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Near-infrared chemical imaging (NIR-CI) of 3D printed pharmaceuticals

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ABSTRACT

Hot-melt extrusion and 3D printing are enabling manufacturing approaches for patient-centred medicinal products. Hot-melt extrusion is a flexible and continuously operating technique which is a crucial part of a typical processing cycle of printed medicines. In this work we use hot-melt extrusion for manufacturing of medicinal films containing indomethacin (IND) and polycaprolactone (PCL), extruded strands with nitrofurantoin monohydrate (NFMH) and poly (ethylene oxide) (PEO), and feedstocks for 3D printed dosage forms with nitrofurantoin anhydrate (NFAH), hydroxyapatite (HA) and poly (lactic acid) (PLA). These feedstocks were printed into a prototype solid dosage form using a desktop 3D printer. These model formulations were characterized using near-infrared chemical imaging (NIR-CI) and, more specifically, the image analytical data were analysed using multivariate curve resolution-alternating least squares (MCR-ALS). The MCR-ALS algorithm predicted the spatial distribution of IND and PCL in the films with reasonable accuracy. In the extruded strands both the chemical mapping of the components in the formulation as well as the solid form of the active compound could be visualized. Based on the image information the total nitrofurantoin and PEO contents could be estimated., The dehydration of NFMH to NFAH, a process-induced solid form change, could be visualized as well. It was observed that the level of dehydration increased with increasing processing time (recirculation during the mixing phase of molten PEO and nitrofurantoin). Similar results were achieved in the 3D printed solid dosage forms produced from the extruded feedstocks. The results presented in this work clearly demonstrate that NIR-CI in combination with MCR-ALS can be used for chemical mapping of both active compound and excipients, as well as for visualization of solid form variation in the final product. The suggested NIR-CI approach is a promising process control tool for characterization of innovative patient-centred medicinal products.

1. Introduction

For more than 200 years the tablet compaction process has been the state-of-the-art approach for commercial scale production of medicinal products. Despite being a robust and reliable manufacturing solution, this processing principle and the current stringent regulatory framework do not allow fast modification of the tableting process, therefore not enabling manufacturing of flexible doses and more personalized medicinal products for patient-centered schemes. There is an increasing need for flexible manufacturing solutions enabling fast production of personalized doses (Losi et al., 2006; Preis et al., 2015; Rantanen and Khinast, 2015). The main advantage of personalized pharmaceutical products is the ability to tailor the solid dosage form for each individual patient and thereby reduce the risk of adverse effects in the form of under- or over-dosing. Combining multiple therapies into one solid dosage form have also been shown to increase patient adherence (Connor et al., 2004). Various techniques have been employed in the manufacturing of personalized dosage forms, a recent development being the use of inkjet printing (Preis et al., 2015; Sandler et al., 2011). Another approach for flexible dosing is the utilization of extrusion-based production that enables innovative product shapes that can be divided into the required dose (Laukamp et al., 2014). Hot melt extrusion (HME) involves processing of molten polymer based formulation in an

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inherently continuously operating process (Crowley et al., 2007). The result is a product of uniform shape such as a filament or a film that can be used for further processing (Breitenbach, 2002), e.g. for 3D-printing into tablets (Khaled et al., 2014). 3D printing is a potential approach that allows production of more innovative product geometries for control of the API release profile (Goyanes et al., 2014, 2015b; Skowyra et al., 2015) For an extensive overview on 3D printing the reader is referred to recent review articles (Alhnan et al., 2016; Jonathan and Karim, 2016). The application of hot-melt extrusion (HME) in the pharmaceutical industry is increasing due to its proven advantages like being a solvent free continuous process with fewer unit operations and better content uniformity (Crowley et al., 2007). Hot-melt extrusion has been used for the production of a diverse range of products, e.g. tablets (Gryczke et al., 2011), pellets (Follonier et al., 1994), films (Repka and McGinity, 2001) and implants (Ghalanbor et al., 2010). Filaments produced by HME have been used as compounds for fused deposition modeling (FDM) printing of relatively simple solid dosage forms (Goyanes et al., 2015a; Sandler et al., 2014), as well as for systems containing multiple drug compounds (Khaled et al., 2014).

With HME being a continuous process, the use of process analytical technologies (PAT) is of special interest as it allows for direct characterization of the extrudates during production. Near-infrared spectroscopy (NIRS) is a well-established process analytical tool (Netchacovitch et al., 2015; Reich, 2005) for various applications (De Beer et al., 2011; Khorasani et al., 2015; Luypaert et al., 2007) and has also been utilized for process monitoring and control of HME processing. Recently, NIRS has been used for in-line characterization of extrudates of metoprolol tartrate (MPT) and Kollidon® SR. A NIR probe was placed in the die area and spectra was integrated every 30 s for monitoring the interactions between MPT and Kollidon® SR. Molecular interactions were observed during the extrusion and MPT turned partially amorphous during processing. The NIR results were confirmed by differential scanning calorimetry, Attenuated total reflectance infrared spectroscopy and Raman spectroscopy (Saerens et al., 2012). Raman spectroscopy has also been used as PAT for characterization of mixtures of metoprolol tartrate and Eudragit® RS PO by placing a Raman probe near the die end using an exposure time of 1 s (Saerens et al., 2011). While these methods are powerful, they have drawbacks as they average the spectral information into one spectrum representing the effective sampling volume and no distribution information or spatial distribution of components can be obtained. One approach for obtaining this spatial information is near-infrared spectroscopy chemical imaging (NIR-CI). A near-infrared chemical image is represented by a 3-dimensional data array, a hyperspectral image. Mathematically a hyperspectral image is represented by $(X \times Y \times \lambda)$, where $X \times Y$ represents the spatial data, while λ represents the spectral data. This means that each (X,Y)-pixel of the image consists of a Near-infrared spectrum, λ (Amigo, 2010). NIR-CI has been used in combination with different multivariate analytical techniques both for characterization of final dosage forms such as tablets (Amigo et al., 2008; Franch-Lage et al., 2011; Ravn et al., 2008), and also for intermediate products, such as predicting roller compacted ribbon porosity (Khorasani et al., 2015) and evaluation of mixing in twin screw granulation (Vercruysse et al., 2014). NIR-CI has recently been used for quality control of inkjet printed personalized dosage forms (Vakili et al., 2015)

A hyperspectral image contains a vast amount of data and must be subjected to various mathematical algorithms to extract the required information, e.g. the spatial API distribution in the sample. Preprocessing algorithms are applied first to reduce noise and artifacts from the data, such as scattering effects due to physical variation and differences in particle size or density. A different range of processing for analysis of hyperspectral images exists, the simplest being the exploratory methods such as principal components analysis (PCA). In PCA, the sources of variance are plotted in loading plots and score plots and can reveal mixing or distribution trends in the samples (Amigo et al., 2008). If full quantitative characterization of the samples is required, partial least squares (PLS) regression is useful. PLS regression requires an extensive calibration set and is therefore labor-intensive (Ravn et al., 2008). Multiplicative curve resolution – alternating least squares (MCR-ALS) is a semi-quantitative method that only requires the spectra of the raw materials in a sample. The algorithm assigns scores to each spectrum of the hyperspectral image depending on its similarity to the raw material spectrum (de Juan and Tauler, 2006).

MCR-ALS has been used for distribution assessment of components in traditional dosage forms, such as tablets, using NIR-CI. The advantage of not needing a calibration set is that the method development phase becomes less labor-intensive, which will enable faster and more efficient analysis of dosage forms during manufacturing (Amigo and Ravn, 2009). We are reporting the application of fast method development for innovative future pharmaceutical products based on melting process and 3D printing of customized products

The aim of the study was to investigate the applicability of near-infrared chemical imaging (NIR-CI) as a quality control tool for hot-melt extruded (HME) products (films and extrudates) and 3D printed dosage forms. HME was used for preparing films containing indomethacin and polycaprolactone, filaments containing nitrofurantoin and polyethylene oxide (PEO), as well as filaments containing nitrofurantoin and polylactic acid (PLA) that was used for 3D printed tablets. Specifically, the use of the Multivariate Curve Resolution – Alternating Least Squares (MCR-ALS) algorithm as an image analytical routine was explored.

2. Experimental

2.1. Materials

Indomethacin (IND) was obtained from Hawkins Pharmaceutical Group (Minneapolis, USA) and polycaprolactone (PCL) was obtained from MakerBot (Makerbot Flexible Filament®) (New York, USA). Nitrofurantoin (NF) anhydrate β-form (NFAH, CSD refcode: LABJON02) was obtained from Fagron A/S (Copenhagen, Denmark). Polyethylene oxide (PEO 100,000) was purchased from Sigma Aldrich (Copenhagen, Denmark). Nitrofurantoin monohydrate (NFMH) was generated from anhydrate by overnight slurry experiment in water at 25 °C. Indomethacin and hydroxyapatite (HA) were both purchased from Sigma Aldrich (Copenhagen, Denmark) and polylactic acid (PLA) was obtained from 3D Nielsen (Helsingør, Denmark).

2.2. Methods

A microextruder with co-rotating twin-scew setup and a re-circulatoin channel (Xplore Instruments, Geelen, Netherlands) was used to produce extruded films, strands, and feedstock for the 3D printing of tablets.

2.2.1. Extruded films

In order to prepare films, a physical mixture of 10% (w/w) IND as the active pharmaceutical ingredient (API) and 90% (w/w) PCL as polymer, was extruded using a film die with a thickness of 0.4 mm and a width of 35 mm. To model the influences of the process parameters on API concentration distribution, a two-factor two-level full factorial design of experiment was estabilished, Table 1. The full factorial design consists of seven experiments including