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Continuous monitoring of API content, API distribution and crushing strength after tableting via near-infrared chemical imaging

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ABSTRACT

Near-infrared chemical imaging (NIR-CI) with high-speed cameras based on the push-broom acquisition principle is a rapidly-evolving and can be used for a variety of purposes, from classification (and sorting) of products to mapping spatial distribution of materials. The present study examined if NIR-CI is suitable for tablet manufacturing. To that end, the tablets were introduced into the CI system via a flat belt conveyor. A formulation, which consisted of 4 wt.%–6 wt.% caffeine, 5 wt.% crospovidone as a disintegrant, 88 wt.%–90 wt.% lactose as a filler and 1 wt.% magnesium stearate as a lubricator, was tableted at compression forces ranging from 5 kN to 30 kN. The intra- and inter-tablet homogeneity of caffeine and the tablet's hardness were analyzed via NIR-CI. For the homogeneity evaluation, two methods were applied: standard deviation (SD) and distributional homogeneity index (DHI). The results showed that the SD of caffeine in a single tablet increased with an increase in the caffeine content. This was attributed to natural variations in a binary mixture of caffeine and excipients. Overall, the chosen NIR-CI setup has strong potential to be transferred to the production scale to monitor all tablets in a production stream.

1. Introduction

Tablets are the most common dosage form that occupies around 80% of the market (Bauer-Brandl and Ritschel, 2012). Thus, improving their manufacturing in terms of automation and quality is of significant interest to the pharmaceutical industry. This particularly concerns in-line monitoring of critical quality attributes (CQAs) and material properties or processing parameters that influence the CQAs. Moreover, in-line approaches are an integral part of a real-time release testing (RTRT) strategy and are the prerequisite for implementing continuous manufacturing. With regard to tablet release, the regulators require testing of the following standard quality attributes: description (appearance), identity, assay (or weight), impurities, dissolution/disintegration, hardness/friability, uniformity of dosage units (UDU), water content and microbial limits (ICH Harmonised Tripartite Guideline, 1999). In order to achieve RTR, all of these CQAs have to be measured, calculated via soft sensor models or proven to be irrelevant by risk analysis. Many of the demanded QAs can currently only be measured at-line at a limited number of samples.

Appearance may be examined with an automatic visual inspection system after coating. At-line HPLC analysis can detect impurities, e.g., via an automated analysis of dissolved final tablets. Identity and physical form can be analyzed through spectroscopic techniques (Simon et al., 2015), often in the transmission mode using the final tablets. Assay and uniformity of the blend (BU) or dosage units (UDU) can be measured by means of spectroscopy either in the powder stream prior to compaction or in the final tablets. For assay and UDU purposes, the tablet weight also has to be determined via automated tablet testers. Dissolution of a BCS class 1 or 3 active pharmaceutical ingredient (API) can be predicted based on the disintegrant distribution (Yekpe et al., 2015) or the particle size (e.g., of granules) and assay. Hardness and friability depend on the properties of raw materials (e.g., elasticity and brittleness, their relative amounts in the final tablet, i.e., UDU) and the compression force of the tablet press. They can be tested via automated tablet testers. Dissolution/disintegration are also impacted by raw material properties, e.g. solubility and chosen disintegrants, but also depend on UDU and compression force. Thus, for hardness/friability and dissolution/disintegration a detailed knowledge of the effect of raw material properties on the final tablets is required, which can be included in soft-sensor

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models for predicting the desired properties in combination with the measurements of in-line accessible UDU and hardness. As such, an in-line analysis of UDU and hardness is an important aspect of a RTRT strategy.

The widest applied spectroscopic technique for in-line analysis is Near-Infrared Spectroscopy (NIR) based on spot probes. This is a well-established technology for monitoring powder blends during or after blending (Besseling et al., 2015; Blanco, 2002; El-Hagrasy et al., 2006; Scheibelhofer et al., 2013a, 2013b; Shi et al., 2008). Monitoring the blend as close to compaction as possible can be achieved by placing a NIR probe into the feed frame of the press (Šašić et al., 2014; Wahl et al., 2014). No further segregation after the point of analysis prior to compaction can occur. Järvinen et al. monitored a continuous direct compaction line via NIR measurements of the powder stream in a continuous mixer and of each tablet on a tablet press (Järvinen et al., 2013). Monitoring all tablets prior to ejection from the tablet press using a NIR probe results in a well-defined sample presentation. Moreover, spectra acquisition can be synchronized with the tablet press. The downside is having to limit the manufacturing speed according to the sensor's acquisition rate and the velocity of the tablet in front of the sensor defined by the turret rotation. Many publications describe determining the API content and the hardness of final tablets via off-line analysis using NIR single-point probes (Blanco et al., 2006; Cogdill et al., 2005; Moes et al., 2008; Schoenmakers et al., 2006; Tabasi et al., 2008).

We focused on monitoring tablets during manufacturing via NIR chemical imaging (NIR-CI), which is a rapidly-evolving technology in food, waste and mineral sorting and, recently, the pharmaceutical industry. A review by Boldrini et al. presents the advantages and disadvantages of CI in in-line analysis (Boldrini et al., 2012). Another review discusses image analysis based on spectral and textural information (Duchesne et al., 2012). NIR-CI has been used to monitor powder blends (Ma and Anderson, 2008; Osorio et al., 2014; O. Scheibelhofer et al., 2012). In contrast to NIR probe sensing of blends, NIR-CI has the advantage of simultaneously acquiring information about spatial and temporal homogeneity. This allows the identification of single objects, which are not within specification. The distribution of API and excipients in the tablets can be monitored via high-resolution imaging using NIR-CI. For example, Cruz et al. evaluated the API distribution (acetyl salicylic acid) in commercial tablets by examining a histogram of the concentration distribution based on the augmented MCR-ALS (multivariate curve resolution based on alternating least squares algorithm) (Cruz et al., 2009). When comparing the ASA distribution in products made by several manufacturers, significant variations were found. Amigo et al. utilized augmented MCR-ALS, which includes spectra of pure components into the MCR-ALS optimization, to monitor low-dose excipients down to 1.5% of nominal content (Amigo and Ravn, 2009; Puchert et al., 2010).

To date, NIR-CI has mainly been used in lab settings, aiming at high resolution per sample, mostly greater than 100×100 pixels. Common imaging systems can acquire about 300 pixel in spatial direction at an acquisition rate (frame rate) of 300 Hz. At a resolution of 100×100 pixels per tablet, the number of tablets that can be monitored by such a system is limited to about 9 tablets per second or 32,400 tablets per hour. For a tablet of 6 mm in diameter, one pixel corresponds to a physical size of 60 μm. According to Sellors et al., this is approximately the maximal resolution that NIR-CI can achieve in the diffuse reflection mode due to the sampled volume defined by the penetration depth of NIR radiation (Sellors and Spragg, 2013). The actual values strongly depend on the scattering and absorption coefficients of the sample.

For an in-line analysis of the entire production stream, a much faster system is needed. Reducing the resolutions to maximal hundred pixels per tablet increases the speed, yet deviations in the content homogeneity can be still detected. In this case, the maximum number of monitored tablets can be drastically increased to approximately one million tablets per hour.

The desired information that should be extracted from chemical images, consisting of thousands of spectra, is often the mean API content per tablet or time period and the homogeneity, i.e., the spatial variation. Thus, data received from an imaging system will be strongly summarized to utilize the imaging information for process control. A common method is a statistical analysis of a histogram of the API content per pixel, which can include standard deviation (SD), kurtosis and skewness (Khorasani et al., 2015). A drawback of the histogram methods is that they neglect the spatial information. To that end, Rosas et al. introduced a homogeneity index H% that includes the spatial information (Rosas and Blanco, 2012a, 2012b) and uses the concept of macropixels (a square with the size of several pixels) to calculate the local homogeneity of a sample. The results of an analyzed sample are compared to a randomized rearrangement of the samples pixels. A further development considers previous knowledge about particle size to define the macropixel size (Rosas et al., 2013). Sacré et al. proposed to vary the macro-pixel size to determine the homogeneity index regardless of particle size and coined the term 'distributional homogeneity index' (DHI) (Sacré et al., 2014). The DHI assesses the distribution of API but not the absolute variation of API content. Different SD can still lead to identical DHI, e.g., if the spatial distribution is identical, but the absolute values of variation is increased. As such, to fully characterize the homogeneity of a tablet both the histogram analysis and DHI should be used. Here NIR-CI can bring significantly more information about each tablet in a batch compared to spot probe NIR.

In this work, we applied NIR-CI to monitor the tablet content uniformity and crushing strength and assessed if chemical imaging could be transferred from the lab to the production floor. For the purposes of analysis, the tablets were placed on a flat belt conveyor, which can potentially be used for integrating the experimental setup into a tableting line and monitoring the entire production stream. Data reduction was accomplished by computing the mean, SD and DHI for each tablet. Inter- and intra-tablet statistics were calculated to provide information for process control strategies.

2. Materials and methods

2.1. Materials

The nominal (base-line) formulation for tableting consisted of 5 wt.% caffeine (caffeine purum anhydrous >90%, Sigma Aldrich) as an API, 5 wt.% crospovidone (Kollidon CL-M, Ph. Eur., BASF) as a disintegrant, 89 wt.% lactose (Tablettose 70, Meggle) as a filler and 1 wt.% magnesium stearate (Applichem Panreac, Ph. Eur. grade) as a lubricant. Mixtures of 500 g each were prepared and mixed in a tumble blender (Turbula T2F, Maschinenfabrik Willy A. Bachofen) for 15 min at 60 rpm, followed by adding the lubricant and 2 more min of mixing. The caffeine content was varied between 4 wt.% and 6 wt.% in increments of 0.5 wt.% and the compaction force between 5 kN and 30 kN in increments of 5 kN. The compaction force varied within ±1 kN at each level. Flat-faced tablets with a diameter of 11 mm and a weight of 550 mg were manufactured using an adjustable single punch press (Stylcam 200R, Medel'pharm).

2.2. NIR spectroscopy

The chemical images were acquired using a NIR diode array spectrometer (EVK Helios G2-320 Class, EVK DI Kerschhaggl) with an InGaAs detector. The spectrometer has spatial and spectral