

Note

Distribution of binder in granules produced by means of twin screw granulation



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ARTICLE INFO

Article history:

Received 11 October 2013

Received in revised form 5 December 2013

Accepted 9 December 2013

Available online 19 December 2013

Keywords:

Twin screw granulation

Binder distribution

CARS

ABSTRACT

According to the quality by design principle processes may not remain black-boxes and full process understanding is required. The granule size distribution of granules produced via twin screw granulation is often found to be bimodal. The aim of this study was to gain a better understanding of binder distribution within granules produced via twin screw granulation in order to investigate if an inhomogeneous spread of binder is causing this bimodal size distribution. Theophylline–lactose–polyvinylpyrrolidone K30 (PVP) (30–67.5–2.5%, w/w) was used as a model formulation. The intra-granular distribution of PVP was evaluated by means of hyperspectral coherent anti-Stokes Raman scattering (CARS) microscopy. For the evaluated formulation, no PVP rich zones were detected when applying a lateral spatial resolution of 0.5 μm , indicating that PVP is homogeneously distributed within the granules.

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Traditionally, the pharmaceutical industry has always relied on batch processing. With changing perspectives from the regulatory bodies (e.g., FDA, EMA) on pharmaceutical manufacturing, it is now possible for companies to switch their production from batch towards continuous production. For wet granulation, a frequently applied intermediate processing step during the production of pharmaceutical solid dosage forms, high shear twin screw granulation, has shown to be a most promising continuous alternative to conventional high shear and fluid bed granulation (Vervaet and Remon, 2005). Nonetheless, twin screw wet granulation is also known for its typical bi-modal granule size distribution (Dhenge et al., 2010; El Hagrasy et al., 2013). Granule loads mostly tend to contain either a large amount of fines (<250 μm) or a large amount of oversized granules (>1400 μm). Increasing the yield fraction without a milling step remains challenging. In 2010, Crean et al. investigated the intragranular microstructure of granules produced with lactose and 3% (w/w) of polyvinylpyrrolidone (PVP, both Povidone[®] K29/32 and K90 were used). X-ray micro-computed tomography, confocal Raman spectroscopy and infrared analysis were applied in order to investigate granules manufactured by means of aqueous high shear granulation (Kenwood CH180 mixer).

They suggested the molecular association of PVP with lactose. PVP was found to be inhomogeneously spread within the granules and PVP rich zones with sizes up to 20 μm were reported.

Earlier findings (Fonteyne et al., 2013b) from our research group showed indeed a bi-modal size distribution when evaluating granules produced with the twin screw granulator module of the ConsiGma[™]-25 (GEA Pharma systems nv, Collette, Wommelgem, Belgium), a fully continuous from powder-to-tablet manufacturing line. A recurring comment on twin screw granulation as an agglomeration technique is the short residence time of the processed material in the granulator barrel, resulting in a short interaction and mixing time between powder, binder and granulation liquid. The aim of this study was to evaluate if the short residence and interaction time between powder and binder results in an inhomogeneous spread of binder, as seen by Crean et al. for batch wise high shear wet granulation. Consequently, the presence of binder rich zones could then be a reason for the bi-modal size distribution of the granules. Therefore, the distribution of the binder within granules produced by means of twin screw granulation was investigated using an optical imaging technique.

PVP Kollidon[®] 30 (BASF, Ludwigshafen, Germany) was used as a binder at a concentration of 2.5% (w/w based on dry mass). Anhydrous theophylline (Farma-Quimica sur S.L., Malaga, Spain) was used as a model API in a concentration of 30%, with lactose monohydrate 200 M (Caldic, Hemiksem, Belgium) as a filling excipient.

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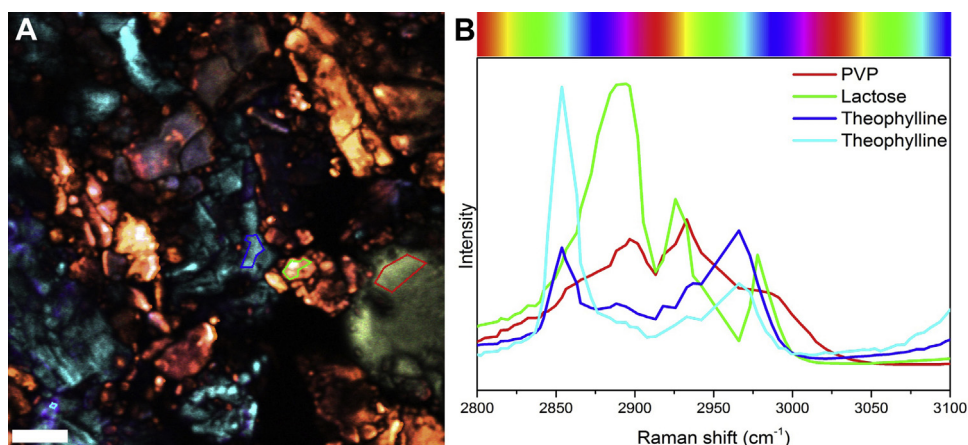


Fig. 1. (a) Hyperspectral image of the surface of a compact consisting of lactose (67.5%), theophylline (30%) and PVP (2.5%), collected in the spectral region of 2800–3100 cm^{-1} . In the figure PVP is coloured yellow, lactose zones are orange and zones containing theophylline are coloured blue. (b) The spectra extracted from the three marked zones, corresponded to PVP (red), theophylline anhydrate (blue) and lactose monohydrate (green), respectively. Scale bar is 20 μm . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

PVP was either added to the dry premix or dissolved in the granulation liquid (distilled water) (Fonteyne et al., 2012; Vercruyse et al., 2012). All granules were produced using the above-mentioned ConsiGma™-25 production line, which has been described extensively elsewhere (Fonteyne et al., 2013a).

Hyperspectral coherent anti-Stokes Raman scattering (CARS) microscopy was selected for the visualization of PVP in the granules because of its high specificity and fast spectrally and spatially resolved imaging (Garbacik et al., 2012). The CARS microscope used for this study, consisted of an Nd:YVO4 picosecond laser (Coherent, USA) operating at a fundamental wavelength of 1064 nm. This laser was frequency doubled to pump an optical parametric oscillator (OPO) (APE, Germany), which produced two dependently tunable laser beams. The fundamental laser beam was used as Stokes and combined with one of the beams from the OPO, after which they are directed into an inverted microscope (Olympus, FluoView 300, IX71, Japan). The backscattered CARS signal was detected with a photomultiplier tube (Hamamatsu, Japan). No spectral data processing was required to interpret the CARS-data.

Preliminary tests were conducted in order to evaluate the feasibility of CARS microscopy for the visualization of PVP in granules. Initial hyperspectral images of the individual materials were collected to identify a spectral region to distinguish between the three compounds. The region between 2800 cm^{-1} and 3100 cm^{-1} was selected for further evaluation. A physical

mixture (theophylline:lactose:PVP; 30:67.5:2.5) was compacted and hyperspectral CARS imaging was conducted collecting backwards scattering light using a 20 \times /0.55NA objective. Each frame of the hyperspectral image was collected with a 4 cm^{-1} interval for a total of 50 frames. Fig. 1a shows a hyperspectral image of the surface of the compact, recorded between 2855 cm^{-1} and 2990 cm^{-1} . Twenty images (160 $\mu\text{m} \times 160 \mu\text{m}$) of the compact were collected in total. Three different chemical components can be distinguished, coloured blue, orange and yellow. Orange was the most abundant colour, followed by blue and yellow. Individual spectra were extracted for each coloured zone (Fig. 1b). These spectra were compared with the spectra of the individual components and represented the theophylline (blue), lactose (orange) and PVP (yellow) zone, respectively. It was shown that CARS microscopy could distinguish between PVP, theophylline and lactose when physically mixed and compacted. Hence, CARS is a suitable technique for the detection of the PVP binder in continuously produced theophylline–lactose granules.

For the evaluation of the actual granules, a 60 \times /1.2NA objective was used, resulting in an axial spatial resolution of 1 μm and a lateral spatial resolution of 0.5 μm . The surface of the granules was evaluated and hyperspectral CARS images were collected from both the theophylline–lactose–PVP granules and blanks, which only contained PVP and lactose (not shown). Fig. 2a shows the hyperspectral image taken from the surface of a theophylline-containing

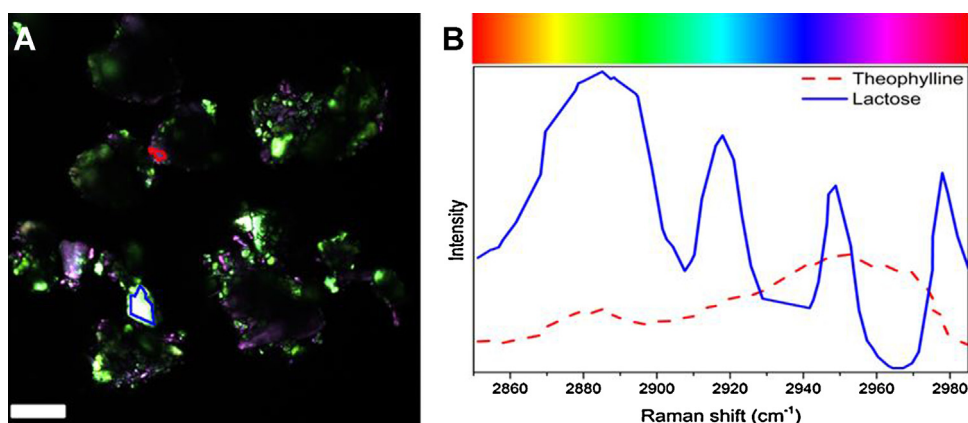


Fig. 2. (a) Hyperspectral image from the surface of a theophylline–lactose–PVP containing granule. PVP was added to the dry premix. The purple colour represents theophylline, green represents lactose. (b) Extracted CARS spectra and hyperspectral image colour map. Scale bar is 20 μm . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

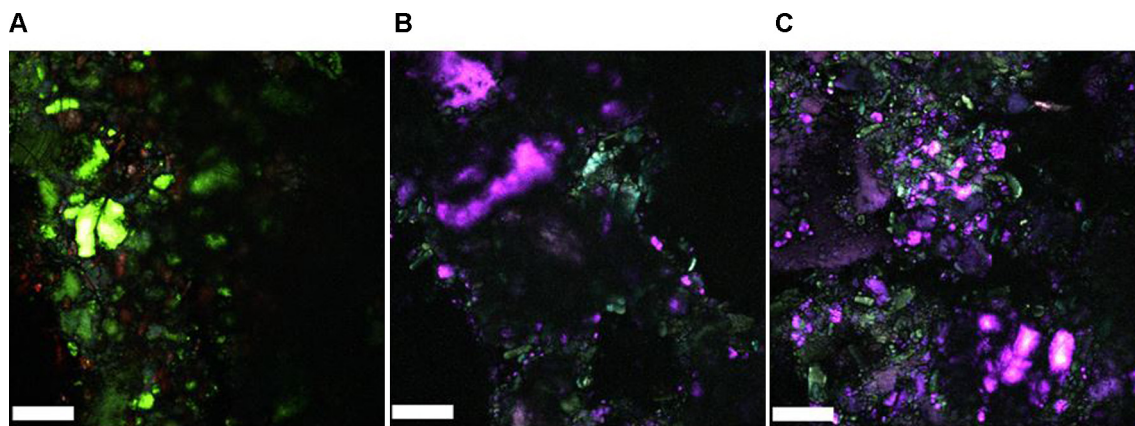


Fig. 3. Three typical examples of hyperspectral images of cross-cuts of theophylline–lactose–PVP granules. The colour map with the highest discriminatory power was selected, resulting in a. theophylline in red and lactose in green, (b) theophylline in blue and lactose in pink, and (c) theophylline in green and lactose in pink. The scale bars are 20 μm . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

granule prepared with PVP added in the dry premix. The same spectral region as for the preliminary experiments was used. Clearly, two components can be determined. The most abundant compound is coloured green, which is representing lactose, whereas purple represents theophylline. From these images collected with a lateral spatial resolution of 0.5 μm , no PVP rich zones could be distinguished, indicating a homogenous spread. Analysis of theophylline-containing granules prepared with PVP dissolved in the granulation liquid (not shown) also identified regions of theophylline and lactose, but no zones of PVP were present. Likewise, when evaluating the lactose–PVP granules (not shown), only lactose was identified.

Next, the internal granular microstructure was investigated. Granules were sieved, after which granules larger than 1000 μm were sliced lengthwise using a razorblade. Again, hyperspectral scans were collected in the 2800–3100 cm^{-1} spectral region. For each mapping measurement, three different colour maps were projected and the map with the highest discriminatory power was chosen for further evaluation. Fig. 3 shows three examples of the mappings performed on theophylline-containing granules. Again, only two components could be distinguished. The colour covering the largest area of the image represented lactose monohydrate, with theophylline covering the rest of the image. Theophylline and lactose are well mixed and homogeneously spread within the granule. Again, no PVP-rich zones were encountered when evaluating the cross-sectional surface of the granules. The hyperspectral images of the blanks resulted in monochrome images in which only lactose could be detected. To sum up, for all the before mentioned experiments, in total 68 images were collected, covering a total area of 13 mm^2 and no PVP-rich zones could be detected in any of those.

In contrast to what has been reported regarding lumps of polyvinylpyrrolidone in granules produced by means of batch high shear aqueous granulation, no PVP-rich zones could be detected in granules manufactured with a twin screw granulator when applying a lateral spatial resolution of 0.5 μm . This study suggests that PVP is well mixed and equally spread within the granules, both when PVP is added in the dry premix or when it is added via the granulation liquid. Even though the residence time within the barrel is very short, PVP is well distributed within the granules. Hence, an inhomogeneous spread of PVP is not the cause of the

typical bi-modal granule size distribution obtained by continuous wet twin screw granulation.

Acknowledgements

Margot Fonteyne thanks FWO Flanders, for the travel grant to perform research at Otago University (V441711N). Andrew Fussell is supported by the Dutch Technology Foundation STW, which is the applied science division of NWO, and the Technology Programme of the Ministry of Economic Affairs (STW OTP 11114). Niko Helkimo (University of Eastern Finland) is thanked for his technical assistance.

The authors are grateful to the Pharmaceutical Solid State Research Cluster (PSSRC) to provide a forum for fruitful scientific discussions.

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