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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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Keywords: pharmaceutical, crystallization, morphology

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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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Keywords: lanthanide orthovanadate, bulk spiral growth, Hartman-Perdok (HP) theory

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Mechanism of formation of $Na_xV_2O_5$ bronze crystals grown from the melt by czochralski method

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Recently a new technique of manufacturing of nanoelectrical and nanomechanical devices has been offered. The method is formation of nanostructures on substrates by thermo-electrical operation of atoms or atoms complex currents in the direction probe-substrate or substrate-probe in automatic regime [1, 2]. Practical realization of such nanostructure formation technique demands to create bulk-active probes with emission-getter functions and to use scanning tunnel microscope of special construction to control the adsorption-desorption processes. The structural peculiarities of oxide vanadium bronze allow to emit interstitial atoms from channels of V-O skeleton on a substrate or, on the contrary, to remove atoms from a substrate and introduce them into the structural channels of the needle- probe. Increasing of cations content in homogeneous region does not influence on V-O skeleton, but physical-chemical properties vary non-monotonously.

The present paper demonstrates the structural-morphological peculiarities of β-$Na_{0.28}V_2O_5$ crystals growing from the melt in air and in reducing atmosphere by Czochralski method. Optical microscopy and STM images of surface relief for as-grown planes and cleavage planes as well as photometric analysis of REM images of lateral surface and spectra of reflex brightness in visible before and after vacuum annealing are given. Scanning tunnel microscopy was also used for observation of absorbtion-desorbtion processes on substrate with the help of emission-active probe ($Na_{0.33}V_2O_5$) in tunnel regime.

It was shown that the difficulties are arising mainly from polycrystallization during growth and breakage after crystal growth. For Cz-bronze a dendritic shape is generated during the crystallization process. Surface morphology is formed of cleavage faces of the crystal. We could observe sets of nearly parallel steps on {100} planes prolonged along growth "b" axis. Thick steps were composed of two to twenty terraces. They have "V-shaped" structures which always tend to become rounded. Terraces were usually around 240nm in height. Lateral planes of such terraces were disoriented of ≈15° relatively to each other. The height of each thick step was around 1.2 μm. The terraces were usually originated from the seed. Such growth mechanism has an important role in the formation of structure imperfections. The bulk consists of two-dimensional layers in a highly crystalline and oriented form which prolong along growth direction. It revealed that oxygen was doped into the bronze ingot while it was grown in air atmosphere. Investigations of as-grown bronze $Na_xV_2O_5$ behavior at thermal treatment in vacuum also estimated the definite role of oxygen in structure formation of Cz-$Na_xV_2O_5$ bronze. X-ray phase analysis of as-grown Cz-bronze and X-ray structure analysis in temperature interval 25-320 °C were carried out to confirm phase homogeneity and thermal stability of Cz-$Na_{0.28}V_2O_5$ crystal.

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Keywords: oxide_vanadium_bronze, Czochralskii_growth, morphology

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High Quality Protein Crystal Growth under Microgravity in JAXA PCG project

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Japan Aerospace Exploration Agency High Quality Protein Crystal Growth project (JAXA PCG) had six flight opportunities from 2009 to 2012, followed by the previous JAXA-GCF, JAXA-New-GCF project. We produced various know-how of protein crystallization experiment in space in these projects.

The protein samples are transported by Russian Progress Spacecraft to the ISS in cooperation with Federal Space Agency of Russia (FSA) and are placed in the Protein Crystallization Research Facility (PCRF) in Japanese Experiment Module "Kibo" (JEM) for 2-4 months.

The experimental opportunities are provided for Japanese national project targeting the biological protein molecules to clarify diseases and life phenomenon, for JAXA strategic mission to get results through the space experiment, for technical development to crystallize membrane protein and protein-ligand complex and for international cooperation for Russian user and Asian nations such as Malaysia.

We used "Gel-Tube method", a kind of counter-diffusion method, for crystallization. In the counter-diffusion method PEG and salt are diffused into the protein solution in a capillary and increased their concentrations gradually up to those in the precipitant solution. We introduce some experiments to know optimum salt concentration for crystallization which will be helpful for reconsideration of the salt concentration in the PEG solution if crystallization fails even by the vapor-diffusion method.

We developed the method by which we estimated the effectiveness of crystallization under microgravity environment and optimized the crystallization condition in space.

We treated more than 100 proteins onboard "Kibo". In this presentation the latest scientific results related to positive effect of microgravity environment for creating high quality crystals are introduced. Some crystals obtained in International Space Station showed the high resolution data to contribute greatly to designing new drug or new functional catalyst.

Key words: microgravity crystallization, international space station, high-resolution protein structures

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Pure $NaNO_3$ crystal growth

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