J Pharm Innov (2013) 8:45–55
DOI 10.1007/s12247-012-9146-6

RESEARCH ARTICLE

Online Monitoring of Pharmaceutical Materials Using Multiple NIR Sensors—Part II: Blend End-point Determination

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Published online: 5 January 2013

Abstract The effect of various blend end-point algorithms on the observed blending time of pharmaceutical powders and content uniformity of subsequent tablets was investigated for a five-component system. The blending process was monitored online, in real time, using two near-infrared sensors. Algorithms based on the standard deviation, average, and distributions of concentration predictions were tested for all major blend constituents, respectively. The potential to combine sensor outputs in the end-point decision was contrasted by the consideration of the two sensor outputs individually or simultaneously. The algorithms employed demonstrated highly variable end-points when compared with the final tablet quality, although blends were deemed to have reached homogeneity faster when only the active ingredient was considered. Some algorithms proved to be either too sensitive to local mixing and demixing phenomena or not sensitive enough, yielding results not consistent with the observed tablet content uniformity. Results showed that the choice of an end-point algorithm must be directed by the product of interest (nature of the active, therapeutic window, etc.), the particular characteristics that the delivery forms should have (immediate release, sustained release), and most significantly, the purpose of blending. A single algorithm is not expected to be adequate across all formulations. However, as the complexity of the blending process increases (multiple sensors, trends of multiple ingredients to follow, etc.) the decision process becomes more complex with not only calibration maintenance issues to consider, but also calibration transfer, relevance of the criteria for the actives, and the desired final product properties.

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Keywords Blending · Pharmaceutics · Near infrared spectroscopy · End-point · Content uniformity

Introduction

As part of the multiple unit operations involved in the manufacturing process of pharmaceutical solid dosage forms, blending is critical in ensuring uniformity of composition in the final dosage form [1]. Problems incurred during blending can lead to inadequate tablet quality attributes, such as content uniformity, assay, disintegration time, dissolution behavior, etc., all of which can directly impact dosage form efficacy, in vivo performance, and patient safety. Controlling blend homogeneity is a necessary step in a drug product manufacturing process. Thief sampling followed by quantitative assay has been the reference method of choice [2, 3], but it is progressively being replaced by process analytical technologies, specifically near-infrared spectroscopy (NIRS) [4–6].

The successful implementation of a blending control system for pharmaceutical products based on NIRS requires the investigation of two elements: the process trajectory and the process end-point. No two blends will follow exactly the same mixing kinetics and will therefore provide a range of homogeneity trends over time, defining the process trajectory. Differences in vessel loading patterns, raw material characteristics (moisture content, lot-to-lot variability), operator practices, etc. will affect blending kinetics. These elements will make the degree of homogeneity vary at any given point in time from batch to batch. During product development and initial manufacturing stages, an understanding of the general trends in mixing kinetics will be acquired and characteristics of a stable blending operation across process and material variability will be determined. Knowledge of these characteristics will allow the evaluation