Imaging Pharmaceutical Tablets with Optical Coherence Tomography

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ABSTRACT: Optical coherence tomography (OCT) is a recently developed optical technique that produces depth profiles of three-dimensional objects. It is a nondestructive interferometric method responding to refractive index variation in the sample under study and can reach a penetration depth of a few millimetres. OCT employs near-infrared (NIR) light and therefore provides a link between NIR spectroscopy and Terahertz (THz) measurements that are often used to characterise tablets. In this article we assess the potential of OCT as a reliable and practical tool in the analysis of pharmaceutical tablets and coatings. A variety of tablets were tested with different shapes, formulations and coatings. We consider the origins of contrast in the obtained images and demonstrate that it correlates strongly with the expected tablet structure. The influence of absorption and scattering are considered for the wavelength ranges used. The results show that OCT is a promising diagnostic tool with an important role to play in the tablet and coating technologies. The high measurement speed of OCT and its relative ease of implementation make it also an attractive candidate technology for in-line quality control during manufacturing. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:385–391, 2010

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INTRODUCTION

During recent years regulatory bodies of the pharmaceutical industry have indicated the need for a complete understanding of all design and functional stages of dosage forms and the requirement for closely monitored manufacturing processes.[1] The aim is to understand, identify, measure and control critical quality attributes so that drug products are continuously manufactured with proven reliability. Tablet coatings are a particular and critical aspect of drug manufacture. Coatings permit the design of products with controlled and delayed release profiles and both their physical and chemical structure are critical to final product performance. There is therefore a need for diagnostic techniques to assess coating structure. To date several imaging techniques have been applied in this effort. These include X-ray computed tomography, terahertz (THz) pulse

Abbreviations: RI, refractive index; API, active pharmaceutical ingredient; OCT, optical coherence tomography; Thz, Terahertz; NIR, near infrared.

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imaging as well as/and nuclear magnetic resonance imaging, and also Raman and NIR spectroscopy.[2–11] Each technique has advantages and disadvantages; for example, the relative superiority in spatial resolution of X-ray imaging is offset by its relative insensitivity to density variations within a tablet. Terahertz pulse imaging in contrast offers a lower spatial resolution but is more sensitive to density and chemical heterogeneities. In contrast to THz pulse imaging, where submillimeter wavelengths are used for probing the sample, OCT exploits the NIR spectrum; hence one expects the sample to have different absorption and scattering cross sections in these wavelength ranges and thus the two techniques provide complementary data. Like THz pulse imaging, OCT is a very rapid measurement technique compared to X-ray tomography or nuclear magnetic resonance imaging.

OCT is noninvasive and has been primarily developed and used for ophthalmic applications.[12] Image contrast stems from sample inhomogeneities in refractive index (RI).[13] Refractive index variations are expected to occur at the interface between two different materials, for example at interface between different layers in a tablet coating. OCT records depth profiles with a penetration depth of approximately half a millimetre into the sample. By rastering the OCT probe across the sample surface, three-dimensional representations of the sample structure can be constructed. The depth resolution is proportional to, and limited by, the wavelength of the probe beam. For an in-depth review of the technique and theoretical background the reader is referred to the literature.[13,14] In what follows we present a brief outline of OCT with reference to the particular fibre based system that was used in the present study.

OCT uses low time-coherence interferometry to produce a two-dimensional image through optical backscattering, similar to ultrasonic pulse-echo imaging. A super luminescent diode serves as a light source with low temporal coherence (i.e. large spectral bandwidth) which is split in a Michelson interferometer (Fig. 1). One beam is focused with a lens into the sample while the second (reference) beam is terminated with a mirror. The sample beam penetrates into the sample and is increasingly scattered the deeper it progresses into the material. The backscattered light from the sample is collected through the same lens and optical path used for light emission. In the interferometer the sample beam is recombined with the reference beam. This procedure encodes the depth information of where backscattering occurred within the sample. The combined light beams travel back through the fibre coupler and their interference pattern is read out with a spectrometer. The depth information can be decoded from the spectrogram through Fourier-transformation. This yields a depth profile underlying a point on the sample surface which, using a term from ultrasonic imaging, is known as an A-scan. Acquiring several A-scans in a line across the sample yields a two-dimensional (transverse) image, also known as a B-scan. In our experiments, transverse scanning is performed by an oscillating mirror controlled by a galvanometer.

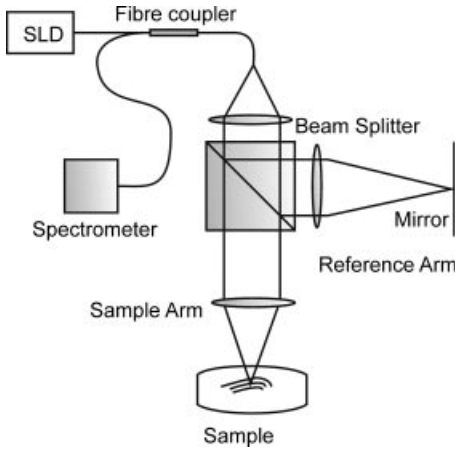

Figure 1. Schematic setup of the fibre-based OCT system. The light source is a super luminescent diode that has a large spectral bandwidth. After travelling through the beam splitter, the light scattered back from the sample is superimposed on the reference beam and travels back to the fibre coupler to give an interference pattern in the spectrometer, which is evaluated after Fourier transformation.

The signal contrast stems from refractive index discontinuities within the sample volume, as these affect the backscattering efficiency of the incident light. Absorption also affects the signal intensity and limits the overall depth of the OCT scan but this is a relatively well understood phenomenon at NIR wavelengths. When interpreting OCT images, it is important to keep in mind that OCT is responsive only to refractive index variations within the sample. Thus contrast may not necessarily stem only from differences in chemical composition, but also from density variations and other physical features such as air gaps in cracks or enclosed voids. Similarly two

layers with similar chemical composition but which happen to feature the same refractive index will not be distinguishable by OCT.

Resolution

Theoretically, the depth resolution can be estimated[13] by the round trip coherence length l_c:

$$l_c = \frac{2 \ln 2}{\pi} \frac{\overline{\lambda}}{\Delta\lambda} \quad (1)$$

where $\overline{\lambda}$ is the mean wavelength and $\Delta\lambda$ the spectral bandwidth of the illumination source. Transversal resolution is defined as the full width at half maximum diameter Δd_{FWHM} of the probe beam amplitude distribution at the beam waist of the focused probe beam:

$$\Delta d_{FWHM} = 2\sqrt{\ln 2} \frac{\overline{\lambda}}{\pi\theta_s} \quad (2)$$

where θ_s is the angular spread of the Gaussian beam. The transverse resolution also depends on the scanning depth.

EXPERIMENTAL

The OCT systems used in this study were the spectral radar OCT OCP930SR and the swept source OCT Microscope OCM1300SS systems from Thorlabs (Ely, UK). They differ in the illumination wavelength: the spectral radar system operates at 930 nm with 2 mW output power and the swept source system at 1325 nm with 10 mW output laser power. The beam diameter gives a transverse resolution of 9 and 15 μm and a power density of 0.03 and 0.06 mW/μm^2 for the spectral radar and the swept source system, respectively. The systems operate at a bandwidth of 100 nm (spectral radar) and 130 nm (swept source). This results in a theoretical axial resolution of 6.5 μm for the spectral radar and 12 μm for the swept source instrument. The axial scan rate (A-scan) is 5 kHz for the spectral radar and 16 kHz for the swept source instrument. The transverse or B-scan rate is 4 frames per second (fps) for the spectral radar and 25 fps for the swept source OCT microscopes. They are both fibre based OCT systems as depicted in Figure 1. Transverse scanning (B-scanning) is performed by use of an oscillating mirror controlled by a galvanometer, which deflects the probe beam. The transversal scan covers a strip of 2 mm length and the beam breadth and it covers an imaging depth of roughly 0.5 mm for the investigated materials due to absorption. The technical maximum imaging depth is 1.3 mm for the spectral radar system and 3 mm for the swept source system. The samples were placed in a tablet holder situated below the OCT probe and not altered in any way prior to OCT measurements. The tablets were measured in air under ambient conditions and not moved during image acquisition. A variety of tablets were investigated taken from development or production batches. The tablet cores consisted of excipients and the active pharmaceutical ingredient (API) and were covered with different cosmetic or enteric coatings. The OCT images presented were further processed with a nonlinear diffusion filter as reported in Ref.[15] (see Supplementary Appendix for detailed information). An assessment of the coating thickness in each image pixel was performed using the Imaging Toolbox of Matlab version R2008a (The MathWorks, Natick, MA).

RESULTS

Figure 2A shows a typical OCT result obtained for an uncoated tablet core. The image is composed of a curved dark line that corresponds to the air/tablet interface. This interface exhibits strong contrast due to the large change in refractive index between air above the tablet surface and the tablet material itself. It is noted that the tablet surface is not only curved, but also rough. A typical intensity profile of going into this tablet is shown in Figure 3A. It consists of a steep initial gradient at the air/core interface followed by a decay of the signal with respect to the imaging depth. This decay is due to absorption of the near infrared light and has been observed in other OCT applications. According to the Beer–Lambert law of absorption, an exponential decay is expected. Superimposed upon the decay curve features can be observed that represent refractive index variations within the tablet caused by density and chemical composition variations. These heterogeneous structures of up to 150 μm in diameter were detected deep into the tablet. Similar variations in chemical and physical structure are typically observed with near-infrared and Raman imaging of microtomed tablets.[7] The contrast that can be observed is not restricted to the surface, but extends into the tablet. In this case at greater depths contrast variations are

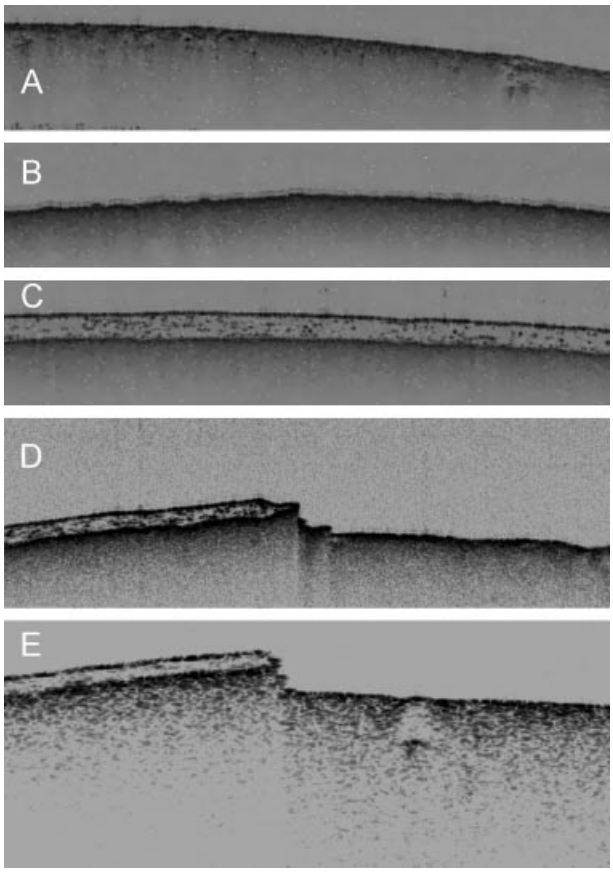

Figure 2. Typical OCT scans of tablets with different coatings. Panels A–D were acquired at 930 nm, whereas the image in panel E was taken at 1325 nm. (A) Uncoated tablet. (B) Tablet with a single cosmetic coating. (C) Tablet covered with cosmetic and enteric coatings. (D,E) A comparison of data from the two different OCT systems, visualising the difference in resolution and contrast. Both panels represent unfiltered raw data taken for a tablet with a cosmetic and enteric coating that has a DiffCore hole (http://www.gsk.com/infocus/diffcore-tablets.htm). In this case the region on the right of the image shows the DiffCore hole and exposed tablet core. In panel D the data was obtained with the Spectral Radar OCT at 930 nm, whereas panel E shows the equivalent data taken with the Swept Source OCT system centred at 1325 nm. The imaging depth is about 0.5 mm in both panels.

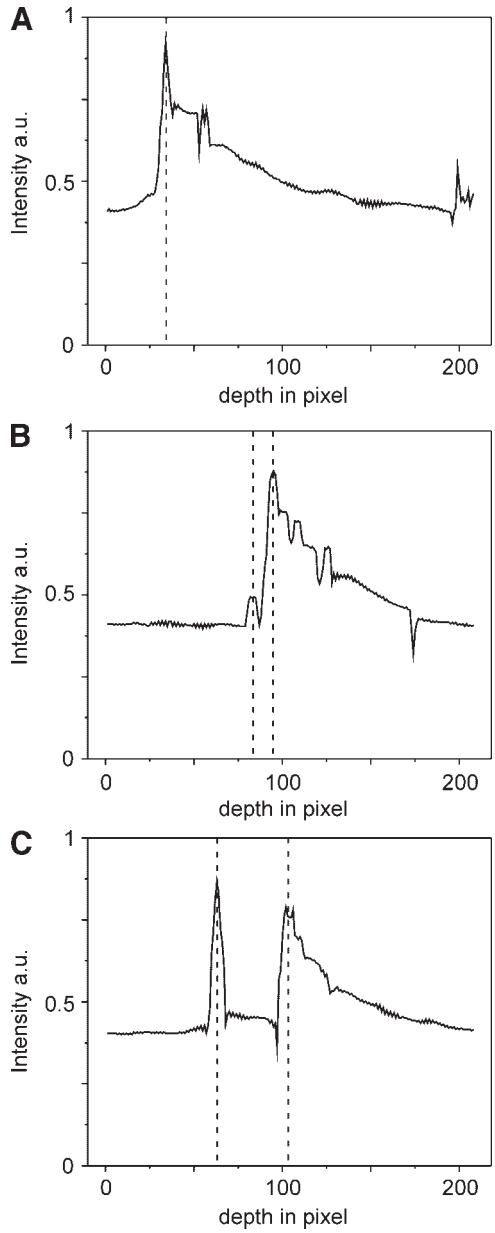

Figure 3. Representative cross-sectional depth (B-scan) OCT scans taken from the images in Figure 2. (A) Uncoated tablet A. (B) Tablet B with a single cosmetic coating. The first peak is small compared to the second peak. (C) Tablet C cosmetic and enteric coatings. (D) Complex tablet with three coatings. The dotted lines mark the characteristic peaks that were used for the coating thickness analysis.

masked by the exponential decay of the signal. In accordance with other imaging studies of microtomed samples these image inhomogeneities are therefore attributed to composition variations from the blending and compaction processes. In obtaining OCT data, regions of 2 mm length by 0.5 mm depth were typically studied. The results shown here are typical of the complete tablet surface. It is noted that due to the relatively short wavelength of the light compared to related techniques such as THz and photoacoustic imaging, OCT offers the advantage of greater resolution. Thus the internal structure of regions

associated with gross surface roughness (such as embossed areas) can be investigated (see later).

Figure 2B represents an OCT image for a tablet with a single cosmetic coating. It shows one very weak refractive index change along the surface, followed by a rather strong one. Figure 3B shows a representative intensity profile across the image. The distance between the first small peak and the following major peak was calculated to be 5.5 ± 1.4 pixels. We speculate that the first peak represents the beginning of the coating, although we currently do not understand why this contrast at the proposed air/coating interface is relatively weak as we would have expected a rather strong RI change at this interface. The hypothesis that the region between the two peaks represents the cosmetic coating is supported by the observation that the signal intensity does not decay appreciably within the region. Such behaviour reflects the spectral properties of the coating material. Across the cosmetic coating region spatial variations are observed which demonstrate that the coating is not completely homogeneous. Inspection of the corresponding intensity profile in Figure 3B confirms the exponential decay of the signal following the large RI change, superimposed upon which are variations indicative of inhomogeneities within the tablet core.

Figures 2C and 3C show typical data obtained for a tablet with both a cosmetic (inner) and enteric coating. As expected this tablet reveals very different OCT data. Examination of Figure 3C indicates that for the more complex tablet structure the intensity profile is quite different. THz pulse imaging measurements of coating properties/thicknesses with tablets from the same batch demonstrated that the coatings are approximately 40 μm (cosmetic) and 80 μm (enteric) thick. It is noted that an exact value of the thickness cannot be quoted as variations are always observed across a tablet surface and within a batch.

From these values, a rough depth calibration of the OCT images can be deduced by evaluating the average pixel distance between the two distinct black lines from Figure 2C (the average peak-to-peak distance of Fig. 3C) and calibrating this to be 120 μm. For a more accurate coating thickness measurement as in quality control or functional coating research, each type of tablet should be calibrated against a microtomed sample separately; as the different refractive indices of the various coatings also change the length calibration. In principle 3D OCT imaging could be used to determine the coating thickness distribution across a complete tablet by acquiring multiple adjacent B-scans in a line (translating the sample).

Inspection of Figures 2C and 3C reveals two large RI changes (marked with dotted lines) which are followed by the exponential signal decay. Given that these changes occur over a distance it is assumed that they correspond to the air/enteric and cosmetic/core interfaces. The mean peak-to-peak distance between the layers was found to be 42 ± 11 pixels. Although other variations are observed it is assumed the enteric/cosmetic coating interface is not clearly resolved. This result is not unsurprising in that a large refractive index change in the NIR may not occur. To fully understand this behaviour an in depth spectroscopic and OCT study is required. Again deeper into the tablet the signal is seen to decay exponentially due to light absorption and signal fluctuations are observed due to the inhomogeneous tablet core.

Within the coating layers contrast is observed in the form of black dots. Visible optical microscopy and scanning electron microscopy of microtomed tablets reveals that such coatings are inhomogeneous, they often contain pores and regions of dense material associated with nonuniform nucleation of the coating during drying. It is noted that such density variations within coatings have previously been observed and often critically influence dissolution behaviour.[16] It is believed that OCT contrast arises from such features.

It is also possible to study tablet embossing sites with the OCT systems. Representative OCT scans of embossing sites can be found in the Supplementary Appendix to this article (Fig. A3).

OCT Imaging at Different Wavelengths

In contrast to THz studies of tablets where the RI is known to be relatively insensitive to the wavelength, in the NIR or in the NIR region, illumination wavelength is critically affected by RI. Spectral absorption characteristics are often used to quantify API and excipient composition as well as features such as coating thickness. To investigate the influence of imaging at different wavelengths, the two OCT systems introduced earlier, operating at 930 nm (spectral radar system) and 1325 nm (swept source system) were compared and evaluated in terms of image resolution and sample penetration depth.

As both the transverse and the depth resolution are proportional to the wavelength, the swept source system was expected to feature a coarser image resolution and a different penetration depth into the sample, as the effective absorption could differ at 1325 nm. Figure 2D and E depict the resulting differences between the two OCT systems, showing a close up of a two layered tablet, which has been drilled to remove its coatings to expose the tablet core (right half of the figure). For better comparison of image resolution the raw, unfiltered OCT data is displayed. In the left half of the figure, the coating structure, similar to that in Figure 2C can be seen. The right half of the figure reveals the tablet core. In Figure 2E similar heterogeneous structures to those seen throughout the uncoated tablet (Fig. 2A) can be seen, supporting the hypothesis that these structures are present throughout the entire tablet core. Note that due to the different refractive indices at the two wavelengths the contrast and resolution change.

As expected, the resolution is greater at 930 nm (Fig. 2D), but the imaging depth of the longer wavelength system (Fig. 2E) is not noticeably increased. Both systems seem to image up to a maximum depth of approximately 0.5 mm.

DISCUSSION AND CONCLUSION

OCT is clearly capable of identifying structural features in coatings and outer tablet cores, although a precise distinction between several coating layers is dependent on the strength of refractive index discontinuities between the layers. It also allows the coating investigation at embossing sites. The nondestructive nature and the high spatial resolution (below 10 μm) and speed (4–25 frames/s in the systems used here) make OCT a very attractive technology for tablet diagnostics, especially since cost and ease of use are favourable compared to alternative technologies. In all cases studied here, operation at 930 nm offered better contrast and spatial resolution compared to operation at 1325 nm whilst differences in depth penetration were negligible. We should emphasise, however, that the optimal wavelength choice is depends on specifics of the coating tablet core materials. At both wavelengths the achieved penetration depth was approximately 0.5 mm, limited by the decay of the signal intensity caused by absorption of NIR light. Precise depth information cannot be recovered from samples with unknown composition. In practical situations during tablet production the refractive index of each layer material can be measured independently and thus a full quantification of layer thicknesses becomes possible.

Other techniques such as X-ray computer tomography and THz pulse imaging have also been reported in the literature for the successful determination of tablet structure. Like OCT these are nondestructive techniques. However OCT offers several advantages over these methods, in particular:

- high spatial resolution (<10 μm),
- sensitivity to variations in physical (density) and chemical properties,
- high image acquisition speed (25 fps),
- low cost instrumentation,
- contrast that could be in principle related to NIR spectra, ability to choose operational wavelength/bandwidth.

It is evident that OCT shows considerable promise as a means to investigate and understand the function of tablet and coating structures. Since OCT is a relatively rapid technique it could also be used evaluate product quality after/during manufacture. OCT also offers the means to understand factors in solid dose form R&D and to comprehend NIR spectroscopy data.

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REFERENCES

1. FDA. 2004. Guidance for industry. PAT—A framework for innovative pharmaceutical development, manufacturing, and quality assurance. Rockville, MD: US Department of Health. In http://www.fda.gov/cder/guidance/index.htm.
2. McGoverin CM, Rades T, Gordon KC. 2008. Recent pharmaceutical applications of Raman and terahertz spectroscopies. J Pharm Sci 97:4598–4621.
3. Sinka IC, Burch SF, Tweed JH, Cunningham JC. 2004. Measurement of density variations in tablets using X-ray computed tomography. Int J Pharm 271:215–224.
4. Fitzgerald AJ, Cole BE, Taday PF. 2005. Nondestructive analysis of tablet coating thicknesses using terahertz pulsed imaging. J Pharm Sci 94:177–183.

5. Zeitler JA, Shen YC, Baker C, Taday PF, Pepper M, Rades T. 2007. Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging. J Pharm Sci 96:330–340.
6. Djemai A, Sinka IC. 2006. NMR imaging of density distributions in tablets. Int J Pharm 319:55–62.
7. Gowen AA, O'Donnell CP, Cullen PJ, Bell SEJ. 2008. Recent applications of Chemical Imaging to pharmaceutical process monitoring and quality control. Eur J Pharm Biopharm 69:10–22.
8. Zeitler JA, Gladden LF. 2009. In-vitro tomography and non-destructive imaging at depth of pharmaceutical solid dosage forms. Eur J Pharm Biopharm 71:2–22.
9. Ricci C, Nyadong L, Fernandez FM, Newton PN, Kazarian SG. 2007. Combined Fourier-transform infrared imaging and desorption electrospray-ionization linear ion-trap mass spectrometry for analysis of counterfeit antimalarial tablets. Anal Bioanal Chem 387:551–559.
10. Wray P, Chan KLA, Kimber J, Kazarian SG. 2008. Compaction of pharmaceutical tablets with different polymer matrices studied by FTIR imaging and X-ray microtomography. J Pharm Sci 97:4269–4277.
11. Juuti M, Tuononen H, Prykari T, Kontturi V, Kuosmanen M, Alarousu E, Ketolainen J, Myllyla R, Peiponen KE. 2009. Optical and terahertz measurement techniques for flat-faced pharmaceutical tablets: A case study of gloss, surface roughness and bulk properties of starch acetate tablets. Meas Sci Technol 20: 015301 (Electronic Article at http://www.iop.org/EJ/sview/0957-0233/20/1/015301).
12. Izatt JA, Swanson EA, Hee MR, Huang D, Lin CP, Schuman JS, Puliafito CA, Fujimoto JG. 1993. In vivo imaging of the human retina with optical coherence tomography. Invest Ophthalmol Vis Sci 34:761–761.
13. Fercher AF, Drexler W, Hitzenberger CK, Lasser T. 2003. Optical coherence tomography—Principles and applications. Rep Prog Phys 66:239–303.
14. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, Fujimoto JG. 1991. Optical coherence tomography. Science 254:1178–1181.
15. Malm H, Sparr G, Hult J, Kaminski CF. 2000. Nonlinear diffusion filtering of images obtained by planar laser-induced fluorescence spectroscopy. J Opt Soc Am A Opt Image Sci Vis 17:2148–2156.
16. Ho L, Mueller R, Gordon KC, Kleinebudde P, Pepper M, Rades T, Shen YC, Taday PF, Zeitler JA. 2008. Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance. J Control Release 127:79–87.