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Short Communication: Test Method

Raman spectroscopic investigation of film thickness

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A B S T R A C T

The determination of film thickness is of prime importance in the quality assurance of coated pharmaceutical preparations. The rapid measurement of this parameter is problematic for multi-particulate pellet systems. The aim of this study was to apply the Raman spectroscopic method for the determination of the thickness of polymer coating on pellets. The change of Raman intensity was compared with measured film thickness, which was calculated from the change of the geometric parameters of the pellets, measured with an image-analyzing system. The results revealed that despite some difficulties Raman spectroscopy is a suitable method for the fast and accurate determination of film thickness on multi-particulate systems.

1. Introduction

The thickness of the film coating on solid dosage forms exerts a large effect on the drug dissolution profile of the preparation. For this reason, the determination of this parameter is of prime importance in the quality assurance of controlled release dosage forms. Traditionally, the film thickness can be determined via the addition of a specific amount of coating material, or by measurement of the geometric parameters. Geometric measurements can easily be performed on tablets, but measurements on granules or pellets are more difficult due to their size. Such measurements can be made only with image-analyzing techniques, which are accurate, but time demanding [1]. In recent years, the use of fast and powerful nondestructive methods such as interferometry [2] or spectroscopic methods (NIR, FTIR, Terahertz) has come into focus [3], which can be used for on line monitoring of the technological process [4,5], particularly as regards tablet coatings. In the case of pellet systems, this measurement is more problematic due to the size ratio of the particles and the laser spot. The present study relates to the applicability of Raman spectroscopy for the measurement of the thickness of films on pellets.

2. Experimental

The multi-particulate pellet samples were prepared in a Strea-1 fluid bed Wurster chamber (Niro Aeromatic Ltd., Switzerland). In the first step, the API was layered onto the surface of indifferent (without API) cores. Dilthiazem HCl (Ph. Eur.) and Kollidon 25 (BASF, Germany), in a relative mass ratio of 5:3, were dissolved in water to give a total solid content of 40%. The liquid was layered onto the surface of preheated Cellet 500 (ShinEtzu, Japan) cores at 50 °C. The other coating conditions for all batches were: nozzle diameter 1 mm, peristaltic pump speed 4 rpm, fan capacity 4.5, air volume 75 m³/h and outlet temperature 43 °C. The dry material consumed was 197 g for 200 g of core. The pellets were further fluidized for 10 min after layering.

Table 1
Film thickness and corresponding peak integrals of products.

	Film thickness (μm)	Integrals		
		Peak 1	Peak 2	Peak 3
Sample 1	0	0	0	0
Sample 2	15.5	9158	5369	22,155
Sample 3	23.5	11,471	7669	24,926
Sample 4	28.9	11,805	9174	26,077
Sample 5	44.4	13,876	10,416	30,428

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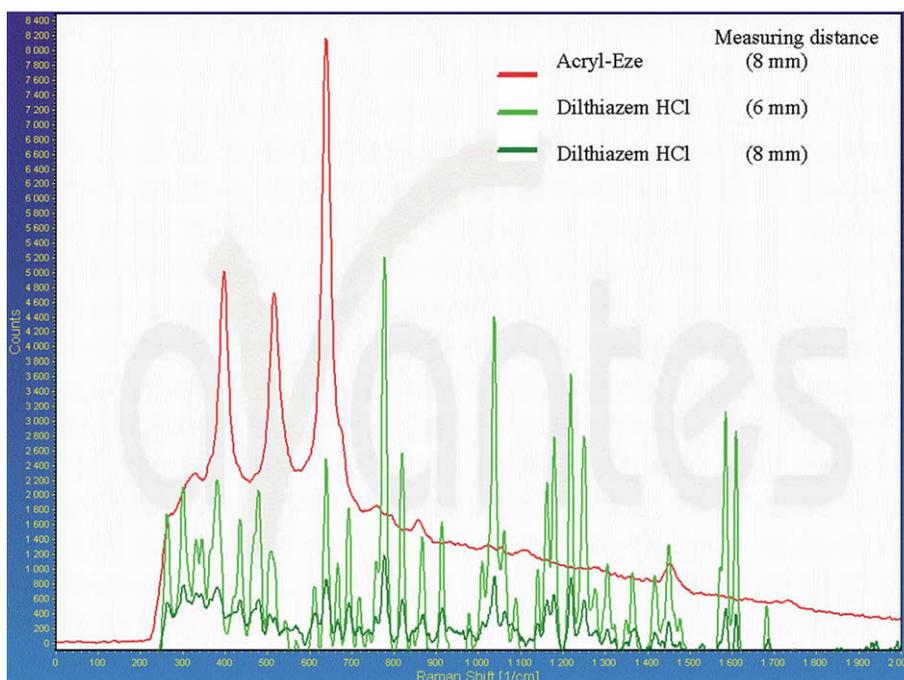E-mail address: klara.hodi@pharm.u-szeged.hu (K. Pintye-Hódi).

Fig. 1. Raman spectra of materials with different measuring distance.

After a 10-min drying time, the coating material was sprayed under the same conditions as above. The coating liquid was a 20% aqueous dispersion of Acryl-Eze (Colorcon, UK), a 1:1 copolymer of methacrylic acid and methyl methacrylate, generally used for enteric coating of dosage forms. The consumed dry material, from Samples 2 to 5 was 59.5 g, 79.5 g, 99.3 g and 125.0 g, respectively.

3. Results and discussion

3.1. Measurement of film thickness

Film thickness was determined from the results of image-analyzing measurements. Samples were taken after the layering of the active pharmaceutical ingredient and
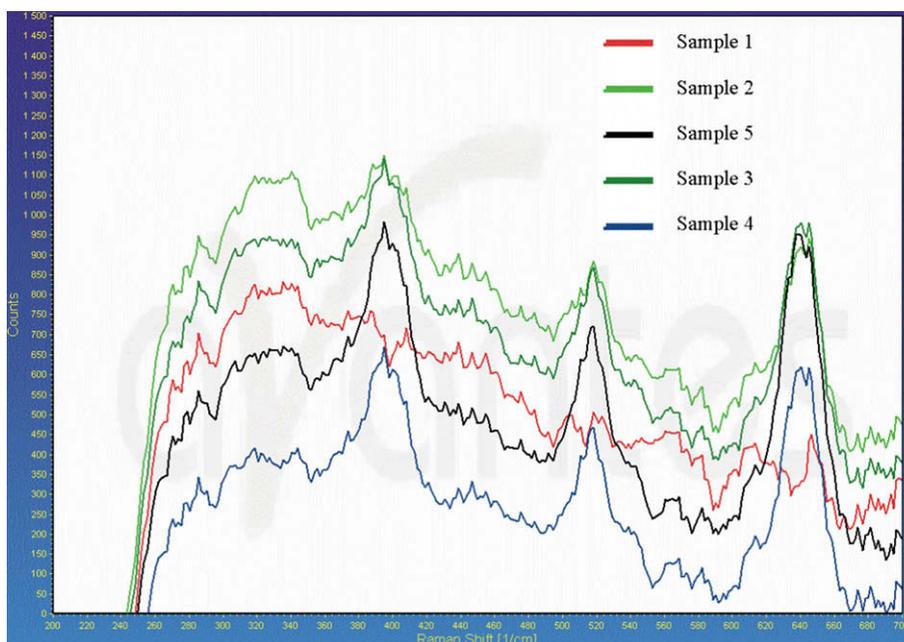

Fig. 2. Raman spectra of the samples.

after coating. The geometrical parameters of 300 particles were determined with a stereomicroscope (Zeiss, Switzerland) and a Quantimet 500 MC image-analyzing system (Leica Cambridge Ltd., UK). The mean film thickness was calculated from the difference between the mean particle diameters of the particles before and after coating. The image analysis demonstrated that the roundness of pellets was good, with calculated values in the range 1.07–1.21. However, there was a small difference between the smaller and the larger diameter of the particles. These were around 780 μm and 860 μm respectively for every batch after layering. The further measurements revealed that the film thickness of the coating layer, which was 15.5, 23.5, 28.9 and 44.4 μm for the various samples (Table 1), correlated well ($R^2 = 0.975$) with increasing amount of the coating material.

3.2. Raman spectrometry

The Raman spectra were detected off-line with an AvaSpec 2048 CCD-array Raman spectrometer (Avantes BV, The Netherlands) using a standard 785 nm laser. Two problems occurred during the spectroscopic measurements. The spectra were taken from bulk samples with a fiber optic detector, where the spot size was about three times larger than the individual particles of the sample. The scattering of the laser light on the rough surface weakened the intensity of the Raman signal, so an increase in the number of scans was necessary. Each spectrum was calculated as the average of 25 scans, which required about 2 min measurement time. The other problem was that the API exhibits many characteristic peaks in the Raman shift range 250–1700 1/cm, which partially overlap with the characteristic peaks of the coating material at 398, 516 and 640 1/cm (Fig. 1). However, the results indicated a strong influence of the measuring distance of the detector on the peak intensities. The optimal distance was 6 mm for the API and 8 mm for the coating material. This difference is a great advantage during the measurements, which were performed with an 8 mm detector distance, because the weakening of the signal of the API (Fig 1) helps the determination of the film thickness. Especially in the case of coated samples, because under these circumstances the

signals of the API were hidden in the noise, the peaks of the coating material could be determined alone without subtracting the spectra from each other (Fig 2). The integral values of the peaks were calculated after baseline correction. The integral values (Table 1) exhibited a strong correlation with the film thickness: the R^2 values of the calibration curves were 0.943, 0.892 and 0.996 respectively for the different peaks. This tendency clearly indicates that the estimation of the film thickness based on the Raman spectra improves with the improvement of the signal/noise ratio.

4. Conclusions

It may be concluded that Raman spectrometry is a suitable method for the estimation of film thickness. The measurement requires only a short time as compared with other methods. The disturbing effects of the different materials can be eliminated through selection of the optimal measuring conditions. This permits monitoring of the film thickness even during the coating process.

Acknowledgements

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