

CHALLENGES IN DETECTING CRYSTALLINE PHASE IN AN AMORPHOUS MATRIX

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A common observation throughout the pharmaceutical industry is that, as the potency and specificity of new drug candidates are improving, the solubility is often becoming extremely poor. This can result in poor bioavailability of the active pharmaceutical ingredient (API), unless basic characteristics of the API are altered. One way to achieve the alteration is to stabilize the API in an amorphous phase. The higher energetic state of an amorphous phase often leads to significantly higher solubility, thus improving the bioavailability of drug molecule.

Poorly soluble crystalline drug molecules are readily converted to the amorphous phase using well known techniques like spray drying, jet-milling, hot-melt extrusion, or drug/polymer co-precipitation. Materials in the amorphous phase are less thermodynamically stable than any crystalline form, leading to a tendency for the amorphous materials to transform to a known or potentially unknown crystalline phase. The time scale for any transformation is also unknown and is evaluated through stability studies. The detection of crystalline phase(s) in mixed system is usually performed by X-ray diffraction. In this work, limit of detection X-ray methods were developed to detect low levels of crystalline material in amorphous materials. New challenges arose during the development of these methods, requiring a better understanding of limitations of the X-ray methods (sampling effects, homogeneity of the preparation of standards, and heterogeneity of the crystalline phase in the amorphous matrix). Therefore, the need for complementary tools such as Modulated DSC (MDSC) and Near IR Spectroscopy (NIR) were also evaluated for these amorphous systems.