In vitro monitoring of drug release kinetics with real-time MP-SPR

A real-time Multi-Parametric Surface Plasmon Resonance (MP-SPR) instrument was used to monitor the release rate of a small molecular weight drug, Perphenazine, from 5 microns thin EUDRAGIT®-based polymer films. The release kinetics was clearly faster from a film containing a film thickening excipient, Polyvinyl-pyrrolidone (PVP), compared to a film without excipient. MP-SPR results had a good correlation with the results of in vitro reference measurements. The MP-SPR experiments revealed additional kinetic information compared to traditional in vitro measurements.

Introduction

Controlled drug release formulations are extensively studied to optimize and control drug absorption from the gastrointestinal tract or parenteral administration sites. Slow release drug formulations prolong drug effect and reduce dosing requirements, whereas delayed drug release is used to achieve site-specific absorption, based on local environment changes such as pH. The drug release can be controlled by the amount of adsorbed drug within a coating of interest.

Surface Plasmon Resonance (SPR) is an optical phenomenon which is highly sensitive for detecting refractive index changes near the measurement surface, in particular molecular binding or release. Using the SPR phenomenon, Multi-Parametric Surface Plasmon Resonance (MP-SPR) is a real-time and label free *in vitro* tool, which can also be applied to the development of drug delivery systems and optimisation of controlled drug release formulations.

MP-SPR measures a uniquely wide angular range, enabling whole SPR curve detection. This provides not only the SPR peak minimum value (as in traditional SPR) but also additional information on surface changes with parameters such as Peak Minimum Intensity and Total Internal Reflection (TIR) angle. Buffer composition changes (so called bulk effects) can be accounted for in-line during the interactions due to the unique PureKinetics™ feature.. The wide angle range makes MP-SPR capable of measuring also films that are significantly thicker than the apparent scanning depth of the SPR field such as hundreds of nanometers thick polymer films.

Materials and methods

Polymer coatings were based on EUDRAGIT® RLPO poly (ethylacrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (RLPO) thin films. Polyvinylpyrrolidone (PVP) film thickening excipient was added to some of the coatings. PVP has been found to enhance solubility and the dissolution rate of poorly soluble drugs. Perphenazine (M(PPZ) = 404 g/mol) was used as a model drug to monitor the release from the film.

The polymer films were prepared by spraying the solution on a gold coated SPR sensor slide attached to a rotating cylinder. Coating was performed during 2 or 4 spins (speed 24 rpm).

The drug release measurements were performed with an MP-SPR Navi™ 220A-L instrument. Constant flow (50 µL/min) of phosphate buffer pH 7.4 (US Pharmacopeia) at 25˚C was used during the measurements (Figure 1).

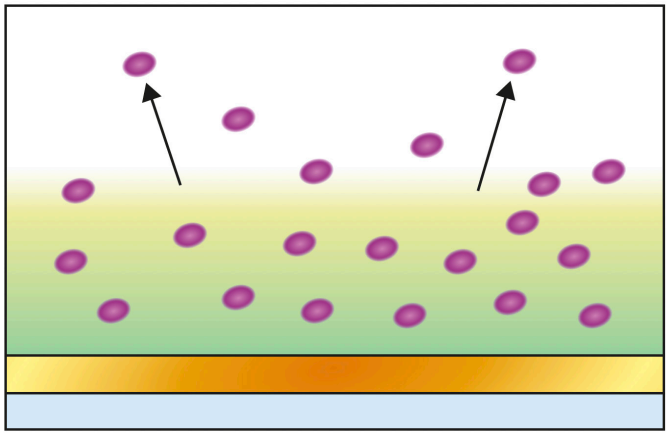

Figure 1. A thin polymer film was deposited on a sensor slide *ex situ* and small molecule weight drug release from the film was monitored in real-time with MP-SPR.

A reference measurement of PPZ *in vitro* release rate was performed in side-by-side diffusion cells with magnetic stirring in a receiver chamber. At specific time points buffer was changed to a fresh buffer to maintain sufficient volume of buffer to dissolve the drug from the product (sink conditions). The PPZ concentration was determined with High Performance Liquid Chromatography (HPLC) comparing results to a calibration curve.

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Results and discussion

Three experiments were carried out; (i) the pure PVP film, (ii) the RLPO-PPZ film and (iii) the RLPO-PVP-PPZ film were exposed to phosphate buffer. The pure PVP film was dissolved immediately when exposed to the buffer due to its high water solubility. MP-SPR measurement revealed a 2-phase release profile in RLPO-PVP-PPZ films (fast and slow phase). The RLPO-PPZ film showed clearly slower release kinetics than RLPO-PVP-PPZ 2-spin film and RLPO-PVP-PPZ 4-spin film (Figure 2 and Table 1). PVP seems to increase the dissolution rate of PPZ by increasing solubility.

Polymer film thickness was estimated to be at least 5 µm based on SPR curve modelling, which is significantly thicker than the SPR scanning depth.

PPZ release rates determined with MP-SPR were in good correlation with *in vitro* reference measurements. Results of MP-SPR can be used to identify also different modes of change in the films such as initial water uptake, which was only visible in MP-SPR measurements.

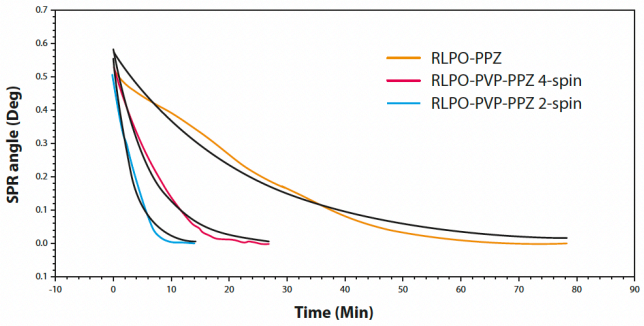

Figure 2. Perphenazine release kinetics from thin polymer films. RLPO polymer films with polyvinylpyrrolidone (PVP) had faster release rate compared to film without PVP. The coloured curves are measured and the black curves are fitted.

	Fast	Slow
RLPO-PPZ		6×10^{-5} s^{-1}
RLPO-PVP-PPZ 2-spin	1.3×10^{-4} s^{-1}	3.4×10^{-5} s^{-1}
RLPO-PVP-PPZ 4-spin	1.4×10^{-4} s^{-1}	3.8×10^{-5} s^{-1}

Table 1. Perphenazine release rates from thin polymer films.

Conclusions

Multi-Parametric Surface Plasmon Resonance (MP-SPR) provides real-time information on drug release from thin polymer films revealing detailed kinetic information. Also, MP-SPR is suitable for measurements on films significantly thicker than the apparent scanning depth of the SPR field (up to few micrometers). Hence, MP-SPR can be well utilized in research, development, and optimization of controlled drug release formulations.

Reference:

Korhonen *et al.*, International Journal of Pharmaceutics 494, 2015

Recommended instrumentation for reference assay experiments

MP-SPR Navi™ 200 OTSO, 210A VASA or 220A NAALI

Sensor surface: Au, other metal or inorganic coating

Software: MP-SPR Navi™ Controller, DataViewer

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