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RESEARCH ARTICLE

Determination of Figures of Merit for Near-Infrared, Raman and Powder X-ray Diffraction by Net Analyte Signal Analysis for a Compacted Amorphous Dispersion with Spiked Crystallinity

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Abstract With the growing interest in solubility enhancement of drugs via solid dispersion formulations, it is becoming more crucial to find appropriate analytical methods for detection of amorphous destabilization (i.e., crystallization). The objective of this work was to compare the performance of reflectance and transmittance near-infrared spectroscopy and Raman spectroscopy methods with powder X-ray diffraction. Specifically, the methods were compared on their ability to detect low concentrations (0–2 % *w*/*w*) of crystalline indomethacin-consolidated dispersions. Partial least squares regression and net analyte signal analyses were performed for the computation of figures of merit. Based on the calibration error statistics, all methods were suitable for the quantitative determination indomethacin content above 0.5 % (*w*/*w*) or 1 % (*w*/*w*) of drug content. However, the sensitivity, selectivity, limit of detection, and data collection time found for the near-infrared reflectance measurements provides the greatest promise for future online stability monitoring of consolidated dispersions.

Keywords Figures of merit · Net analyte signal · NIRS · PXRD · Amorphous · Dispersions

Teaser This study demonstrates the usefulness of multivariate FOM determined from NAS theory in comparing calibrations from multiple analytical instruments which detect crystalline material based on different physical phenomena.

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Introduction

The theory of amorphous solids has been published and reviewed widely [1–6]. Amorphous solids are characterized as a non-equilibrium phase lacking long-range order, although sufficient nonbonded intermolecular interactions results in a condensed phase which behaves mechanically like crystalline solids [7]. The absence of periodicity in nonbonded interactions results in high internal energy and, consequently, enhanced apparent aqueous solubility relative to the crystalline state. Accordingly, this strategy has been explored as a potential solution for the many low-solubility drug candidates entering the development process. However, spontaneous reversion of the metastable drug to a more thermodynamically stable state (i.e., recrystallization) is an inherent risk, making strategies which kinetically stabilize the amorphous phase of particular interest to the pharmaceutical industry.

Indomethacin (IMC) has been selected as a model drug for this study because it is both amenable to amorphization and prone to recrystallization in pharmaceutically relevant storage conditions. Solubility-limited IMC exists in two nonsolvated monotropic polymorphic crystalline forms, including the low-temperature stable γ-form and high-temperature metastable α-form [8]. The polymorphs exhibit differences in the carboxylic acid group interactions as well as in molecular conformation.