THE APPROPRIATE INTERNAL STANDARD FOR PHARMACEUTICALS: THE ART OF DEALING WITH COMPROMISES

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Early detection of unwanted spontaneous polymorphic interconversion in drug products plays a crucial role in the drug development cycle. As a consequence, the pharmaceutical industry is showing an increasing interest in accessing new methodologies to quantify these traces with the highest achievable accuracy and precision. Among all quantification methods via X-ray powder diffraction, the greatest precision is generally obtained using an internal standard [1, 2], provided that the latter satisfies a number of criteria (e.g. high symmetry, small and isometric particles, absorption similar to the analyte mixture, non-reactive). Not only the use of an internal standard allows us to quantify on an absolute scale, but it allows us to quantify by means of whole pattern methods even when a valid structural model is not available. However, the application of this method to organic powders using a position sensitive detector and synchrotron-radiation as a source of X-rays sets additional constraints on the expected properties of the Internal Standard material. In this context, we aim to identify an Internal Standard appropriate for absolute quantitative phase analysis of organic materials.

In the initial phase of this project, two internal standard candidates (one organic, one inorganic) were compared with alumina (Al_2O_3). Preliminary results highlighted issues related to: i. the ability to characterize the degree of crystallinity of the candidate materials; ii. the reactivity of the organic candidate in the mixture; iii. the inhomogeneous distribution of the internal standard within the powder volume to analyze.

At the light of these results, efforts were made to control the extrinsic contribution to the background of the diffraction pattern and assess the degree of crystallinity of the Internal Standard candidates. Although isometric particles are preferred, a new material with unconventional particle shape, known to improve the homogeneity of the mixtures, was identified and tested. The benefits and disadvantages of different particle geometry on the peak shape, homogeneity and resulting quantitative phase analysis will be discussed. A new protocol to test the candidates and additional promising materials will be presented.

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