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Optics-based compressibility parameter for pharmaceutical tablets obtained with the aid of the terahertz refractive index

Mousumi Chakraborty[a,*], Cathy Ridgway[b], Prince Bawuah[a], Daniel Markl[c], Patrick A.C. Gane[b,d], Jarkko Ketolainen[e], J. Axel Zeitler[c], Kai-Erik Peiponen[a]

[a] Institute of Photonics, University of Eastern Finland, P.O. Box 111, FI-80101 Joensuu, Finland
[b] Omya International AG, CH-4665 Oftringen, Switzerland
[c] Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge CB3 0AS, United Kingdom
[d] Aalto University, School of Chemical Engineering, Department of Bioproducts and Biosystems, FI-00076 Aalto, Helsinki, Finland
[e] School of Pharmacy, Promis Centre, University of Eastern Finland, P. O. Box 1617, FI-70211, Kuopio, Finland

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ABSTRACT

The objective of this study is to propose a novel optical compressibility parameter for porous pharmaceutical tablets. This parameter is defined with the aid of the effective refractive index of a tablet that is obtained from non-destructive and contactless terahertz (THz) time-delay transmission measurement. The optical compressibility parameter of two training sets of pharmaceutical tablets with *a priori* known porosity and mass fraction of a drug was investigated. Both pharmaceutical sets were compressed with one of the most commonly used excipients, namely microcrystalline cellulose (MCC) and drug Indomethacin. The optical compressibility clearly correlates with the skeletal bulk modulus determined by mercury porosimetry and the recently proposed terahertz lumped structural parameter calculated from terahertz measurements. This lumped structural parameter can be used to analyse the pattern of arrangement of excipient and drug particles in porous pharmaceutical tablets. Therefore, we propose that the optical compressibility can serve as a quality parameter of a pharmaceutical tablet corresponding with the skeletal bulk modulus of the porous tablet, which is related to structural arrangement of the powder particles in the tablet.

1. Introduction

For pharmaceutical applications tablets are the most accepted and widely used dosage form due to their being cost effective to manufacture, having relative ease of large scale of production, resulting product stability, related to the availability of reliable manufacturing processes, and ability to provide correct reproducible dosage of drug from tablet to tablet and the convenience for patients (Aulton, 2002; Lieberman et al., 1990). Critical quality attributes, such as disintegration time or amount of drug dissolved after a certain time, are linked to their physical, mechanical, chemical, biological and also optical properties. During formation of a tablet, the mixture of drug and excipient particles is compacted, usually directly or following a granulation step, into a stable porous solid.

Historically, mechanical properties have played an important role in order to assess the functionality of a pharmaceutical tablet following the compaction step. Indentation, elasticity, tensile strength, brittle fracture index, bonding index, strain index, viscoelasticity, compressibility, compatibility, and tabletability are among the various mechanical properties of a tablet that have been explored in depth (Knudsen, 1959; Spriggs, 1961; Fell and Newton, 1970; Alderborn, 2002; Choren et al., 2013; Peiponen et al., 2015). The mechanical properties of pharmaceutical tablets can be described by the relationship between the applied force during the compression and the resulting plastic deformation, and inter-particle bonding within the tablet (Zhou and Qiu, 2010). These dictate the behaviour of pharmaceutical powder mixtures both during and after compaction. Stress and strain are the basic mechanical properties to describe the relationship between compressive pressure and the resulting deformation (Peiponen et al., 2015). Compressibility (solid fraction as a function of compaction pressure) and compactibility (tensile strength in relation to solid fraction) (Tye et al., 2005) are terms commonly used to describe the densification and reduction in volume of a

* Corresponding author.
E-mail address: mousumi.chakraborty@uef.fi (M. Chakraborty).

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powder bed by the application of pressure alone, and both properties are considered to be the major parameters contributing to tabletability, defined as the dependence of tensile strength on compaction pressure (Hart, 2015). In this study, we propose to establish an optical parameter that is related to the mechanical properties, such as the bulk modulus of pharmaceutical tablets. This topic is of high importance in pharmaceutical sciences (see, for example, reference to strain (Spriggs, 1961; Fell and Newton, 1970; Alderborn, 2002; Choren et al., 2013; Peiponen et al., 2015; Tye et al., 2005) and compressibility (Heckel, 1961; Leuenberger and Rohera, 1986; Ishino et al., 1990; Patel et al., 2007; Choi et al., 2010; Khomane et al., 2013; Hamad et al., 2015)). In this study, the emphasis is on the research of the development of non-contact sensing and data analysis methods to quantify structural and mechanical properties of pharmaceutical tablets using terahertz (THz) time-delay measurement techniques (Peiponen et al., 2013).

Recently, we have introduced a novel structural parameter (S), which describes the pattern of arrangement of different constituents in porous pharmaceutical tablets (Bawuah et al., 2016a). By pattern arrangement we mean the arrangement of drug and excipient constituting the skeletal-pore elements (solid phase) in series, parallel or a mix of both patterns. This structural parameter is assumed to play an important role both in the compressibility of a tablet, and in the description of the ingress and permeation of liquids in pharmaceutical tablets. In addition to developing the optical compressibility parameter, we consider in more detail the structural parameter S in respect to the explicit dependence of S on a range of various tablet properties, and analyse the correlation of the optical compressibility parameter with S.

This study continues our work to retrieve physical parameters, which directly affect critical quality attributes of a tablet, from non-destructive and contactless terahertz measurements. So far, we have established correlation between the effective THz refractive index and porosity (Chakraborty et al., 2016), surface roughness (Chakraborty et al., 2016), lumped structural parameter (Bawuah et al., 2016a), and Young's modulus (Peiponen et al., 2015). Here, we suggest a new optical compressibility parameter and compare it with the measured bulk modulus of tablets.

2. Theory

The data analysis in this study is based on the measurement of time delay (Δt) of a terahertz pulse. The time delay is caused by the more optically dense tablet compared to the undisturbed propagation of the pulse through nitrogen gas, which is typically used as a reference medium in laboratory terahertz measurements. Hence, we assume the validity of the following equation

$$(n_{\text{eff}} - 1)H = c\Delta t \tag{1}$$

where n_{eff} is the effective refractive index of the tablet, H is the height of the round flat-faced tablet, corresponding in direction to the normal of incidence, and c is the velocity of light in vacuum. The refractive index of nitrogen is assumed to be equal to unity.

In the derivation of the structural parameter S of a porous pharmaceutical tablet we exploited the concept of effective permittivity of the tablet and Wiener bounds that define the boundary range for the effective permittivity in the absence of scattering of the terahertz waves. Aspnes (Aspnes, 1982) provides a nice description of Wiener bounds for composite materials by considering two limiting cases, namely no screening and maximum screening of microstructures in the direction of the external electric field. This means that, for example, a needle−shaped particle orientated parallel to the external electric field (in our case direction of propagation of the THz pulse) would develop little screening, whereas a disc-shaped particle of the same volume would yield strong screening. The effective permittivity of a porous pharmaceutical tablet can be assumed to be constructed from parallel and series connections of the internal solid structures as follows (Bawuah et al., 2016a):

$$\varepsilon_{\text{eff}} = \frac{1}{\frac{1-S}{\varepsilon_{\text{U}}} + \frac{S}{\varepsilon_{\text{L}}}} \tag{2}$$

where ε_{U} and ε_{L} are the upper and lower Wiener bounds of the permittivity, respectively, and S is the structural parameter. S is a measure of that fractional part of the randomly distributed structures in a porous medium that can be lumped together in parallel and in series coordination, respectively. Since the true value of the effective permittivity of the tablet is always confined between the upper and lower values of the effective permittivity, the structural parameter S is a number that ranges from zero (all constituents in parallel) to one (all constituents in series). The definition of S holds equally for multiphase systems. In our study, we will only deal with a three-phase system, air and two solid phases, respectively. Eq. (2) was originally defined for effective heat conductivity (Krischer and Kast, 1978) of porous media, such as coated paper products, but for the sake of analogy we have modified the concept for this analogous case, namely to represent the effective permittivity of porous media.

In the case of a three-phase system, such as air (or nitrogen gas), micro-crystalline cellulose (MCC) and the drug in this study, the equations for the upper and lower Wiener bounds of the effective refractive index are as follows:

$$n_{\text{U}}^2 = f_{\text{air}} + f_{\text{MCC}} n_{\text{MCC}}^2 + f_{\text{drug}} n_{\text{drug}}^2 \tag{3}$$

and

$$\frac{1}{n_{\text{L}}^2} = f_{\text{air}} + \frac{f_{\text{MCC}}}{n_{\text{MCC}}^2} + \frac{f_{\text{drug}}}{n_{\text{drug}}^2} \tag{4}$$

where f_{air}, f_{MCC} and f_{drug} are the volume fractions of air (i.e. the pores constituting the tablet porosity), MCC and drug, respectively. The symbols n_{MCC} and n_{drug} denote the intrinsic refractive indices of MCC and drug. If we apply the well-known relation from optics for the real relative permittivity and the refractive index of a non-absorbing insulating medium, namely, $n = \sqrt{\varepsilon}$, we get from Eqs. (2)–(4) the expression

$$S = \frac{1}{n_{\text{U}}^2 - n_{\text{L}}^2}\left[\frac{n_{\text{U}}^2 n_{\text{L}}^2}{n_{\text{eff}}^2} - n_{\text{L}}^2\right] \tag{5}$$

In the pharmaceutical industry, the compressibility of pharmaceutical tablet formulations is an important factor which determines the required applied force on the composition of powder mixture to turn it into a structurally stable porous tablet. It greatly affects a range of tablet properties such as disintegration, dissolution, structural integrity, bioavailability and absorption as well as the mechanical properties, such as hardness and friability. The compressibility is defined as a mechanical property, which describes the relationship between the resulting compact density or strength (hardness/friability) and the compaction pressure (Adetunji et al., 2006).

We propose an "optical compressibility" parameter to estimate the mechanical compressibility of an excipient or complex formulation based on a simple analysis of the transmitted terahertz pulse. This "optical compressibility" is defined by using Eq. (1) as an optical state equation in analogy to the equation of state of a medium in thermodynamics. For the sake of clarity, we first consider the simple thermodynamic equation of state of an ideal gas, which is defined with the aid of the pressure (p), volume (V), absolute temperature (T), the number of gas molecules (υ) and the gas constant (R) as $pV = \upsilon RT$. The optical state equation, namely