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Noninvasive Characterization of Pharmaceutical Solids by Diode Laser Oxygen Spectroscopy

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INTRODUCTION

Characterization of solid pharmaceuticals, ranging from monitoring of solid-state reactions to understanding tablet dissolution, is of great interest for pharmaceutical science.¹ The quality of the finished product highly depends on knowledge about the pharmaceutical materials used and the different unit operations involved in manufacturing of pharmaceuticals. Thus, availability of appropriate and reliable tools for measurements of physical and chemical properties of drug materials *in situ* during chemical and physical processing is a key for optimized processing. In early stages of pharmaceutical development a whole range of techniques for characterization of the solid state is available, addressing, for example, particle size and shape, density, porosity, calorimetry, thermo-mechanical properties, specific area, and crystallinity.² However, most of these techniques are slow and not well suited for fast laboratory-based or process applications. Process analytical technology (PAT) is a term describing a holistic approach to pharmaceutical manufacturing based on in-depth understanding through advanced process sensors and modeling tools.³ In order to succeed with this, new tools are needed, e.g., with capability to directly measure physico-chemical attributes *in situ* of the mechanical process. In this context, tools based on spectroscopic techniques offer obvious advantages owing to their speed, compactness, versatility, and ability to perform noninvasive analysis.

By employing the spectroscopic technique referred to as gas in scattering media absorption spectroscopy (GASMAS), it is possible to extract information related to gas dispersed within highly scattering (turbid) materials.⁴ In our case, the key is

contrast between the sharp (GHz) absorption features of molecular oxygen located around 760 nm and the broad absorption features related to tablet bulk material. The technique is based on high-resolution diode laser absorption spectroscopy, and its main principle is illustrated in Fig. 1. Light is injected into a highly scattering sample, often utilizing optical fibers. The actual path length distribution of transmitted photons will depend on the scattering properties of the sample. Due to significant multiple scattering, the average photon path length greatly exceeds sample dimensions. For example, the average path length of photons that have traveled through a pharmaceutical tablet typically exceeds 10 cm.⁵ During passages through air-filled pores, photons in resonance with an absorption line in the A-band of molecular oxygen can be absorbed. Oxygen absorption can be distinguished from bulk absorption due to the extremely narrow absorption features (GHz) exhibited by free gases. To resolve such narrow features, high-resolution spectroscopy must be employed. The resulting absorption signal depends on both the oxygen content and the scattering properties (photons path lengths) of the sample. Indirectly, it is thus related to mechanical properties such as porosity and particle size.

The GASMAS technique has previously been used to study the gas content in, for example, polystyrene foam, wheat flour, granulated salt, wood materials, fruit, and human sinuses.^{4,6–9} Gas exchange dynamics has been studied by placing samples of wood and fruit in nitrogen atmospheres and monitoring the re-invasion of oxygen.^{7,8}

In this paper we show the potential of using GASMAS for determination of physical and structural parameters of pharmaceutical solids. We present results from a study of pharmaceutical tablets made from two different sieve fractions (particle size distributions) and with different compression forces. In addition, the prospects of a broader use of this technique for pharmaceutical analysis are discussed.

EXPERIMENTAL

Instrumentation. A simplified schematic of the setup is given in Fig. 2. The instrumentation and corresponding data evaluation has been described in detail elsewhere.¹⁰ Briefly, a temperature stabilized distributed feed-back (DFB) diode laser (NanoPlus, Germany) is repetitively wavelength tuned over one of the narrow absorption lines in the oxygen A-band (R11Q12, 760.445 nm vacuum wavelength). The DFB diode laser is pigtailed using a single-mode (SM) optical fiber, yielding an output of about 4 mW. Sensitivity was vastly increased by employing wavelength modulation spectroscopy (WMS), in this case implemented by imposing an $f = 9$ kHz harmonic modulation on the laser diode injection current. A 90/10% fiber splitter (Laser2000, Sweden) is used create a double-beam arrangement (reference and sample arm), allowing balanced detection. This maneuver is important in order to minimize the influence of optical interference fringes. The lower intensity optical fiber is immediately directed to a silicon

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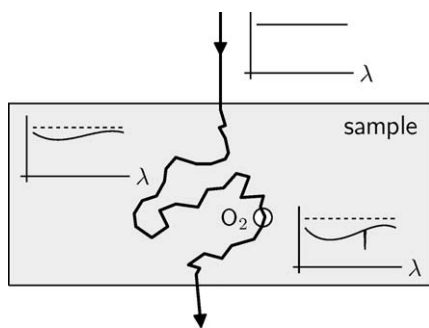


FIG. 1. The principle of GASMAS. The key is the contrast between the sharp absorption features of free gases (e.g., oxygen) and the broad absorption features related to bulk material. This is illustrated by the change in absorption spectra along a particular photon path. The gas absorption is typically much weaker than bulk absorption and is thus exaggerated in the graph.

photodiode (PIN-10DP/SB, UDT Sensors), producing a reference signal. The other fiber guides light to our sample (e.g., tablet).

Samples were placed in contact with a long-pass filter (Schott RG715), which in turn was placed directly on top of a photomultiplier tube (PMT, 5070A, Hamamatsu) detecting diffuse transmittance. The long-pass filter in combination with the PMT sensitivity fall-off effectively suppressed unwanted ambient light. Signals from the reference and sample detectors are sent to lock-in amplifiers detecting at the second harmonic ($2f$) of the modulation frequency f . The $2f$ signal is normalized using direct detector signals. Software-based balanced detection is employed to remove contributions originating from optical interference fringes. In addition, vibrators positioned close to the sample were used to further suppress such effects.

Data Evaluation. Acquired $2f$ signals are evaluated using curve fitting of an experimental long-path recording of the oxygen absorption feature. This recording was performed using the same setup as for tablet measurements. The oxygen imprint is measured in terms of mm of equivalent path length through air, L_{eq} . That is, if $L_{eq} = 10$ mm, the oxygen absorption exhibited by the turbid sample equals that of a 10 mm path length through ambient air. The absolute relation between the

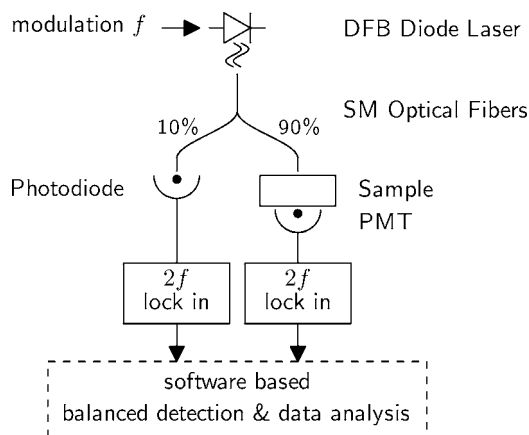


FIG. 2. Simplified schematic of the setup. A 90/10% optical fiber splitter is used to achieve the double-beam arrangement typical of applications requiring high sensitivity. Lock-in amplifiers detect at the second harmonic of the modulation frequency f . Software algorithms handle balanced detection and data evaluation.

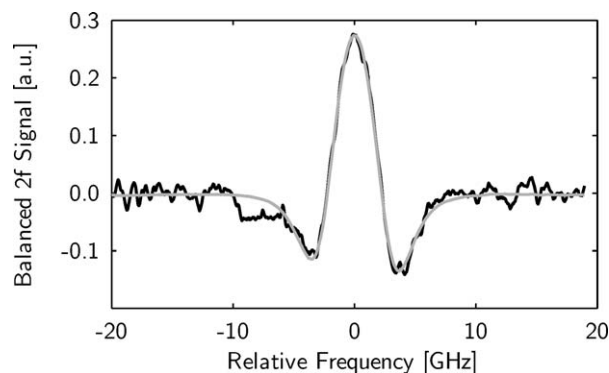


FIG. 3. Data obtained for a 3.38 mm thick tablet from PS > 400 μm . The $2f$ signal after balanced detection (black) is shown together with a fitted oxygen absorption signature (grey). The signal corresponds to an L_{eq} of 17.4 mm. The optical frequency is given relative to the oxygen absorption line (760.445 nm). The corresponding wavelength range is 760.41–760.48 nm, where the lower wavelength is to the right.

$2f$ signal and the equivalent path length is established experimentally by means of a standard addition calibration. In this particular case, the standard addition involves adding known path lengths of air to the sample arm. A detailed description of these procedures is found in a previous publication.¹⁰

Pharmaceutical Samples. Measurements were performed on 22 model tablets with microcrystalline cellulose as the main constituent, manufactured using a wet granulation process.¹¹ The influence of particle size distribution was studied by sieving the granulate, producing two different batches consisting of 11 tablets each (particle sizes: <150 μm and >400 μm). The tablets were compressed manually into various thicknesses (3–4 mm). The tablets were round, without score or engravings, and had a 10 mm diameter.

RESULTS

Examined tablets exhibited oxygen absorption corresponding to 5–50 mm propagation through ambient air. A typical example of the acquired $2f$ absorption signature is given in Fig. 3. To illustrate that obtained signals are related to oxygen absorption, additional nitrogen atmosphere experiments were performed. Tablets were then stored for several hours in plastic

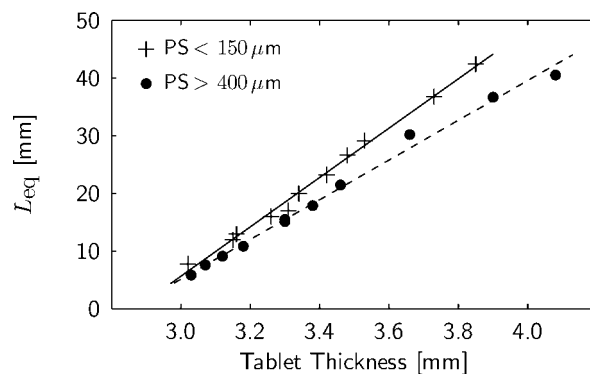


FIG. 4. Equivalent path length L_{eq} versus tablet thickness. Shown values are averages from four consecutive measurements. All tablets have the same weight (300 mg) and diameter (10 mm), but intentional variations in applied compression force yielded variations in tablet thickness.

bags filled with nitrogen. When inserting them into the setup (while still in their plastic bags), obtained signals exhibited nothing but the ordinary 3 mm L_{eq} noise floor. When the plastic bags were opened and ventilated, the expected signal quickly appeared. This oxygen re-invasion could, however, not be temporally resolved.

The overall influence of tablet compression and particle size is shown in Fig. 4. Here, each tablet was measured four times consecutively, and the average derived L_{eq} is presented. The acquisition time was 25 s in each of the four measurements, and the standard deviation in these sets of four repetitions was on average 0.8 mm ($<150\ \mu\text{m}$) and 1.0 mm ($>400\ \mu\text{m}$). However, these measures of uncertainty do not include systematic errors due to optical interference fringes that remain after balanced detection. The systematic errors due to such fringes can be estimated by looking at the amplitude of interference noise in spectral regions free from oxygen absorption (consider, for example, the 10–20 GHz range in Fig. 3). Furthermore, this noise was found to be stable between the four consecutive measurements. In the current configuration, optical noise remaining after balanced detection limits the accuracy to about 3 mm L_{eq} . This corresponds to an optical absorption fraction of 7.5×10^{-5} .

In the range of examined tablet thicknesses, there is a highly linear relation between tablet thickness and equivalent path length. It is also clear that in case of comparable thickness, tablets manufactured from the smaller granule particles ($<150\ \mu\text{m}$) exhibited the largest oxygen absorption.

DISCUSSION

Our results clearly show that it is possible to detect oxygen dispersed within pharmaceutical tablets. Hence, a new tool is available for characterization of pharmaceutical solids. Using the GASMAS technique, parameters such as porosity and particle size may be determined in raw materials as well as finished tablets. This may in turn lead to a better optimization of pharmaceutical manufacturing processes. Required instrumentation involves standard components and is simple and fairly compact. Further development is expected to improve data quality.

The porosity of pharmaceutical tablets is normally estimated by employing mercury intrusion porosimetry.¹² This method has several limitations: it is a destructive technique, it includes hazardous handling of mercury, and it is not suitable for fast laboratory-based or on-line analysis. Furthermore, mercury porosimetry is only sensitive to open pores, while the presented technique is sensitive to all pores containing oxygen. It would thus be of interest to compare results from this technique with results from mercury porosimetry. Moreover, this will also provide opportunities for accessing functional properties such

as tablet hardness. Preliminary data on such parameters has been shown before.^{13,14}

In addition to the results reported here, we propose monitoring of gas diffusion dynamics. It would be attractive to study oxygen reinvansion in samples that have been placed in, for example, a pure nitrogen environment or a vacuum chamber. Such dynamic experiments have been successfully demonstrated in, for example, wood and fruit materials.^{7,9} In addition, we propose GASMAS measurements on tablets in blister packages, allowing study of gas exchange through blister materials.

Although the oxygen absorption signal clearly correlates to relevant physical parameters, a detailed understanding of the interaction of near-infrared light with the turbid sample requires further studies. The signal is influenced by both oxygen concentration and photon path length, both being unknown quantities and adding to the total response. It would thus be of great interest to separate these effects in future research. Such a separation is possible by combining GASMAS with time- or frequency-domain photon migration techniques.⁶ These techniques are frequently used in biomedical optics, but have also been applied to pharmaceutical solids.^{5,15} More such work is forthcoming.

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