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Original Research Paper

X-ray micro tomography and image analysis as complementary methods for morphological characterization and coating thickness measurement of coated particles

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ABSTRACT

This work demonstrates the potentiality of X-ray micro tomography as a powerful tool for morphological characterization of coated particles and, in particular, of their coating layer. X-ray micro tomography provides a high level of details at both micro and macro-scale. It was, in this work, used in the determination of density, porosity, surface/volume ratio, and thickness of the coating layer. Special emphasis was put on evaluation of the adhesion core/coating shell due to its strong influence on the acceptance and goodness of the final coated compound. Different definitions of coating thickness are evaluated. The variance of these properties is assessed within particles and between particles. A novel protocol was developed in order to segment the coating shell out from the core particles. The segmented out images were used to create 3D models of such coating shells. General aspects of theses models are discussed. The potential and limitations of X-ray micro tomography are finally highlighted based on the experimental work. Image analysis was used to determine the coating thickness applied on the core particles as complementary and reference method. As case study, two series of coated particles, prepared using top-spray fluidized bed coater, were obtained, each one employing three standard well-know coating agents.

1. Introduction

Aqueous film coating is a process commonly employed in the food and pharmaceutical industries. Agglomerates, granules, tablets, pellets and nonpareil seeds are often coated with polymers in order to control the dissolution of drug from the dosage form to give the product specific functionalities. Microencapsulation is a very popular method for the preparation of coated particles and, in general, for controlled release systems. Since small changes in processing parameters have the potential to greatly affect the properties of the final product, a rapid and non-destructive analytical method which detects these differences and gives an indication of the final product characteristics could be employed profitably as a quality control tool. Examples of these characteristics are: the thickness of the coating applied and the surface area of the coating shell [1,2], intra and inter-coating thickness uniformity and homogeneity [3], adhesion core-coating shell [4,5] and micro-level structure of the coating layer (e.g. porosity, micro-cracks, air bubbles). For many reasons it is of interest to assess the above mentioned parameters and to confirm non-ambiguously the quality of the both coating process and coating shell. In fact, evaluating the properties of coatings has the double purpose of assessing the adequacy of the process controls and ensuring the optimal performance of the final product.

Several techniques are currently available for coating analyses which provide the spatial resolution necessary for thin coating layer uniformity and structure measurements as well as prediction of coating thickness.

The most widely used techniques to visualize coated particles, coating structure and thickness, surface morphology are conventional light microscopy (LM) and scanning electron microscopy (SEM) [6–8]. Among several applications, Atomic Force Microscopy (AFM) studies surface roughness. Other methods are near-infrared (near-IR) spectroscopy [1,9–11] and laser profilometer [12] that are fast and highly accurate. Alternatively, a technique that potentially can be used for routine in-process testing of coatings is Laser Induced Breakdown Spectroscopy (LIBS), which has the potential to provide both rapid in-line analyses of multiple samples as well as the necessary spatial resolution [13]. X-ray photoelectron

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spectroscopy (XPS) is a powerful technique widely used for the surface analysis of materials mainly, but it has also been used for coating thickness estimation [14]. Confocal scanning laser microscopy (CLSM) [15–21] minimizes scattered light from out-of-focus structures, and permits, through use of different fluorescence labels [22], not only analysis on the surface but also inside the material [23].

X-ray micro tomography is a relative new technique developed in the late 1970s, which enables the non-destructive, three-dimensional, visualization of the internal structure of objects [24,25]. It is based on the interaction of X-rays with matter. When X-rays pass through an object they will be attenuated in a way depending on the density and the atomic number of the object under investigation and of the used X-ray energies. By using projection images obtained from different angles a reconstruction can be made of a virtual slice through the object, non-destructively. By implementing mathematical algorithms, X-ray micro tomography creates cross-sectional images of the internal structure of the object. When these different consecutive slices are reconstructed a 3D visualization can be obtained with high resolution.

The objective of this study was to demonstrate the feasibility of X-ray micro tomography to successfully quantify film coating quality and to show the capability of this technique for measuring the thickness, its uniformity, the porosity, the density, the volume and the surface of a polymeric coating on not-spherical core particles. Particular attention was put on the valuation of the internal structures of coating layer as well as the interface core-coating shell. First a theoretical description of the technique is presented then its performance will be illustrated by both the quantification of coating quality and the calculation of coating thickness of coated particles produced via top-spray fluidised bed coating. The particles were coated by aqueous solutions of three different polymer materials and three coating levels. Two types of core particles were used. The present work aims also to demonstrate the simplicity and speed of this procedure as well as the value of the additional information that could be obtained by simple analysis.

2. Experimental section

2.1. Materials

Polymer-coated sodium benzoate and microcrystalline cellulose particles were chosen as a model system for this work. The sodium benzoate, Purox-S®, was supplied by DSM, Geleen, The Netherlands while the microcrystalline cellulose Cellets 1000 was provided by Syntapharm, Mülheim an der Ruhr, Germany. Their particle sizes, after sieving, were approximately 1150 and 1200 μm for Purox-S and Cellets, 1000, respectively. PolyVinyl Alcohol, PVA, (Mowiol® 4-98, Sigma–Aldrich, UK) with an M_w of 27,000, a viscosity of 4–4.5 Pa s (3% solution in water at 25 °C) [26], and two grades of HydroxyPropyl MethylCelluloses, HPMC, (Pharmacoat® 603 and Pharmacoat® 615, Syntapharm, Mülheim an der Ruhr, Germany) with a M_w of 13,000 and 65,000 and a viscosity of 4.5–5 and 29–31 Pa s [26], respectively were used, as received, as coating agents. The three film forming agents are referred to as PVA 4-98, HPMC 603 and HPMC 615 further in this article.

2.2. Preparation of solutions and particle coating

The aqueous solutions of PVA 4-98, HPMC 603 and HPMC 615 at 3% weight content as well as the top-spray fluid bed coating processes were performed as described previously [27]. Neither additives nor plasticizers were added to the solutions. All the polymers were used without any pre-treatment and the coating solutions were obtained according to supplier's specifications.

2.3. Scanning electron microscopy, SEM

Scanning electron microscopy is an effective method for qualitative analysis of the surface structure and morphological homogeneity of the coating shell. All images were produced with secondary electrons using a Philips XL 20 Scanning Electron Microscope (electron source from conventional tungsten's filament) operated at an acceleration voltage of 15 kV. Samples were prepared by attaching approximately 15 particles to a metallic support with araldite adhesive and a thin layer of gold was applied using an Edwards Sputter Coater (pulse mode, 6 min plasma coating) to improve the conductivity and reduce charging.

2.4. X-ray micro tomography

For the micro tomography measurements the SkyScan 1172 was used. This is a high resolution desktop X-ray micro-CT system with a closed X-ray micro-focus source. The maximum peak voltage of this tube is 100 kV with a maximum power of 10 W. It has a Tungsten reflection target and a focal spot of 5 μm. The detection system consists of a gadox (Gd_2O_2S) scintillator with a 2:1 fibre optic coupling to a 4000×2096 large format 12-bit cooled CCD camera.

The particles under investigation were put in a small Plexiglas container with an inner diameter of 3.5 mm. This sample holder was placed between the X-ray source and detector where the distance of the sample holder to the source determines the magnification of the system as a consequence of the cone beam of the source. This magnification will be set so that the container stays within the field of view of the detector for the full rotation cycle. In order to get high resolute images by X-ray micro tomography the diameter of the sample is of utmost importance and represents the key factor of the imaging process. By using the Plexiglas container it was possible to scan several particles at once and still obtain a good pixel resolution. With the camera binning of 2 by 2 pixels taken together giving 2000 pixels on a row instead of 4000, an isotropic pixel resolution of 2 μm was obtained. In Fig. 1a and b a projection image of the coated Purox-S and Cellets 1000, respectively, in the Plexiglas container can be seen.

Since the particles have a low density, an optimal contrast can be obtained using the lower X-ray energy part of the X-ray spectrum. This can be done by setting the peak voltage of the source at 40 kV with a current of 250 μA. Projection images were taken every 0.4° rotation step over 180°. To improve the signal to noise of the projection images a frame averaging of 3 was taken.

After the acquisition of the projection images the reconstruction was done using a modified Feldkamp cone beam algorithm [28]. Finally the 2D cross-sectional images of the sample were obtained in consecutive slices throughout the object. This 3D dataset can then be viewed in any direction as shown in Fig. 1c and d for coated Purox-S and Cellets 1000, respectively.

The entire acquisition took approximately 35–40 min with an exposure time of 590 ms per projection. After acquisition of the projection images, the reconstruction was performed and a series of 489 2D cross-sectional images of the specimen were obtained in consecutive slices throughout the object (Fig. 2a). Once the Region of Interest, ROI, has been chosen (Fig. 2b), the coating shells were segmented out. Only pixels belonging to the coating shell were taken into account for further calculations. After the segmentation process the coating shells were threshold and black–white (binary) images were obtained (Fig. 2c). After coating shell binarization, we generated 3D visualisations of the polymer coating shells (Fig. 2d). Investigation of the 3D structure leads to further information about the quality of the structure in terms of eventual orientation, porosity, density and core-coating layer adhesion, and thus, more in general, about the quality of the coating process.