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A structure parameter for porous pharmaceutical tablets obtained with the aid of Wiener bounds for effective permittivity and terahertz time-delay measurement

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ABSTRACT

A structure parameter that can be used to predict the pattern of arrangement of porous inclusions in pharmaceutical tablets is introduced. By utilizing the effective refractive index of a pharmaceutical tablet obtained from terahertz time-domain measurements, we have shown that there exists a promising correlation between the calculated structural parameter and the porosity of training sets of pharmaceutical tablets, having well-defined characterization. Knowing of the structural arrangement, i.e. combined constituent skeletal-pore elements in series, parallel or mixed within porous media, could serve as a basis for understanding the ingress and permeation of liquids in such media. In the realm of pharmaceutical applications, such knowledge of the structural arrangement of air voids within a medicinal tablet could enable correlation with mechanical strength and dissolution behaviour in aqueous systems.

1. Introduction

Prediction of transport properties of porous media, such as heat conductivity, fluid uptake and permeation, disintegration etc., is of key importance in order to enable design and control of the functional properties of porous products. Typical porous products having topologically connected porosity include, for example, paper, ceramics and pharmaceutical tablets. Additionally, bone, teeth, soil and plant materials are typical examples of functional porous media present in nature. Depending on the physical quantity of interest, namely heat conduction, elasticity, liquid or gas flow inside the porous medium, and optical properties like light transmission, different measurement techniques are applied to extract information concerning these quantities. If we consider a porous medium from the viewpoint of electromagnetic wave interaction with said medium, under the assumption that the effective medium approximation (EMA) (Bruggeman, 1935; Maxwell Garnett, 1904) is valid, prediction of the magnitude of the porosity is possible from measured optical spectra. In such a case, the scattering of light is assumed negligible, and the electric permittivity of the constituents of the two or multi-phase porous medium, such as a nanocomposite, are known (Aspnes, 1982; Boyd and Sipe, 1994; Zeng et al., 1988). The effective medium model, apart from being useful in photonics and the applications thereof, has also been used to extract the thermal properties of porous media. Actually, similar EMA models can be shown to be valid for various different physical properties of porous media as described in the review article of Hale (Hale, 1976).

One shortcoming of EMA models is that assumptions are usually made on the shape of pores embedded in the medium. For example, spherical voids are assumed in the frame of the models of Maxwell Garnett and Bruggeman (Bruggeman, 1935; Maxwell Garnett, 1904). The concept of a spherical inclusion can be reasonable because of the fact that a sphere presents usually a minimum interfacial energy preferred by nature. However, artificial porous effective media can show complex structures that cannot be described with the aid of a simple spherical model of a void. Fortunately, there is a rather general EMA model that

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provides upper and lower limits for the electric permittivity of porous insulators, namely Wiener bounds (Wiener, 1912). These bounds, apart from assuming a negligible scattering of an electromagnetic wave, place no restriction or assumption on the shape of the constituents of a multi-phase porous medium. In the case of two-phase composites, tighter parameter estimates than those of Wiener bounds have been presented in the literature in the example of a light absorbing effective medium (Bergman, 1980; Milton, 1980). Furthermore, the theory related to Wiener bounds of three or multi-phase composites have been developed further (Peiponen and Gornov, 2006).

In the case of pharmaceutical tablets, they are compressed from a powder mixture, which includes excipients and one or more active pharmaceutical ingredient(s) (API). Microcrystalline cellulose (MCC), used in this study, is one of the most popular excipients to be found in pharmaceutical tablets, known for its properties of binding and water absorption, in turn providing simultaneous swelling and enhanced break-up of the tablet. Instead of the typical case of using the concept of a polyethylene (PE) pellet as a matrix in THz measurements, we report here, rather, on the evaluation of a structural parameter for three-phase real pharmaceutical compacts, namely MCC plus air (pores) plus indomethacin, used commonly in painkillers, as API. THz waves have a relatively long wavelength, which can be considered as an advantage when studying porous media due to low to negligible levels of scattering of the incident wave. The presence or absence of THz scattering from a porous tablet can be detected and analysed using the methods introduced in (Silfsten et al., 2011; Tuononen et al., 2010). The applicability of the THz measurement techniques has been shown to be valid in industrial conditions that correspond to the production of pharmaceutical tablets (Shen, 2011; Zeitler and Shen, 2013). Our goal is to develop a simple and fast measurement method, which is based on a single THz pulse detection, which would yield simultaneously information on various parameters of pharmaceutical tablets, such as the structural parameter, which is based on utilization of Wiener bounds, as suggested in this article.

Recently, we have been studying effective refractive index of MCC pharmaceutical compacts with a priori known properties such as height, diameter, weight, surface roughness and porosity by detection of THz time delay from such samples (Bawuah et al., 2014b; Chakraborty et al., 2016). These and other samples, we have used as training sets to learn the correlation between the effective refractive index and porosity of the tablets (Bawuah et al., 2014b), and also porosity dependent elastic properties such as the Young's modulus of elasticity which is related to the effective refractive index of the porous tablet (Bawuah and Peiponen, 2016; Peiponen et al., 2015). In the latter case we have suggested that a mechanical property of the porous tablet can be predicted by THz sensing. Hence, this sensing method provides a non-destructive method to gain information on the elasticity of porous media. We expect that information on the structural parameter of this study can play an important role in the description of the different arrangement of microstructures inside pharmaceutical tablets by THz sensing.

2. Theory

We start with the Wiener bounds for the effective permittivity of a porous effective medium. These are obtained by considering the one-to-one homomorphic equivalence to having different dielectrics in parallel and series connection inside a capacitor, and dealing with the total capacitance of a plate capacitor. From the expression of the total capacitance, one can solve the effective permittivity of the dielectric medium. Wiener bounds describe the two extreme cases where all the different constituents are either in parallel or in series connection (Aspnes, 1982). Hence, in the case of a finite number of constituents, the upper (denoted by subscript U) and lower (subscript L) Wiener bounds are as follows:

$$\varepsilon_U = f_1\varepsilon_1 + f_2\varepsilon_2 + \ldots + f_J\varepsilon_J = \sum_{j=1}^{J} f_j\varepsilon_j \tag{1}$$

and

$$\frac{1}{\varepsilon_L} = \frac{f_1}{\varepsilon_1} + \frac{f_2}{\varepsilon_2} + \ldots + \frac{f_J}{\varepsilon_J} = \sum_{j=1}^{J} \frac{f_j}{\varepsilon_j} \tag{2}$$

where f_j is the fill fraction and ε_j is the relative permittivity (in the general case a complex number) of the component j. Obviously, it holds that

$$\sum_{j=1}^{J} f_j = 1 \tag{3}$$

In the case of air voids, the fractional air volume that occupies the pores (i.e. the porosity) is obtained from the volume ratio V_{air}/V_{total}, which can be taken to correspond to, for instance, f_1. For air, we assume that its relative permittivity is unity, and hence the refractive index of air is also assumed to have the value 1 in the THz spectral range 0.1–1. 5 THz of this study. It is well known that the bounds given in Eqs. (1) and (2) are not tight, and much tighter bounds, e.g. in the case of a two-phase system have been derived with the aid of the calculus of variations (Hashin and Shtrikman, 1962) and utilized to characterize properties of pharmaceutical compacts (Bawuah and Peiponen, 2016). As we already mentioned, the advantage of Eqs. (1) and (2) is that no assumption is made concerning the shape of the structures of the porous medium. Furthermore, the true value of the effective permittivity is always between ε_L and ε_U. In reality, part of the randomly distributed structures of the porous medium can be considered to have a share in parallel and the rest in series connection. Using such a model for the share, the effective heat conductivity, for example, can be calculated as shown in (Krischer and Kast, 1978). We utilize such a share as a structure parameter, S, using the concept of relative permittivity and Wiener bounds, and deal with an inverse problem in comparison with the method of (Krischer and Kast, 1978), namely we get experimental information on the effective THz refractive index of a porous medium as a function of porosity and, therefrom, calculate S. The appealing feature with using the structure parameter S is that it holds for multi-phase systems. Following the definition given in (Krischer and Kast, 1978) for heat conductivity, we apply it to the relative permittivity as follows:

$$\varepsilon_{eff} = \frac{1}{\frac{1-S}{\varepsilon_U} + \frac{S}{\varepsilon_L}} \tag{4}$$

According to the definition in Eq. (4), S is always a real number between zero and one. In Eq. (4) it is assumed that once the totals for parallel and serial effective permittivity are given, they can be effectively stuck together (concatenated) end-to-end, i.e. a region of parallel construction itself put in series with a serial grouping. This is the case since a further "in parallel" makes no sense. This type of lumped parameter expression has been shown to be useful in the description of heat conductivity in porous medium (Gerstner et al., 2008).

Next, we assume that absorption of THz radiation by the porous medium is negligible because THz wave absorption of indomethacin is weak in the THz frequency range (Shen, 2011; Shibata et al., 2015). Thus, the assumption is valid for the present relatively thick samples of the current study because the THz pulse time delay could be measured in the transmission measurement mode. In the case of strong THz wave absorption, one may face the problem of lack of signal in the transmission measurement geometry. Then one may try to find an appropriate THz spectral window for transmission measurement. In the absence of, or low, absorption of THz waves in an insulator, we have the well-known relation