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Research paper

In silico dissolution rates of pharmaceutical ingredients

Berna Dogan [a], Julian Schneider [b], Karsten Reuter [a,*]

[a] Chair of Theoretical Chemistry and Catalysis Research Center, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
[b] QuantumWise A/S, Fruebjergvej 3, DK-2100 Copenhagen, Denmark

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ABSTRACT

The correlation between in vitro dissolution rates and the efficiency of drug formulations establishes an opportunity for accelerated drug development. Using in silico methods to predict the dissolution rates bears the prospect of further efficiency gains by avoiding the actual synthesis of candidate formulations. Here, we present a computational protocol that achieves such prediction for molecular crystals at low undersaturation. The protocol exploits the classic spiral dissolution model to minimize the number of material parameters that require explicit molecular simulations. Comparison to available data for acetylsalicylic acid and alpha lactose monohydrate indicates a tunable accuracy within one order of magnitude.

1. Introduction

Dissolution testing for pharmaceutical ingredients developed into a standard procedure in drug development since the realization of correlations between dissolution rates and the bioavailability of solid drug formulations [1]. Even though efficient, a major roadblock to using this approach for massive screenings of candidate molecules is the required actual synthesis and crystallization prior to testing. The availability of a computational protocol to reliably predict dissolution rates of molecular crystals *in silico* would eliminate this problem and represent an important step towards a future all-computational drug discovery process. Aimed for screening, such a protocol would not need to be fully quantitative, yet accurate enough to identify promising candidates for experimental validation.

The benefits of molecular modeling for screening in pharmaceutical research are already impressively demonstrated by docking studies of small molecule drug candidates to protein targets [2]. Although there are some modeling studies of the dissolution process [3–5], these are mostly on an abstract conceptual level that does not meet the accuracy requirements of material-specific screening. In contrast, significant progress has recently been made for crystallization as the time-reversed process to dissolution [6–9]. In particular Doherty et al. [6,7,9] have developed general expressions to calculate the growth rates of single crystals and therewith achieved a correct prediction of crystal morphologies. Their approach centers on the classic spiral growth model of Burton, Cabrera and Frank (BCF) and applies to the principal growth mode at low to moderate supersaturation [10]. In this model, crystals of organic molecules grow via advancing step edges that rotate around screw dislocations terminating at the surface. Kink sites on the step edges are the primary growth sites. With the propagation of each step edge, new step edges are exposed. This leads to a spiral-like, self-sustaining process, in which each rotation around the dislocation core adds a new layer that then spreads radially outward.

In appealing elegance the BCF model requires only a minimal number of material-specific quantities that need to be determined through molecular simulation. With the focus on relative growth rates necessary to predict crystal morphologies, Doherty et al. could rely on coarse approximations for these quantities [6,7,9]. However, recently efficient molecular dynamics (MD) based approaches for their accurate determination have become available [11,12]. As the time-reversed process to crystal growth, the BCF model can be readily applied to dissolution at low undersaturation and then describes dissolution through the formation of etch pits, cf. inset in Fig. 2 [10]. Here we show that combining the BCF model with accurate MD-derived material parameters then establishes a general computational protocol that allows not only to efficiently predict relative dissolution rates, but in fact absolute rates with sufficient accuracy. This is illustrated in the application to single-crystal facets of two prototypical compounds, acetylsalicylic acid (aspirin) and alpha–lactose monohydrate (alpha-LM). For both show cases comparison to available experimental data suggests a tunable accuracy down to about an order of magnitude.

Within the layered dissolution picture of the BCF model the macroscopic dissolution rate R of a crystal face is given as

$$R = \frac{h}{\tau}, \tag{1}$$

* Corresponding author.
E-mail address: karsten.reuter@ch.tum.de (K. Reuter).

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where τ is the time for one spiral rotation. h is the height of the molecular layer that is lost through one rotation and can be obtained from crystallographic data. For a surface exposing N stable edge directions along its periodic bond chains (PBCs) [13], the rotation time of the resulting convex N-sided polynomial spiral is derived as [6,9]

$$\tau = \sum_{i=1}^{N} \frac{l_{c,i+1} \sin(\alpha_{i,i+1})}{v_i}, \quad (2)$$

with $l_{c,i+1}$ the critical length of edge $i+1$, $\alpha_{i,i+1}$ the geometric angle between edges i and $i+1$, and v_i the step velocity of edge i. Considering the kink sites along step edges as primary sites for the detachment of dissolution units, the step velocity, $v_i = a_{p,i}\ \rho_i\ u_i$, can be related to the kink density ρ_i and the net flux out of kink sites u_i. Here, $a_{p,i}$ is the distance retraced due to the loss of a row of single dissolution units, which can again be taken from crystallographic data. For low to moderate undersaturation quasi-equilibrium conditions in the proximity of the step edge can be assumed. The kink density can then conveniently be calculated from thermodynamics [6]

$$\rho_i = [1 + 0.5 \exp(\Delta G_{\mathrm{kink},i}/k_B T)]^{-1}, \quad (3)$$

with $\Delta G_{\mathrm{kink},i}$ the free energy cost of creating a kink site along step edge i, k_B the Boltzmann constant and T the temperature. The same holds true for the critical lengths of the edges, i.e. the length at which addition or retraction of a dissolution unit leaves the free energy of the system unchanged [13]

$$l_{c,i} = \frac{2 a_{e,i} \Delta G_{\mathrm{kink},i}}{k_B T \ln(S)}. \quad (4)$$

Here, $S = c/c_{\mathrm{sat}}$ is the undersaturation defined as ratio of actual and equilibrium concentrations of the solute near the crystal, c and c_{sat}, respectively, and $a_{e,i}$ is another geometry parameter in form of the length of one dissolution unit along step edge i. Exploiting detailed balance the net flux out of kink sites can finally be written as

$$u_i = (1 - S) k_i^-, \quad (5)$$

where k_i^- is the rate constant for the molecular detachment process from the kink site. In case of non-centrosymmetric dissolution units it is possible to have more than one kink type along a given step direction. Generalized flux expressions for this case have been established [14] and would then enter our approach. For the present applications we instead consider in Eq. (5) only the slowest detaching kink site, which can be expected to control the kinetics (see below).

Apart from a number of readily available geometry parameters, the only quantities entering the model and requiring explicit molecular simulations are thus the rate constants k_i^- and the free energy costs $\Delta G_{\mathrm{kink},i}$. To calculate kink free energies at the solid/liquid interface, we have adapted free energy methods employed mostly for ligand/receptor complexes [12,15]. In these methods, the free energy difference between initial and final states is decomposed into several stages along a thermodynamic cycle and each state is computed separately. This allows to sequentially decouple and couple non-bonded interactions between the kink unit and its surrounding with the unit restrained, shifted, and unstrained in its new and old position [12]. For the rare detachment events of hydrophobic units from the pharmaceutical compounds we rely on accelerated MD methodology that uses metadynamics simulations to determine an optimized bias potential for subsequent hyperdynamics simulations [11]. This accurately evaluates the reactive flux across the complex and high-dimensional transition regions, and thus even accounts for barrier in the resulting rate constants.

We demonstrate the derived protocol for two model compounds: Aspirin, an active pharmaceutical ingredient (API), and alpha-LM, a widely used excipient. Knowledge of excipient dissolution is equally important as for APIs to optimize tablet solubility, extending the value of our dissolution protocol to an even wider range of molecular crystals. Specifically, we choose aspirin(001)/water and alpha-LM(010)/water interfaces, representing the dominant facets of crystals grown from solutions, respectively [16,17]. Along this surface normal every layer of alpha-LM exposes an equivalent surface termination. In the case of aspirin this is also the case even though the unit-cell comprises two molecular layers in this orientation. Moreover, strong hydrogen bonds form only within the molecular layers, such that growth and dissolution is expected to also proceed via single layers. For both compounds we therefore consider step edges of the height of a single molecule. At both surfaces strong PBCs indicate three stable step directions [6]. For each step direction, opposite edges, e.g. [100] and [$\bar{1}$00], expose slightly different terminations. In case of aspirin for instance in form of terminal acetyl moieties pointing upward into solution or downwards to the crystal surface. We assess the relevance of such subtle differences for the dissolution modeling by first explicitly calculating k_i^- and $\Delta G_{\mathrm{kink},i}$ for both opposite edge types.

As mentioned before, in case of the non-centrosymmetric aspirin molecule there can be several possibilities to create kink arrangements at a given step edge [12]. We identify the slowest detaching kink site type that will dominate the dissolution process with regular MD simulations. These simulations indeed revealed essentially all defect structures unstable even on the time scale of a few nanoseconds. There was always just one kink site type per edge direction where detachment of the next molecule would require breaking a strong bond and where detachment was never observed on MD time scales. We correspondingly concentrate on these metastable kink types for the BCF model and consider as one dissolution unit the slowly detaching molecule plus any subsequent fast detaching molecules. As illustrated in Fig. 1 for aspirin this dissolution unit comprises one centrosymmetric aspirin dimer, in which the more stable molecule is attached via hydrogen bonds. For alpha-LM it comprises one water-lactose complex. After the dissolution of one such dissolution unit the step thus exhibits exactly the same kink site as before, just reduced by one unit. As also apparent from Fig. 1 the lower symmetry of the molecular units leads thereby to two slightly different versions of this kink site. We systematically calculated the detachment rate constants k_i^- for both cases and obtained differences up to one order of magnitude that could always readily be rationalized with the solvent accessibility to the strong hydrogen bonds, cf. SI. For a fast screening protocol we neglect these differences in the following and focus

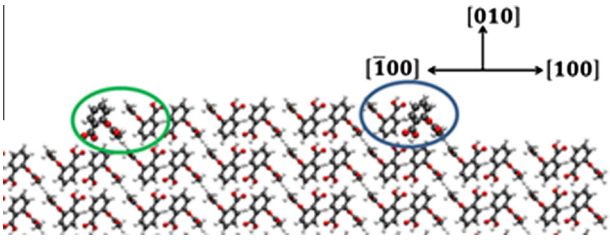

Fig. 1. Top view of the stable kink structure at the [010] step edge of the aspirin (001) face. For clarity only the terrace top layer above the step edge is displayed and (green and blue) circles highlight the considered dimeric dissolution unit at the two (inequivalent) kink sites shown. C, O, and H atoms are shown as grey, red and white spheres, respectively. The slowly detaching kink molecules are shown with bold spheres.