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Detection of porosity of pharmaceutical compacts by terahertz radiation transmission and light reflection measurement techniques

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ABSTRACT

We report on the non-destructive quantification of the porosity of pharmaceutical compacts (microcrystalline cellulose tablets) by using both optical and terahertz techniques. For the full analysis of the porosity of pharmaceutical tablets, the results obtained in both cases have shown that optical and terahertz techniques are complementary. The intrinsic refractive index of microcrystalline cellulose was estimated using the effective refractive index obtained from the time delay of the THz pulse together with the Bruggeman model for effective media. Once this intrinsic refractive index is known, the unknown porosity of the tablet can be estimated with the aid of the measured effective refractive index as well as the thickness of the pharmaceutical tablet. The method was tested using a set of thirteen tablets having different porosities. It is shown that the error in the estimation of the unknown tablet's porosity is less than 1%. In addition, surface roughness was measured by using an optical interferometer and gloss by using a diffractive-optical-element based glossmeter. The measurement was achieved by scanning the tablets with a probe beam and detecting the reflected light. The surface roughness and gloss data show relatively good correlation with the porosities of the tablets.

1. Introduction

Terahertz (THz) radiation has a unique ability to excite low frequency bond vibrations, crystalline phonon vibrations, hydrogen-bonding stretches, torsion vibrations and molecular rotations in gases (Chantry, 1971). This enables a range of interesting applications in materials characterization and the interaction of terahertz radiation with pharmaceutical tablets for the identification of pharmaceutical ingredients is one example for an emerging field of this technology (Taday, 2004; Shen, 2011). In this industry, process analytical technology (PAT) applications have been reported based on this technology: a typical example is the use of terahertz sensing for in-line monitoring of the coating thickness of pharmaceutical tablets (May et al., 2011).

Recently, a number of studies have investigated the potential of terahertz spectroscopy for the characterization of pharmaceutical solids. In the realm of differentiating pharmaceutical polymorphism and crystallinity, terahertz spectroscopic techniques have proven great sensitivity. A clear manifestation to this claim is the differentiation of benzoic acid and some monosubstituted derivatives, including salicylic acid and acetylsalicylic acid (aspirin) using terahertz time-domain spectroscopy (THz-TDS) (Walther et al., 2002). Just a year later, Taday et al. (2003) succeeded in using THz-TDS to clearly identify ranitidine hydrochloride crystalline forms 1 and 2. In an attempt to extend the work of Taday et al. (2003), Strachan et al. (2004) showed the applicability of the THz-TDS technique to a broad range of solid-state forms of pharmaceutical compounds by differentiating crystalline, amorphous and super cooled liquid crystalline forms.

Although the characterization and control of all possible polymorphic forms of a new active pharmaceutical ingredient (API) are key factors for successful product development in the pharmaceutical industry, the knowledge of the microstructure, with porosity of the final product (i.e. tablets) being a significant parameter, also plays a major role since it affects the functionality of the solid dosage form. The porosity of a pharmaceutical tablet is defined as the fraction of air voids with respect to the total volume of the tablet. Porosity plays an important role in the ingress of dissolution medium (Delalonde and Ruiz, 2008), subsequent disintegration and release of the active API from the tablet

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(Pajander et al., 2009) in the gastrointestinal tract. Furthermore, porosity has been used as a yardstick in the evaluation of the elasticity and the integrity of pharmaceutical tablets using a non-destructive method based on pulse photoacoustics (Ketolainen et al., 1995) and THz pulsed imaging (May et al., 2013).

Several techniques have been used over the years to determine the porosity of pharmaceutical tablets as have been extensively reviewed by previous papers of the authors (Ervasti et al., 2012; Peiponen et al., 2013a,b). Among these techniques are mercury porosimetry, gas absorption, infrared (IR) and Raman spectroscopic techniques. Others include ultrasound transmission techniques, gamma-ray transmission and terahertz spectroscopy. By carefully comparing and contrasting both the merits and the demerits of these techniques and bearing the PAT requirements in mind, terahertz spectroscopy has great potential as a PAT tool to measure tablet's porosity (Ervasti et al., 2012).

In a recent attempt to nondestructively measure the porosity of pharmaceutical tablets, we have shown that in the absence of terahertz scattering, the effective refractive index (RI) that is obtained by the detection of the terahertz pulse delay correlates with the porosity of the tablet (Ervasti et al., 2012). In addition, we have proposed that the broadening of the THz pulse could be a measure of porosity of tablets that scatter terahertz radiation (Peiponen et al., 2013a,b).

Parrott et al. have investigated the frequency-dependent RI and the absorption coefficient of porous media in the case of media that exhibit low porosity and weak scattering of terahertz radiation (Parrott et al., 2009) using the Maxwell Garnett effective medium model (Maxwell Garnett, 1904; Parrott et al., 2012). Furthermore, they have also considered the Bruggeman model (Parrott et al., 2012; Bruggeman, 1935) for a case when the porosity of a sample can be relatively high.

The purpose of this paper is twofold. Firstly, the work of Ervasti et al. (2012) on microcrystalline cellulose (MCC) tablets is extended by investigating the dependence of porosity on other physical quantities such as gloss and surface roughness. Knowledge of these parameters also plays a significant role in terms of drug release, the adhesion of coating materials in regular/irregular surfaces, and possible crack formation during and after tablet compression. For instance, the surface roughness of a tablet is indicative of the surface quality of the tablet and can even be used to predict the success of the tablet's compression process. In a study conducted by Juuti et al. (2006), the average surface roughness and the average gloss of sodium chloride tablets as a function of the compression force was investigated. A good correlation between these parameters was obtained. In another paper written by the same author (Juuti et al., 2009); the dependence of the gloss on the surface roughness was quantified. However, in this work our central focus is on the dependence of porosity on these parameters as discussed above.

Secondly, this paper introduces a method for the nondestructive and the noninvasive estimation of the porosity of sample pellets measured with terahertz pulse delay and using the Bruggeman effective medium approximation (BR EMA).

The applicability of the BR method for inspecting porosity using THz data was tested for a set of thirteen tablets with a relatively wide range of porosity values. The surface quality of the same set was measured using optical probes.

2. Theory

Quantitative models for approximating the properties of heterogeneous materials/mixtures have been discussed since the early 19th century. In the realm of THz spectroscopy, two effective medium approximations (EMAs) have become particularly popular nowadays: these are usually ascribed to Maxwell–Garnett, MG EMA, (Parrott et al., 2009) and to Bruggeman, BR EMA, (Bruggeman, 1935). The MG approximation is known to be valid within a fairly low volume fraction of inclusion (Parrott et al., 2012). However in this study, MCC powders were pressed into porous tablets, i.e. a mixture of solid medium and air, with a wide range of volume fractions (porosities) and hence the use of the BR approximation is more appropriate in this case (Parrott et al., 2012). Both of these effective medium models assume low scattering losses of the incident electromagnetic radiation.

By taking f_a to be the volume fraction of air and therefore f_b as the volume fraction for the tablet solid content, and by summing up the polarizabilities of the components the BR formula is rendered as (Parrott et al., 2012):

$$f_a\frac{\varepsilon_a-\varepsilon_{eff}}{\varepsilon_a+2\varepsilon_{eff}}+f_b\frac{\varepsilon_b-\varepsilon_{eff}}{\varepsilon_b+2\varepsilon_{eff}}=0 \tag{1}$$

where ε_a and ε_b are the relative permittivity of air and tablet sample, respectively. The quantity ε_{eff} is the effective permittivity of the tablet. By setting $\varepsilon_a = 1$ (air) and $f_a = f$ hence $f_b = 1 - f$, ε_b can be solved from Eq. (1) as:

$$\varepsilon_b=\frac{3\varepsilon_{eff}}{\left(1-(f/(1-f))\left(\left(\varepsilon_{eff^{-1}}\right)/(1+2\varepsilon_{eff})\right)\right)}-2\varepsilon_{eff} \tag{2}$$

Once we know ε_b the intrinsic refractive index, n_b, of the powder material can be calculated. The most straightforward case is for a material that exhibits low absorption of terahertz radiation where the simple relationship of $\varepsilon_b = n_b^2$ and $\varepsilon_{eff} = n_{eff}^2$ holds. For a simple two-phase system of MCC and air this equation can be used to describe the permittivity as it was previously shown that the present tablets have a low absorption as well as low scattering at terahertz frequencies (Silfsten et al., 2011). For more complex dosage forms with three or more components, the model of Eq. (1) can be generalized by introducing the appropriate permittivities and fill fractions (Aspnes, 1982). For materials that absorb terahertz radiation the permittivities are complex numbers. This in turn means that the square equation that couples the relative permittivity and the refractive index is generalized to hold for a complex permittivity and a refractive index, respectively. In this proof of concept study we aim to show that the proposed method of measuring the porosity of a tablet holds for a two-component system. The estimation of the porosity of more complex systems, e.g., multiple excipients, requires further investigations. In principle, Wiener bounds could provide rough tools for such estimation (Peiponen and Gornov, 2006).

The key idea of this method is to extract the porosity from tablet samples using a measured effective refractive index together with the reference data from a single tablet of known porosity. The porosity and thickness of this reference tablet can be measured/calculated by other methods (Ervasti et al., 2012) and using this porosity value, we can estimate the intrinsic permittivity of the tablet material using Eq. (2). This intrinsic permittivity can in turn be used to calculate the unknown fill factor, f, (the porosity) of any subsequent tablet using,

$$f=\frac{1}{1-((1-\varepsilon_{eff})/(1+2\varepsilon_{eff}))((\varepsilon_b+2\varepsilon_{eff})/(\varepsilon_b-\varepsilon_{eff}))} \tag{3}$$

Eq. (3) is derived from Eq. (2). For practical purposes it is important to know the error of the estimate for f. This can be calculated as an absolute relative error $|\Delta f/f|$ from Eq. (3).

3. Materials and methods

3.1. Materials

The tablet sets were compacted using the pharmaceutical excipient, microcrystalline cellulose (MCC; Avicell PH-200, FMC