Broadband photon time of flight spectroscopy: advanced spectroscopic analysis for ensuring safety and performance of pharmaceutical tablets

Faisal Kamran[1], Otto Højager Attermann Nielsen[2,3], Stefan Andersson-Engels[4], Dmitry Khoptyar[4]
[1]Department of Photonics Engineering, Technical University of Denmark, Frederiksborg 399, 4000 Roskilde Denmark
[2]NKT Photonics A/S, Blokken 84, DK-3460 Birkerød Denmark
[3]Department of Informatics and Mathematical Modelling, Technical University of Denmark, Asmussens Allé, 321, DK-2800 Kgs. Lyngby
[4]Department of Physics, Lund University, P.O Box 118 S-221 00 Lund Sweden
dmitry.koptyar@fysik.lth.se

Abstract :We report on extended spectroscopic analysis of pharmaceutical tablets performed with broadband photon time-of-flight absorption/scaring spectroscopy. Precise monitoring of absorption and scattering spectra enables cost-efficient monitoring of key safety and performance parameters of the drugs.

OCIS codes: (300.1030) Spectroscopy, Absorption; (300.6190) Spectrometers; (290.7050) Turbid media; (290.4210) Multiple scattering; (00.6250) Spectroscopy, condensed matter.

Introduction

Diffuse optical spectroscopy (DOS) applied to evaluation of absorption and scattering in turbid materials is an indispensable component in the modern photonics toolbox. Applications of DOS range from biomedical diagnostics[1] and medical treatment monitoring [2], to quality control and product analysis in food [3], pharmaceutical[4], and timber[5] industries.

The key advantage of near-infrared (NIR) DOS spectroscopy in industrial applications is that, combined with chemo-metric analysis, it is capable of resolving subtle variations in the chemical composition, and in the physical, structural, and morphological properties of different kinds of turbid samples, without the need for costly and lengthy sample preparation. Furthermore, NIR DOS spectroscopy is relatively cheap, fast, and easy to implement, and can be set up for remote operation. As a result, it is suitable for on-line process monitoring and quality control.

The main challenge associated with DOS measurements is differentiating between the effects of absorption and scattering in evaluated optical attenuation. The precise measurement of absorption is essential for the accurate evaluation of the chemical composition of a sample. Scattering can be utilized for the characterization of the structural and morphological properties of the sample.

Conventional DOS techniques that are currently widely employed in diverse applications are based on monitoring transmission of CW light through turbid sample. In order to discriminate absorption and scattering effects they necessitate using an extensive chemometric modeling that is based on sophisticated design and costly maintenance of elaborated calibration databases. Recent advance in source and detector technology enables the development of the new advanced spectroscopic techniques such as photon time of flight (PTOF) spectroscopy that provide means for direct monitoring of absorption and scattering spectra of turbid samples. This enables better understanding the physics of the light interaction with the sample and facilitates advance in new spectroscopic analysis methods which eventually leads to chanced efficiency and decrease cost of the analysis.

Photon time of flight (PTOF) spectroscopy

The principle PTOF spectroscopy is based on monitoring of the photon time of flight distribution through a turbid sample. Fitting the PTOF distribution with the appropriate model of the turbid light propagation enables determination of the absorption coefficient (μ_a) and the reduced scattering coefficient (μ'_s). The reduced scattering coefficient is defined as $\mu'_s = (1-g)\mu_s$ where g is scattering anisotropy, and μ_s is scattering coefficient which is reciprocal to scattering mean free path. Scanning the wavelength for which PTOF distribution is measured and evaluated allows μ_a and μ'_s spectra to be evaluated.

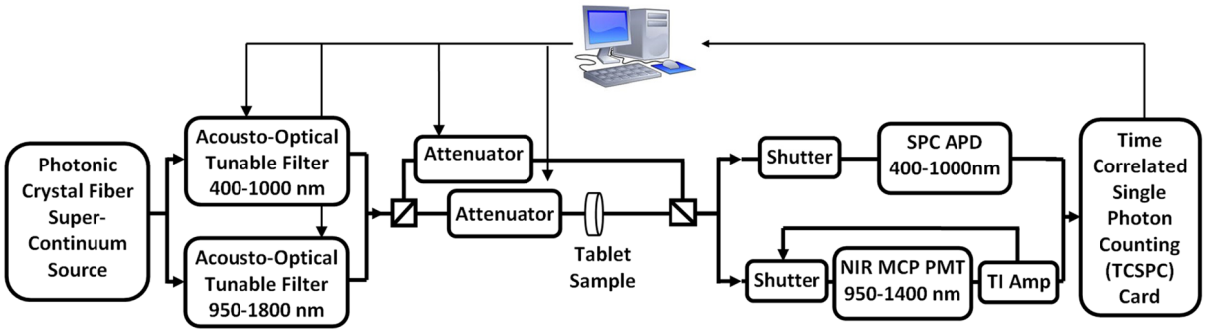

Figure. 1. Schematic of the PTOF spectrometer APD-avalanche photodiode; MCP micro-channel palate; PMT photomultiplier tube; TI Amp – trans-impedance amplifier.

A schematic of the PTOFS spectrometer used in our experiments is depicted in Figure 1. A Photonic Crystal Fiber (PCF) Super Continuum Source (SCS) (SuperK Extreme, NKT Photonics A/S, Denmark) is used in combination with one of two AOTFs to generate tunable probe pulses which are sent to sample. A small fraction of the pulse power is split off prior the sample and routed directly to the detector for timing stabilization. Signal levels are adjusted by attenuators. One of two single photon counting (SPC) detectors is used in combination with TCSPC electronics for precise monitoring of the PTOF distribution. The setup is controlled by a computer. The setup is fully automated and enables continues monitoring of abortion and scattering spectra of diverse turbid media in VIS and close NIR spectral range

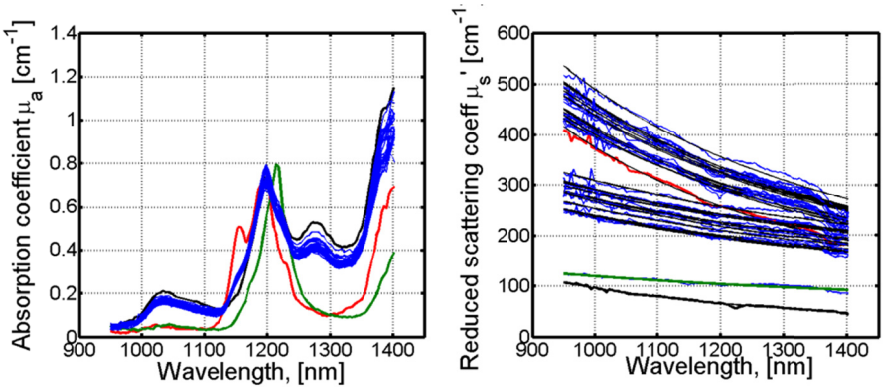

Figure 2. Absorption (left) and scattering (right) spectra of test pharmaceutical tablets. The spectra of mixes tablets are shown as blue lines. The spectra of the drug, filler and auxiliary excipient are shown as red black and green lines respectively. Mie theory fit of the scatting spectra is

Spectroscopic analysis of pharmaceuticals

In our contribution we present extended spectroscopic analysis of the test set of pharmaceutical tablets performed with novel PTOF spectrometer. The test tablet set was prepared by compressing the mixtures of three ingredients representing drug, filler material and auxiliary excipients. In order to vary the scattering properties of the samples ingredient powders with different particles sizes were used. The characteristic absorption and scattering spectra of the tablets are depicted in the Figure 2. The absorption spectra of the mixed tablets are superposition of the ingredients absorption spectra which enable spectroscopic evaluation of tablet chemical composition.

Drug concentration in mixed tables evaluated using the abortion spectra is plotted in Figure 3 versus the concentration available from the reference method. For concentration evaluation we designed a chemometric PLS calibration model using half of the spectra as learning set. Remaining half of the spectra was used to test the model and then the calibration and test set were swapped. Comparison between predicted and references values shows the current model provides 1% of root mean square evaluation errors.

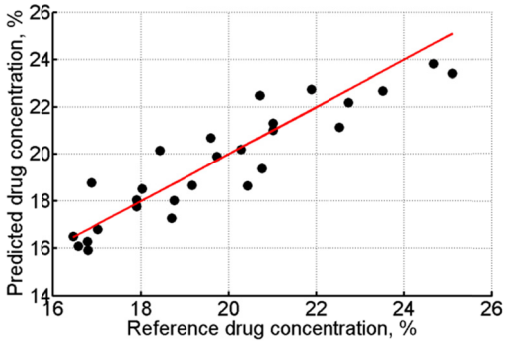

Figure 3. The tablet drug concentration predicted form absorption spectra vs. concentration provided by the reference measurement.

Tablets scattering spectra depicted in Figure 1 are well consistent with predictions from Mie theory and can be well fitted by $\mu_s' \sim A(\lambda/\lambda_c)^{-\beta}$ dependence also plotted therein. It is generally known that smaller particle sizes result in larger β values and the larger concentration of the particles leads to higher scattering. However a notable observation following from the present experimental data suggest that the parameters A, β and λ_c are consistent for the whole test set as it apparent in the Figure 4. Therein we plot $\log\left(\frac{\mu_s'}{\lambda}\right) = \log(A) + \beta\log(\lambda_c)$ vs. β which shows that all the tablet scattering spectra can be fitted with A=133 and $\lambda_c = 1995\text{nm}$. Furthermore tablets compressed form the powders of different size clearly cluster in the plot. It may be speculated that the effect results from the compression of similar powders with different particle sizes under very similar conditions.

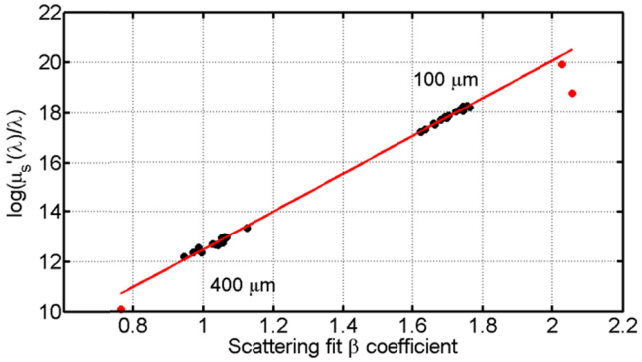

Figure 4. On tablet scattering spectra analysis. Mixed and poor ingredient tablets are plotted as black and red dots respectively.

Conclusions

Drug concentration and tablet dissolution speed are examples of the most essential safety and performance parameters of the tablets. The drug concentration can be deduced from optical absorption spectra whereas the dissolution speed is correlated to the tablet microstructure that in turn can be probed by observing the light scattering. PTOF spectroscopy is an advance spectroscopic technique that enables independent monitoring of scattering and absorption. It enables advanced spectroscopic analysis of pharmaceuticals far beyond ability of the conventional CW light based spectroscopic techniques. By enhancing fundamental understanding of light interaction with pharmaceutical samples PTOF spectroscopy facilitates development of the dedicated cost-efficient techniques of industrial control.

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