On the pK of API aggregate surfaces: molecular rationalisation of oral administration drug release models

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The kinetics of drug release from molecular crystals is commonly described by the Nernst-Brunner model developed in 1904 – and since then, numerous empirical evidence supporting its suitability as a mathematical approximation has been gathered [1]. However, providing mechanistic rationales turned out to be much more complex [2,3]. Elaborating on the molecular mechanisms of acid-induced carbamazepine (CBZ) dissolution, a molecular simulation case study of "Nernst-Brunner type" drug release into an aqueous solution featuring an interfacial "diffusion" layer is presented [4].

Here, we demonstrate the application of the 'instantaneous pK' approach to the molecular dynamics simulation of a carbamazepine form III crystallite exposed to an acidic solvent environment [5,6]. Mimicking pH = 2, we find drastic protonation of the drug crystallite model, followed by the dissolution of both single CBZH+ solutes and fragments from the crystal edges. The latter results in the release of [CBZHn]n+ aggregates (with n = 2–8) into solution, thus creating a dynamic interplay among different solute species. Similar to the concept of two-step crystal nucleation, we propose a two-step crystal dissolution mechanism that encompasses solute aggregates within a "dense-solutes domain". Within an interfacial region between the crystal and the bulk solvent, these aggregates are suggested as "puffer species" that account for a constant concentration of fully solvated solute species.

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