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Monitoring of drug release kinetics from thin polymer films by multi-parametric surface plasmon resonance

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ABSTRACT

The aim of the present study is to monitor the release of perphenazine (PPZ) from thin polymer films in real-time by the multi-parametric surface plasmon resonance method (MP-SPR). The MP-SPR method is capable of measuring changes in polymer films that are significantly thicker than the apparent scanning depth of the SPR field. The in vitro reference measurements confirm that the MP-SPR results can be correlated to the in vitro release of PPZ. However, information gained by MP-SPR can be used to identify three different modes of change in the films with different kinetic timescales, which are not visible in the in vitro testing. The EUDRAGIT® RL PO-PVP-PPZ—film shows significantly faster changes than the film without polyvinylpyrroline (PVP). This information can be used to optimize the drug-release profile of different film formulations for different pharmaceutical purposes.

1. Introduction

Polymeric films are used as drug delivery systems to achieve a systemic drug effect through transdermal, sublingual and buccal routes (Cilurzo et al., 2014; Kumar et al., 2014). Acrylic polymers are used for both pH-dependent and pH-independent controlled release and site-specific formulations (Nollenberger and Albers, 2013). Cationic or neutral poly(meth) acrylates are often used in order to achieve sustained release of the drug, since they are permeable, have pH-independent swelling, and dissolution from the film is diffusion controlled. Plasticizers are added to the formulation to increase film flexibility, enhance film formation and modify the drug release profiles (Glaessl et al., 2010; Nollenberger and Albers, 2013; Siepmann et al., 2006). A drug itself that lowers the glass transition temperature (T_g) of a polymer film can also act as an efficient plasticizer (Glaessl et al., 2009; Siepmann et al., 2006; Wu and McGinity, 2001). In general, drug release from the thin films follows Higuchi kinetics, i.e. the drug release is diffusion controlled and linear with the square root of time (Ahmed et al., 2004; Siepmann and Peppas, 2011). However, unpredictable factors include the drug-polymer interactions in controlled drug-delivery systems, the impact of the presence of water, and the effects of formulation parameters on the resulting drug release kinetics (Glaessl et al., 2010).

In this study, the multi-parametric surface plasmon resonance (MP-SPR) method was used for real-time monitoring of physical changes and drug release from EUDRAGIT® RL PO poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (RLPO) thin films. Surface plasmon resonance (SPR) is an optical method typically used for label-free monitoring of almost any type of molecular interactions of different types of biological molecules (Rich and Myszka, 2010). Thus, it has been used in pharmaceutical analysis in drug discovery as well as in the quality analysis of pharmaceutical compounds (Olaru et al., 2015). In addition, the SPR method can be used to characterize thin films on the nanometer to micrometer scale (Albers and Vikholm-Lundin, 2010; Granqvist et al., 2013). Hybrid measurements with both biomolecules and material coatings have been performed, for example, SPR biosensors have been used to study the affinity of polymers with drug surfaces (Liu et al., 2015), and to study protein interactions with cellulose (Orelma et al., 2011). The method can be also used to determine the amount of solvent bound in a matrix in combination with a mechanical detection method (e.g. quartz crystal microbalance)(Liu et al., 2010; Mohan et al., 2014) and MP-SPR can detect the solvent content of thin films by itself using advanced multiple-wavelength detection and analysis (Kontturi et al., 2013). MP-SPR is a novel derivative of the SPR method, and hence provides more information from the same experiment. This study presents the first

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demonstration of using the MP-SPR method to monitor drug release from polymeric drug delivery systems.

RLPO, used as a film-forming polymer in this study, is water-insoluble and shows pH-independent swelling (Nollenberger and Albers, 2013). Polyvinylpyrroline (PVP) was used as a film-thickening excipient. PVP has good water solubility and has been found to have the capacity to enhance solubility and the drug dissolution rate of poorly soluble drugs (Kadajji and Betageri, 2011; Kumar et al., 2014). Perphenazine (PPZ) was used as a model drug in the films. PPZ is a poorly water-soluble drug (M_w = 404, pK_a = 7.8, logP = 3.1, T_g value of 15.3 °C) (Laitinen et al., 2009). The films were prepared by spraying ethanolic solutions, containing predetermined amounts of RLPO, PVP and PPZ, directly on an SPR sensor. Drug release from the film was then monitored with MP-SPR in real-time under controlled flow conditions of buffer (United States Pharmacopeia (USP) phosphate, pH 7.4). In addition, similarly prepared pure RLPO and PVP films were monitored for comparison. Furthermore, in vitro drug-release studies from the PPZ containing films were conducted and the results compared with the MP-SPR studies.

2. Experimental

2.1. Materials

PPZ was purchased from Hangzhou Dayangchem Co., Ltd. (Hangzhou, China). 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 used as received.

2.2. Film preparation

Based on the composition optimized in preliminary studies (unpublished data), a 10 wt% RLPO solution was prepared in ethanol (≥99.5% m/m). Thereafter, 4 wt% and 10 wt% of PVP and PPZ were added. Films were prepared by spraying the solution with a pneumatic airbrush (Badger 200NH, Franklin Park, IL, USA) on 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 14 ml/min by moving a screw in the head of the pen. The spraying was carried out during four spins of the rotating cylinder with a rotation speed of 24 rpm.

In the case of MP-SPR studies, films were prepared by spraying the solution on a SPR gold-coated sensor slide (standard gold slide, BioNavis Ltd., Finland), which was attached to the rotating cylinder. Different spraying solutions in this case were pure RLPO (film 1), pure PVP (film 2), RLPO-PVP (film 3), RLPO-PPZ (film 4) and RLPO-PVP-PPZ (film 5)(Table 1). The spraying was carried out during four spins of the rotating cylinder. In the case of the RLPO-PVP-PPZ—film, two spins was also used (film 6). Two spins were used, because the MP-SPR method has limited penetration depth (approximately 0.5 micrometers), and it was appropriate to test if this would have any effect on the experiment.

2.3. Multi-parametric surface plasmon resonance measurements

The MP-SPR measurements were performed using the SPR Navi 220A-2L instrument (Oy BioNavis Ltd, Tampere, Finland), equipped with 670 nm and 785 nm light sources. Phosphate buffer solution pH 7.4 (USP 36) was used, and measurements were performed at 25 °C temperature and in constant flow of 50 μl/min. The angular scanning mode of the instrument, where full SPR angular curves are measured constantly, was used in the measurements. The full SPR curve can be processed for different parameters, most typically at least for the SPR angle (the inverted peak minimum). The results were processed using the SPR Navi Data Viewer (4.0) and kinetic analysis was performed using TraceDrawer for SPR Navi (1.6) software. Based on the SPR angle, the refractive index (RI) of the films was calculated according to Albers and Vikholm-Lundin (2010).

Table 1
The formulation compositions of the different thin films and the kinetic analysis results.

Sample/ religion	Formulation	RLPO (wt %)	PVP (wt %)	PPZ (wt %)	Rate constant [s^{-1}]
Film 1	RLPO	10	0	0	nd
Film 2	PVP	0	4	0	nd
Film 3	RLPO-PVP	10	4	0	nd
Film 4	RLPO-PPZ	10	0	10	
($t < 0$)					7.53E-04
($t > 0$)					5.99E-05
Film 5	RLPO-PVP-PPZ, 4-spin	10	4	10	
($t < 0$)					5.26E-03
fast ($t > 0$)					1.35E-04
slow ($t > 0$)					3.79E-05
Film 6	RLPO-PVP-PPZ, 2-spin	10	4	10	
($t < 0$)					2.57E-03
fast ($t < 0$)					1.33E-04
slow ($t > 0$)					3.35E-05

nd = not determined.

2.4. In vitro drug release studies

The in vitro release rate of PPZ from the films 4 and 5 was determined in six parallel measurements in side-by-side diffusion cells (DC-100, Crown Class, Somerville, NJ, USA) at 32 °C with magnetic stirring in the receiver chamber. The film and a plastic card were placed in the diffusion cell so that only one side of the film (surface area 0.64 cm^2) was exposed to the dissolution medium (i.e. two films were measured in one side-by-side unit). Phosphate buffer solution pH 7.4 was used as the dissolution medium with a volume of 3.0 ml. The receiving phase was completely emptied and at fixed time intervals it was replaced with a fresh buffer to maintain sink conditions. The films were allowed to dry at ambient temperature and 20% relative humidity for 20 h before the in vitro release studies.

The concentration of PPZ was analyzed by Gilson High Performance Liquid Chromatography (HPLC), consisting of an Autoinjector 234 (Gilson, Roissy-en-France, France), a Pump 321, a UV/vis-151 Detector, a System interface module and Unipoint TMLC system version 3.01 software (all from Gilson, Middleton, WI, USA). A reverse-phase column Gemini-NX C18 250 × 4.6 mm (Phenomenex Inc., Torrance, CA, USA) was used. UV detection was conducted at the wavelength of 254 nm and the sample injection volume was 100 μl. The mobile phase was acetonitrile–water–triethylamine (70:30:0.03, v/v/v). At a flow rate 1.2 ml/min, the retention time of PPZ was 4.8 min. The standard curve was linear (r^2 = 1) over the range of concentrations of interest (0.1–100 μg/ml). The repeatability of the HPLC method was tested by analyzing the 10 μg/ml standard solution four times in a row before every analysis. The RSD for the peak area was 3.2% (Glaessl et al., 2010).

3. Results and discussion

3.1. Multi-parametric surface plasmon resonance measurements

The surface of film 1 did not exhibit any changes during an MP-SPR measurement. It has been reported that EUDRAGIT® RL