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Mathematical modelling of liquid transport in swelling pharmaceutical immediate release tablets

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ABSTRACT

Oral dosage forms are an integral part of modern health care and account for the majority of drug delivery systems. Traditionally the analysis of the dissolution behaviour of a dosage form is used as the key parameter to assess the performance of a drug product. However, understanding the mechanisms of disintegration is of critical importance to improve the quality of drug delivery systems. The disintegration performance is primarily impacted by the hydration and subsequent swelling of the powder compact. Here we compare liquid ingress and swelling data obtained using terahertz pulsed imaging (TPI) to a set of mathematical models. The interlink between hydration kinetics and swelling is described by a model based on Darcy's law and a modified swelling model based on that of Schott. Our new model includes the evolution of porosity, pore size and permeability as a function of hydration time. Results obtained from two sets of samples prepared from pure micro-crystalline cellulose (MCC) indicate a clear difference in hydration and swelling for samples of different porosities and particle sizes, which are captured by the model. Coupling a novel imaging technique, such as TPI, and mathematical models allows better understanding of hydration and swelling and eventually tablet disintegration.

1. Introduction

Oral dosage forms, such as tablets, are one of the most widely used drug delivery systems for treating patients today. There are strict regulations on how these tablets should perform: immediate release formulations should release their entire active pharmaceutical ingredient (API) within 10 min of ingestion (Gupta et al., 2006; Battu et al., 2007; Corveleyn and Remon, 1997), while for sustained release tablet formulations the requirement is to release their full API content within 24 h (Davis et al., 1986). Furthermore, generics manufacturers have to pass bio-equivalency studies with respect to the original products on which the generic product is based (Sarantopoulos et al., 1995). Two key pre-requisites are required to achieve this: (1) a comprehensive understanding of the excipients used and how they will affect tablet disintegration as well as dissolution; and (2) reliable and accurate analytical techniques for assessing tablet dissolution, disintegration and API release and the underlying mechanisms (Lin, 1988; Yu, 2008). Progress has been made experimentally to understand hydration phenomena and API release kinetics observed in tablets and thus relate them to the choice of excipient and resulting tablet microstructure using destructive (Segale et al., 2010) and non-destructive analytical techniques (Battu et al., 2007; Bi et al., 1999; Chen et al., 2010; Kazarian and van der Weerd, 2008; Kazarian and Chan, 2006; Rajabi-Siahboomi et al., 1996).

Magnetic resonance imaging (MRI) has been used extensively to investigate the hydration and swelling processes in sustained released formulations (Chen et al., 2010; Fyfe and Blazek, 1997; Rajabi-Siahboomi et al., 1996, 1994). For example MRI has shown that multiple phases of hydration co-exist in hydroxypropylmethylcellulose (HPMC) compacts: viz. a dry phase at the core of the tablet, followed by a glassy phase, a swollen glassy phase and finally a gel phase in direct contact with the dissolution medium (Chen et al., 2010; Zhang et al., 2011, 2013). More recently it was shown that terahertz pulsed imaging (TPI) can be used to measure the liquid ingress and the swelling of rapid disintegrating tablets simultaneously (Yassin et al., 2015a).

Alongside the need for good analytical techniques to assess the tablet performance, there is a need for theoretical models predicting tablet disintegration, dissolution and API release to rationalise formulation design (Siepmann and Siepmann, 2013; Colombo et al.,

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1995; Quodbach and Kleinebudde, 2016). In order to successfully predict tablet disintegration and API release, at least two mechanisms have to be considered: hydration kinetics, and the swelling of a tablet thereafter within complete release is achieved (Zuleger and Lippold, 2001; Narasimhan, 2001). It is important to note that the force necessary to break up the particle–particle bonds causing the disintegration of the tablet may also be generated by strain recovery (Desai et al., 2016; Quodbach and Kleinebudde, 2016; Markl and Zeitler, 2017). In contrast to the omni-directional enlargement of the swelling particles, strain recovery causes a uni-directional increase in size of the particles. The processes are interlinked and influenced strongly by the microstructure of the tablet. While a number of studies have investigated the effects on one of the mechanisms in isolation, only limited data are available on both. Absorption isotherms based on the weight of the samples during hydration were used to assess the extent of swelling (Schott, 1992b,a). It was observed that the rate of liquid uptake into their polymer matrix followed the same profile as the swelling; this indicates that both processes were controlled by the transport of the solvent into the polymer matrix (Schott, 1992b,a). Compacts of samples that contained a large amount of cross-linked polymer or micro-crystalline polymer both typically exhibit two subsequent phases of swelling: initial swelling due to liquid penetration and secondary swelling due to the disentanglement and diffusion of the polymers into the hydrating solution (Schott, 1992a,b).

In this work we demonstrate how mathematical models can be used to give detailed insight into liquid ingress and swelling dynamics. The model for the liquid ingress in a swelling tablet is based on Darcy's law and is compared to simulations using the well-known Washburn equation. The swelling is modelled by a Schott model, which was modified to enable the comparison with the experimental data and to describe the reduction in pore size. The models are calibrated and compared to experimental data from pure micro-crystalline cellulose (MCC) powder compacts measured by TPI during hydration in a flow cell.

2. Theory

2.1. Liquid penetration in a rigid porous medium

One of the key processes involved in the disintegration of a tablet is liquid penetration driven by capillary forces. Capillary transport is an important field of research due to its numerous applications, such as in petroleum engineering, in hydrology (e.g., movement of ground water), in consumer products (e.g., marker pens, candle wicks and sponges) or in plants (e.g., transport of water from the roots to the tips). The first analytical solution for capillary rise as a function of time was derived by Lucas and Washburn (1921). They described the flow through porous media by considering the pore space as a bundle of capillary tubes of varying diameter embedded in the solid matrix (see Fig. 1).

The location of the liquid front, L, across the entire porous medium can thus be expressed by the well-known Washburn equation as

$$L = \sqrt{R_e \frac{\gamma \cos\theta}{2\eta} t}, \tag{1}$$

where $R_e = R_h^2/R_{c,0}$ (with R_h as the hydraulic radius and $R_{c,0}$ as the pore radius of the dry material) is the mean effective pore radius, γ is the surface tension of the liquid, θ is the contact angle and η is the viscosity of the fluid.

Furthermore, the total volumetric flux of Newtonian liquids in an isotropic porous medium can be described by Darcy's law:

$$q = -\frac{K}{\eta}\frac{\Delta P}{L}. \tag{2}$$

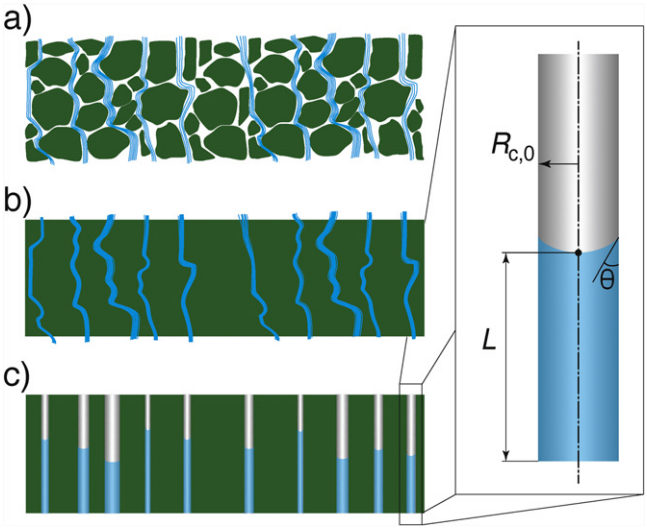

Fig. 1. Approximation of the porous structure of a powder compact. (a) The actual tablet consisting of forged particles forming channels through the powder compact. (b) Only the effective channels (with an effective pore size) are considered in the model. (c) Cylindrical channels are approximated from the pore structure. The inset highlights the capillary action in a cylindrical channel. Each channel is characterised by its liquid height L and its pore radius $R_{c,i}$ with an initial pore radius $R_{c,0}$. The contact angle θ is a fluid/matrix property which is assumed to be constant for all channels.

ΔP is the pressure difference and K is the intrinsic permeability, which is related to the properties of the porous pharmaceutical powder compact. The pressure difference can be described by the Young–Laplace equation ($\Delta P = P_c = \gamma\cos\theta/R_{c,0}$) considering only the capillary pressure, P_c, and neglecting the effect of gravity.

Assuming that the net mass flow in and out of the porous system must be zero (where inflows are negative and outflows are positive) in a rigid porous system, the continuity equation for incompressible fluids can be expressed as

$$\nabla q = 0. \tag{3}$$

In order to calculate $L(t)$ from Eq. (2) one needs to account for the fact that only a fraction of the volume is available for the liquid flow. Therefore, dividing q by ε_0 yields an equation for the liquid front depending on time in the form of

$$L = \sqrt{K \frac{4\gamma \cos\theta}{\varepsilon_0 \eta R_{c,0}} t}. \tag{4}$$

A detailed derivation of this equation was previously provided by Masoodi et al. (2007).

2.2. Liquid penetration in a swelling porous medium

Swelling of a porous medium causes a change in the intrinsic permeability, porosity and pore radius. Therefore, the aforementioned models are no longer valid and one has to consider the affect of swelling on liquid penetration. Schuchardt and Berg (1991) presented a model where they assumed a linear decrease with time of the pore radius in the wetted area of the porous medium (a composite of cellulose and superabsorbent fibres). They considered R_h as the effective hydrodynamic radius in the wetted region behind the advancing liquid front, which changes over time. $R_{c,0}$ is the capillary radius in the dry material and thus it is the length scale related to the liquid meniscus. R_h is approximated as a linear function of time by $R_h = R_{c,0} - a \cdot t$, where a is a constant and expresses the rate of