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Reflectometric monitoring of the dissolution process of thin polymeric films

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ABSTRACT

Pharmaceutical thin films are versatile drug-delivery platforms i.e. allowing transdermal, oral, sublingual and buccal administration. However, dissolution testing of thin films is challenging since the commonly used dissolution tests for conventional dosage forms correspond rather poorly to the physiological conditions at the site of administration.

Here we introduce a traditional optical reflection method for monitoring the dissolution behavior of thin polymeric films. The substances, e.g. drug molecules, released from the film generate an increase in the refractive index in the liquid medium which can be detected by reflectance monitoring. Thin EUDRAGIT® RL PO poly(ethyl acrylate-co-methyl methacrylate-co trimethylammonioethyl methacrylate chloride) (RLPO) films containing the model drug perphenazine (PPZ) were prepared by spraying on a glass substrate. The glass substrates were placed inside the flow cell in the reflectometer which was then filled with phosphate buffer solution. Dissolution was monitored by measuring the reflectance of the buffer liquid. The method was able to detect the distinctive dissolution characteristics of different film formulations and measured relatively small drug concentrations. In conclusion, it was demonstrated that a traditional optical reflection method can provide valuable information about the dissolution characteristics of thin polymeric films in low liquid volume surroundings.

1. Introduction

Pharmaceutical thin films are gaining popularity as alternatives to the more traditional pharmaceutical dosage forms, e.g. tablets and capsules. These polymeric films can be used to administer drugs in diverse ways e.g. via transdermal, oral, sublingual and buccal routes (Bala et al., 2013; Kunst and Lee, 2016).

The drug release from different thin film preparations can be fast or prolonged, depending on the dosage form and the site of administration (Preis et al., 2014a). However, the volume of liquid in which the drug needs to dissolve is often very low, e.g. orodispersible films (ODFs) disintegrate within seconds after contact with saliva in the oral cavity, enabling fast release of the drug (Preis et al., 2014b). Therefore, dissolution testing of thin films is challenging, and the dissolution tests commonly used for other dosage forms are rarely suitable for films (Garsuch and Breitkreutz, 2009; Preis et al., 2013). For example, it has been claimed that dissolution testing of films can be carried out in the traditional USP 24 apparatus type 2 using various types and volumes of the dissolution media (Garsuch and Breitkreutz, 2009), however this approach corresponds rather poorly to the physiological conditions actually present at the site of administration. Alternatively, a film can be placed in a side-by-side diffusion cell in which a fixed area of the film is in contact with a small volume of liquid (e.g. 3 ml) (Korhonen et al., 2015). However, these and other methods currently in use have their inherent limitations, such as the need for relatively large sample amounts, long sampling times, the disruptive effect on the dissolution process due to removal of aliquots as well as limitations related to the analytical method (e.g. UV–vis detection) (Laitinen et al., 2010). Thus, *in situ* monitoring of dissolution would be an advantage in the dissolution analysis of thin film formulations.

Several methods for monitoring of drug dissolution from different dosage forms have been developed (Kuentz, 2014). These include UV fiber optics (Mirza et al., 2009), UV imaging alone (Østergaard et al., 2014) or combined with Raman spectroscopy

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(Boetker et al., 2011), methods based on infrared (IR) (Coutts-Lendon et al., 2003) or near-infrared (NIR) spectroscopy (Sarraguça et al., 2016), potentiometric methods (Bohets et al., 2007) and optical particle analysis (Laitinen et al., 2010). Recently, multi-parametric surface plasmon resonance (MP-SPR) was used for real-time monitoring of the drug release process from EUDRAGIT® RL PO poly(ethyl acrylate-co-methyl methacrylate-co trimethylammonioethyl methacrylate chloride) (RLPO) thin films (Korhonen et al., 2015). MP-SPR, a method generally used for a label-free monitoring of almost any type of molecular interactions of different biological molecules (Kari et al., 2016), made possible the measurement of changes in polymer films significantly thicker than the apparent scanning depth of the SPR field and thus it was feasible to acquire real-time information about physical changes occurring in the films as well as monitoring the dissolution rate of the drug from the thin films.

An SPR setup typically consists of a dielectric material such as a glass prism, a metal layer, and the sample along with an optical detection system. The target compound is selected by a (bio) molecular recognition element on the sensor's surface. Due to the method's high sensitivity to detect small changes in the refractive index of the sample, it has been exploited in various applications e.g. as a biosensor (Homola, 2003; Haes and Van Duyne, 2004). The metal layer on the prism face is typically gold or silver and its thickness is less than 100 nm in order to generate surface plasmon resonance. Unfortunately, such a thin metal film is sensitive to wear and contamination, (the latter phenomenon can cause saturation of the signal) and therefore SPR sensor chips are often disposable. In this study, we demonstrate that a traditional optical reflection method can provide valuable information about the drug release from thin polymeric films. This type of optical sensor detects in real-time minuscule changes in the refractive index occurring in the sample similarly as in the case of SPR-experiments, but without a disposable measurement unit. Furthermore, the sensor is easy to construct to allow practical measurements in a laboratory, and also relatively cheap compared with commercial SPR-sensors.

2. Materials and methods

2.1. Materials

Perphenazine (PPZ) was purchased from Hangzhou Dayangchem Co., Ltd. (Hangzhou, China). Polyvinylpyrrolidone (PVP) K30 and RLPO were obtained from Sigma–Aldrich Chemie GmbH, (Steinheim, Germany) and Evonik Industries (Darmstadt, Germany), respectively. All other materials were analytical or HPLC grade and they were used as received.

2.2. Preparation of the films

The films were prepared according to the protocol developed in previous studies (Korhonen et al., 2016). Briefly, a 10 wt% RLPO solution was prepared in ethanol (>99.5% m/m), in which 4 wt% and/or 10 wt% of PPZ and PVP were dissolved to obtain the three formulations (Table 1). The films were prepared by spraying the solution with a pneumatic airbrush (Badger 200NH, Franklin Park, IL, USA) onto a contact plastic that was placed around the cylinder of a rotating apparatus device (Erweka TAP, Offenbach am Main, Germany). The spraying distance was 15 cm and the solution feed was adjusted to 9 ml/min by moving a screw in the head of the pen. The spraying was carried out for 60 s while the rotation speed of the rotating cylinder was 24 rpm. For the reflectometric measurements, the films were prepared by spraying the solution on a round glass plate (BK7 glass, diameter 15 mm, USA), which was attached to the rotating cylinder.

2.3. Reflectometric measurements

2.3.1. Theory of the method

The so-called internal reflection occurs when a light beam propagates in an optically denser medium 1 and is reflected from the surface of optically rarer medium 2. The most fundamental application of the internal reflection method or internal reflection spectroscopy is the determination of the optical constants i.e. the refractive index and the extinction coefficient. For example, in water, the contents of sugar, salt, proteins, acid etc. contribute to the refractive index of the solution. The theory of reflectometry and its applications in science and in industry have been reviewed e.g. in textbooks by Mirabella, 1993 and Räty et al., 2004.

The reflection of light from a smooth and plane surface of two transparent media can be accurately described by the Fresnel reflection equation providing that the refractive indices of the two media (n_1, n_2) and the incidence angle θ are known. From the reflectance curve $R = R(\theta)$, where R is the relative portion of the reflected energy, we can observe a point where the smooth R-curve becomes folded. This point is called the critical angle; it is the minimum incidence angle which generates the total reflection i.e. all light is reflected. Just below the critical angle, the reflectance decreases rapidly and this swift change can be exploited to observe small refractive changes occurring in the optically rarer medium. Here we employed s-polarized light (i.e. light is linearly polarized and oscillates in a direction that is perpendicular to the plane of light incidence) and according to the Fresnel equation, the corresponding reflectance is (Eq. (1)):

$$R_s(\theta, n_r) = \frac{\cos\theta - (n_r^2 - \sin^2\theta)^{1/2}}{\cos\theta + (n_r^2 - \sin^2\theta)^{1/2}} \cdot \left(\frac{\cos\theta - (n_r^2 - \sin^2\theta)^{1/2}}{\cos\theta + (n_r^2 - \sin^2\theta)^{1/2}} \right)^* \quad (1)$$

where n_r is the refractive index ratio of the two media (n_2/n_1) and * denotes the operation of the complex conjugate of a complex number (Hecht, 1998). It should be noted that the indices are dependent on the light wavelength, $n_r = n_r(\lambda)$. In this study, medium 1 and medium 2 represent the prism and a buffer liquid including the dissolved drug, respectively. The concept is that the drug molecules released from the solid layer, translocate to near the glass/liquid interface and generate an increase in the refractive index in the buffer liquid, which can be detected by reflectance monitoring. The refractive index of the medium 2 (liquid) can be resolved using Eq. (1) by knowledge of the data for the incidence angle and the prism index and by measuring the reflectance.

Because there are no external forces to generate liquid flow during the experiment, molecular diffusion is the main translocating mechanism for molecules and diffusion is a function of

Table 1
The thin film formulations containing EUDRAGIT® RL PO (RLPO), polyvinylpyrrolidone (PVP) and perphenazine (PPZ) prepared in this study.

Formulation code	Amount of RLPO wt%	Amount of PVP wt%	Amount of PPZ wt%
RLPO-PVP	10	4	–
RLPO-PPZ	10	–	10
RLOP-PVP-PPZ	10	4	10