power law equation for AAP experiments at different temperatures. (b) Comparison of growth rates obtained at 298 K for the different API studied.

**4. Conclusions**

The power law equation and the BCF model provided the best fit to the experimental desupersaturation data for the six API’s studied in methanol. The crystal growth rates decreased in the order PCM>FF>AAP>PBZ>RIS>CBMZ, which can be correlated to fundamental physicochemical properties as solubility, mass transfer coefficients, molecular volume and crystal lattice energies.

**References**

[1] W. Du, A. J. Cruz-Cabeza, S. Woutersen, R. J. Davey, and Q. Yin, Chem. Sci., 6; 6 (2015) 3515–3524.

[2] A. Mersmann, Crystallization technology handbook. 2nd ed., Marcel Dekker, New York, 2001.

[3] V. Verma, J. Zeglinski, S. Hudson, P. Davern, and B. K. Hodnett, Cryst. Growth Des., 18; 11 (2018), 7158–7172.