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Investigating elastic relaxation effects on the optical properties of functionalised calcium carbonate compacts using optics-based Heckel analysis

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ABSTRACT

Heckel analysis is a widely used method for the characterisation of the compression behaviour of pharmaceutical samples during the preparation of solid dosage formulations. The present study introduces an optical version of the Heckel equation that is based on a combination of the conventional Heckel equation together with the linear relationship defined between the effective terahertz (THz) refractive index and the porosity of pharmaceutical tablets. The proposed optical Heckel equation allows us to, firstly, calculate the zero-porosity refractive index, and, secondly, predict the in-die development of the effective refractive index as a function of the compressive pressure during tablet compression. This was demonstrated for five batches of highly porous functionalised calcium carbonate (FCC) excipient compacts. The close match observed between the estimated in-die effective refractive index and the measured/out-of-die effective THz refractive index supports the validity of the proposed form of the equation. By comparing the measured and estimated in-die tablet properties, a clear change in the porosity and hence, the effective refractive index, due to post-compression elastic relaxation of the FCC compacts, has been observed. We have, therefore, proposed a THz-based compaction setup that will permit in-line monitoring of processes during tablet compression. We envisage that this new approach in tracking powder properties introduced in this preliminary study will lead to the onset of further extensive and detailed future studies.

1. Introduction

The numerous advantages that come with the use of pharmaceutical tablets have led to significant investments by the pharmaceutical industry into the study of powder compaction as well as controlling the quality of the finished products. Typical pharmaceutical tablets are composed of several excipient and active pharmaceutical ingredient (API) particles that undergo a vast complexity of processes during compression. The initially loose powder bed undergoes dramatic changes as a function of the relative density due to the force of compaction applied by the tablet punch. These changes include particle rearrangements, elastic and plastic deformation as well as brittle fracture of particles depending on their mechanical properties. Moreover, porosity, distribution of internal stress and density (Kawakita and Lüdde, 1971; Ryshkewitch, 1953), as well as the crystal habit of a drug (Rasenack and Müller, 2002), affect the tableting behaviour and the quality properties of the finished tablet.

Despite sustained research into powder compaction, there are still open questions regarding the complex nature of tableting processes. It is still challenging to predict successfully the properties of the end-tablet product even when all the compositions of the powder mixture are exactly known. Over the past decades, a number of experimental techniques and a wide variety of compaction models (Çelik, 1992; Çelik and Marshall, 1989; Krycer et al., 1982; Paronen, 1986; Salleh et al., 2015; Sun and Grant, 2001) have been developed and utilised to characterise compression behaviour, i.e. compressibility,

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compactibility, and pressure susceptibility of pharmaceutical powders. These models are mostly empirical and define criteria to guide the rational selection of suitable excipients to meet the desired properties of the dosage form. However, many of these models are valid within a restricted range of compaction force and can only describe the compaction process of specific pharmaceutical materials (Çelik, 1992; Kolařík, 1994; Van Veen et al., 2004; Wu et al., 2005).

The most widespread models are described in terms of the Heckel equation (Heckel, 1961a, 1961b), the Kawakita equation (Lüdde and Kawakita, 1966), the Drucker-Prager-Cap model (Han et al., 2008), the modified Heckel equation by Kuentz and Leuenberger (Kuentz and Leuenberger, 1999) and the approach according to Cooper and Eaton (Cooper and Eaton, 1962). The Heckel model, which is by far the most popular in the field of powder compression, is of special interest for the present study. Although several authors have highlighted a number of limitations (Rue and Rees, 1978) and have proposed modified versions of the Heckel model (Stirnimann et al., 2014), its chief merit is its simplicity together with the readily available reference dataset for different kinds of pharmaceutical materials. This makes the analysis and comparison of different pharmaceutical materials more convenient when the Heckel equation is adopted.

Based on the inevitable need for an analytical model during the preparation of solid dosage formulations, the present study considers the Heckel equation but introduces an optical-related version, which is henceforth referred to as “optical Heckel”. The proposed optical Heckel concept originates from the linear correlation observed between the terahertz (THz) based bulk refractive index (effective refractive index) and the bulk porosity of pharmaceutical tablets (Bawuah et al., 2016b; Markl et al., 2018a). With terahertz time-domain spectroscopy (THz-TDS), the effective refractive index, which is a function of the total porosity of a given tablet, can be measured in a non-destructive and contactless fashion within seconds. Based on the unique advantages associated with optical/THz based measurement techniques, we believe that this new optical Heckel equation can serve as a complementary model for rendering comprehensive insight into the processes and compaction mechanisms of pharmaceutical powders.

Pharmaceutical industry is currently under transition from traditional batch manufacture to continuous manufacture (Lee et al., 2015; Nasr et al., 2017). One improvement that is usually coupled with continuous manufacture is continuous process monitoring using process analytical technology (PAT) tools. A key to successful implementation of real-time release (RTR) is the ability to monitor processes continuously based on real-time analysis and control of the manufacturing process. Since the compaction process is one of the key operations in a continuous manufacturing plant, it is particularly important to control the physical and chemical properties of tablets. RTR testing is only possible on the basis of a firm understanding of the process and the relationship between process parameters, material and product attributes (European Medicines Agency, 2012). A robust physical model that is sensitive enough and intuitive to use is a key requirement to design and control tablets with required/specific out-of-die properties. This is possible by utilising observed relations between THz-TDS and important tablet parameters, as we have reported in our previous THz-TDS based experiments (Bawuah et al., 2016a,b; Bawuah et al., 2014a,b; Chakraborty et al., 2017, 2016; Markl et al., 2017a,b).

Here, we support verification of the validity of the proposed optical Heckel method using a two-phase pharmaceutical compact consisting of air-filled pores and a solid material, in the form of a recently developed excipient, functionalised calcium carbonate (FCC), chosen due to its complex porous particle behaviour unlike that of other commonly used solid excipients. This excipient presents a more challenging case study for applying conventional modelling approaches.

The present study also investigates the existence of elastic relaxation of the FCC compacts after compression based on their in-die and out-of-die porosity as well as height values. To further ascertain the influence of the elastic relaxation on the optical properties of tablets during and after compression, this study estimates the in-die effective refractive index based on the proposed optical Heckel method and compares to the measured counterpart. Elastic relaxation during (Anuar and Briscoe, 2009) and after (Baily and York, 1976) ejection has a major influence on, especially, the mechanical and microstructural properties of the finished tablets. We believe that by successfully introducing these optical methods through a carefully engineered compaction setup, it is possible to realise in-line quality control of each tablet during and after compression.

2. Theory

The conventional Heckel equation (Heckel, 1961a, 1961b) describes the relationship between the logarithm of the inverse of the porosity, $f = 1-\delta$ with δ as the relative density, and the applied compressive pressure, p. The Heckel equation was derived based on the assumption that the in-die densification of the bulk powder obeys first-order kinetics as,

$$\ln\left(\frac{1}{f}\right) = -\ln f = Kp + A \tag{1}$$

where K is a constant of proportionality describing the development of a log-linear response of the structure to the application of pressure, i.e. the Heckel slope, and A is an intercept constant describing densification by particle movement and rearrangement. The inverse of K is the mean yield pressure and it represents the limit of plastic deformation of materials or the resistance of a material to deformation (Hersey and Rees, 1971).

The measurement of the refractive index of tablets via THz-TDS has been studied extensively using both the frequency-domain (Bawuah et al., 2016b; Markl et al., 2017b) and time-domain analytical approaches (Bawuah et al., 2016b, 2014a; Markl et al., 2017b). The bulk THz refractive index measured for a given tablet is also referred to as the effective refractive index (n_{eff}) due to the multicomponent nature of a typical pharmaceutical tablet (Bawuah et al., 2014a). Based on empirical evidence, a linear correlation between the effective refractive index and the porosity of pharmaceutical tablets composed of different materials and covering a wide range of porosities was observed (Markl et al., 2018a).

$$n_{\text{eff}}(f) = n(0) + (1-n(0))f \tag{2}$$

where $n(0)$ represents the zero-porosity refractive index, i.e. the inherent refractive index of the solid material constituent in the absence of any imperfections or porosity. During data acquisition, nitrogen gas was used to purge the sample compartment to reduce the effect of water vapor on the terahertz transmission measurement and, hence, the unity in Eq. (2) represents the refractive index of air/nitrogen gas ($n_{\text{air}} = 1$). Eq. (2) is called the zero-porosity approximation (ZPA) method, which is a complementary method, vis-a-vis effective medium theory (EMT), for the estimation of the porosity from known n_{eff} of a given tablet (Markl et al., 2017b). However, the estimation of porosity of pharmaceutical tablets using Eq. (2) is outside the scope of this study. In the present study, we intend to rather monitor the in-die development of n_{eff} during the compression process using Eq. (2). With a compaction simulator, it is possible to measure the in-die porosity based on in-die densification of the bulk powder, i.e. change in the relative density with respect to increasing compressive force. Equation (2), therefore, serves as the basis for the derivation of the proposed optical counterpart of the Heckel law. From Eqs. (1) and (2) we can solve the following expression for the pressure-dependent effective refractive index as follows:

$$n_{\text{eff}}(p;f) = n(0)-(n(0)-1)e^{-(Kp+A)} \tag{3}$$

From Eq. (3), we claim that n_{eff} is directly proportional to the result of the Heckel law, and hence it can be used as an alternative or a complementary quantity to $\ln(1/f)$. Moreover, based on the direct use