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In-situ Measurement and Characterization of Crystal Growth by X-ray Diffraction

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Many industrially crystallized compounds are obtained by nucleation and growth from solution. Either for formation or purification of the product, investigation of intermediates, or prevention of crystallization in amorphous products, crystallization is always a key aspect of manufacturing and development, with a significant impact on the efficiency and profitability of the overall process. Especially in the pharmaceutical industry undetected fluctuations in the crystallization process can alter the crystal structure, affecting the safety and the bioavailability of the product.

The ability to fully understand crystallization processes, the parameters that influence the yield and stability of a polymorph, solvate or hydrate form (solvents, concentrations, pH, stirrer geometry and speed, reactor geometry, temperature, temperature ramps, pressure, etc.) are of crucial importance in this industry. Therefore, the ability to reliably monitor these precious crystallization processes on-line has become a strong need in the industry. This process understanding is the most critical part for a QbD (Quality by Design) approach.

We present the results of *in situ* crystallization studies of DL-Alanine performed with a slurry flow cell that was integrated in an X-ray diffraction system. The crystallizations were performed from a saturated solution at different pH values. The different crystallization conditions show distinct differences in crystallization initiation and resulting crystal morphology.

Keywords: crystallization, in-situ, morphology

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Study of nanostructure and morphology of deflazacort

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Deflazacort (DEF) is a methyloxazoline derivate of prednisolone and has been proposed to have major advantages over other corticosteroids.[1] It represents an inactive prodrug, which is rapidly converted in the body to is active alcohol metabolite, 21-desacetyldeflazacort.[1] Indeed at present, there are no official specifications to control its physicochemical quality or biopharmaceutical properties, hence the importance to study the solid state characteristic of DEF. This compound is a crystalline solid, practically insoluble in water, with m.p. 256 °C . The crystal structure presents space group P212121 and the following lattice parameters (Å): a = 11.2300(5), b = 12.8161(8), c = 16.171(1) [2] In general, the pharmaceutical laboratories use micronized process to reduce the particle size in order to increase the dissolution velocity of the drugs. However, this process causes changes like: polymorphic transitions, particles agglomeration, less fluidity and wettability etc. Therefore, this methodology needs to be controlled not only by the routine analysis, particle size distribution, but also the crystalline size reduction and the strain increase should be determined. These solid state properties impact in the dissolution behaviour and stability performance of drugs so that it is advisable to have methodologies to controlled them. In this work we studied crystallization in different solvents and preparation conditions (several percentages of methanol / water, stirring and evaporation rates etc.) in order to compare their physicochemical properties with raw materials of Brazilian market with and without micronized process. We studied crystalline structure, morphology, particle size, crystallite size, strain and their correlation with a Intrinsic Dissolution Velocity (IDV) as a relevant biopharmaceutical property. We achieved crystallization conditions to obtain crystalline samples like hollow-shaped crystals with internal channels which increase the dissolution rate of this drugs. Hollow-shaped crystals showed better performance than micronized raw materials.

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Morphological study of czochralski-grown lanthanide orthovanadate single crystals and implications on the mechanism of spiral formation

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Single crystals of monoclinic Nd:$LaVO_4$ with dimensions up to $\phi 28\times 21$ mm^2 have been grown from the stoichiometric melt by the Czochralski method, making use of different seed orientations that are perpendicular to the (010), $(1\bar{0}0)$, (001) and $(00\bar{1})$ crystal planes, respectively. A sample was also prepared with the seed orientation in an arbitrary direction relative to the crystal. The atomic structure of Nd:$LaVO_4$ was determined at room temperature by using X-ray single-crystal diffraction. The anisotropic properties of the crystal are reflected in the growth morphology of the as-grown crystals, where different degrees of spiral growth were observed. Based on the Hartman-Perdok (HP) theory, a morphology prediction was made for both monoclinic $LaVO_4$ and tetragonal YVO_4 orthovanadate single crystals. The as-grown crystals morphology developed along different seed orientations was compared to the prediction, and the influences of seed orientation on spiral growth, crystal quality, and utilization ratio are fully discussed. We find that axial symmetry breaking at the ideal atomic-level interface between crystal and melt plays a crucial role in the formation of spiral growth in the lanthanide orthovanadate single crystals. Selecting the proper seed orientation that can yield such a highly axially symmetric interface structure consisting of a series of large area facets with similar growth velocities greatly reduces spiral formation and thus is more preferable for obtaining large-sized and high quality crystals.

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