Correlation between calculated molecular descriptors of excipient amino acids and experimentally observed thermal stability of lysozyme

Meng-Lund Helena

https://erepo.uef.fi/handle/123456789/4253

Downloaded from University of Eastern Finland's eRepository
Accepted Manuscript

Title: Reflectometric monitoring of the dissolution process of thin polymeric films

Authors: Riikka Laitinen, Jukka Räty, Kristiina Korhonen, Jarkko Ketolainen, Kai-Erik Peiponen

PII: S0378-5173(17)30204-1
DOI: http://dx.doi.org/doi:10.1016/j.ijpharm.2017.03.028
Reference: IJP 16500

To appear in: International Journal of Pharmaceutics

Received date: 15-12-2016
Revised date: 2-3-2017
Accepted date: 16-3-2017

Please cite this article as: Laitinen, Riikka, Räty, Jukka, Korhonen, Kristiina, Ketolainen, Jarkko, Peiponen, Kai-Erik, Reflectometric monitoring of the dissolution process of thin polymeric films. International Journal of Pharmaceutics http://dx.doi.org/10.1016/j.ijpharm.2017.03.028

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Reflectometric monitoring of the dissolution process of thin polymeric films

Riikka Laitinen\textsuperscript{a\*,b}, Jukka Räty\textsuperscript{b}, Kristiina Korhonen\textsuperscript{a}, Jarkko Ketolainen\textsuperscript{a}, Kai-Erik Peiponen\textsuperscript{c}

\textsuperscript{a}School of Pharmacy, University of Eastern Finland, P.O.Box 1627, FI-70211 Kuopio, Finland

\textsuperscript{b}Unit of Measurement Technology, MITY, Technology Park P.O.Box 127, FI-87400 Kajaani, Finland

\textsuperscript{c}Institute of Photonics, University of Eastern Finland, P.O.Box 111, FI-80101 Joensuu, Finland

\*Corresponding author

riikka.laitinen@uef.fi
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.

Keywords: thin film; dissolution, monitoring, reflectometry, refractive index, internal reflection

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 (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., 2016). 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 \( \theta \) 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):
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 molecule mass, fluid viscosity and the temperature. The buffer liquid and solid layers in a liquid cell give rise to a concentration gradient. The diffusion of released drug molecules tends to minimize concentration differences toward the self-diffusion and dynamic equilibrium and as a result, the refractive index of the buffer liquid changes.

2.3.2 Measurement set-up

This study used a self-made reflectometer. Its main components were an intensity/frequency stabilized HeNe-laser operating at 632.8 nm (Thorlabs HRS015B, USA), a silicon detector connected to current amplifier (Femto DLPCA-100, Germany), and a BK7 prism. The refractive index of the prism was 1.51509 at 632.8 nm. The incident angle was set to 60.0°. The reflectometer is well suited for a long measurement - the reflectance stays within pro mil (1/1000) window for tens of hours with a stable liquid sample. The uncertainty related to the reflectance is estimated to be better than +/- 0.001. This means that the refractive index can be determined with the uncertainty better than +/-0.0001. The setup calibration utilizes either known sample such as water or air (R=1).

Sample disks were attached to the holder placed inside the flow cell. The distance from the sample surface to the prism is adjustable; in the current measurements it was 1 and 2 mm, corresponding to flow cell volumes of 190 µl and 380 µl, respectively. The buffer liquid (40mL, USP phosphate buffer, pH 7.4) which was initially in the storage container was fed to the flow cell by a peristaltic pump (Watson Marlow 505S, England). A film surface area of 1.13 cm² was exposed to the dissolution medium. Figure 1 shows a schematic drawing of the flow cell.

First, we measured a glass substrate without any film to evaluate the stability of the system. Buffer liquid was introduced into the flow cell and the pump was stopped. The system collected reflection data for 8 hours.
at one minute intervals (data collected and averaged for approximately 3 s and idled the rest of the minute). The refractive index was calculated using Eq. 1 and as can be observed from Figure 2, the setup was stable, showing no observable or disturbing drift. Next, glass substrates with films were measured using the same protocol. Three film types were examined three times (sets 1, 2 and 3) and the average refractive index and standard deviation were calculated as a function of time. The system monitored the ambient temperature and temperature of the buffer liquid. During the tests, the temperature of the buffer liquid was 20.5 ± 0.5°C. We also studied the effect of the sample-prism distance: sample sets 1 and 2 used a distance of 1 mm whereas a 2 mm distance was used for sample set 3. The time for drug molecules to diffuse from the film to the vicinity of the prism was longer for sample set 3 compared to sample sets 1 and 2. However, this ‘delay’ was not observed when one examined the whole 8 hours n vs. time dissolution curve.

2.4 In vitro drug release studies

The in vitro drug release testing was used as a reference for the optical method. The rate of PPZ from the films was determined in six parallel measurements in side-by-side diffusion cells (DC-100, Crown Glass, Somerville, NJ, USA) at 32 °C with magnetic stirring in the receiver chamber, as described previously in Korhonen et al., 2015 and Korhonen et al., 2016. A film surface area of 0.64 cm² was exposed to the dissolution medium. Phosphate buffer solution pH 7.4 (USP) was used as the dissolution medium with a volume of 3.0 ml. The receiver chamber 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 at least 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 250x4.6 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 of 1.2 ml/min, the retention time of PPZ was 4.8 min. The standard curve was linear over the range of concentrations of interest (0.1–100 µg/ml). The repeatability of the HPLC method was tested by analyzing the 10 mg/ml standard solution four times in a row before every analysis. The RSD for the peak area was 1.8%.

The drug release kinetics from the films were determined by fitting the data obtained from the drug release studies to the model of Higuchi:

\[ Mt = kt^{1/2} \quad \text{Equation 2.} \]

where \( Mt \) is the cumulative amount of drug released at time \( t \) and \( k \) is a rate constant.
3. Results and discussion

3.1 Reflectometric measurements

The changes in average refractive index of the measurements are shown in Figure 2. The figure demonstrates that all film formulations displayed distinctive release characteristics. The refractive index curve of the RLPO-PVP film differed from that of the other film types - the index increased rapidly within 30 minutes but remained stable for the remainder of the test. In addition, the measurement repeatability in terms of the refractive index with the RLPO-PVP film was outstanding compared to other cases. This indicated rapid water uptake (Glaessl et al., 2010) followed by fast and complete release of the water-soluble PVP from the film (Korhonen et al., 2015). Instead, the other two films showed a larger but slower change in the RI as a function of time (Figure 2). RLPO-PPZ displayed a slow initial change for up to 200 mins after which the decline in RI was faster with a total decrease of approx. 0.001 RI units during the measurement. During the initial phase, the film became wetted with the buffer solution and the PPZ release was slow but after wetting, the drug release rate increased. Instead with RLPO-PVP-PPZ, the decrease in RI was largest (>0.01 units) and it occurred faster than with RLPO-PPZ (Figure 2). Previous studies have shown that RLPO films with PVP release the drug significantly faster than films without PVP (Korhonen et al., 2015; Korhonen et al., 2016). This is because pores are created by the released PVP which allow faster wetting of the hydrophobic RLPO film and thus dissolution and release of PPZ (Glaessl et al., 2010; Nollenberger and Albers, 2013). In addition, the dissolved PVP is able to solubilize PPZ in the dissolution medium (Laitinen et al., 2009), reducing the interfacial tension between the drug and the release medium (Wiranidchapong et al., 2016) and increasing the driving force for PPZ release from the film to the medium.

The changes in average refractive index, reflecting dissolution, were linear with all films. In the case of RLPO-PVP, the change was linear for up to 24 minutes, with a rate constant (i.e. slope of the linear fitting) of $2.37\times10^{-5}\, \text{s}^{-1}$. During this phase, the water-soluble PVP was released and dissolved completely and subsequently no changes were observed. Instead, in the case of RLPO-PPZ, the change was clearly two-phased, i.e. for the first 150 min, the process was linear with a rate constant of $4.61\times10^{-6}\, \text{s}^{-1}$, but after that time, the rate constant was found to be $1.02\times10^{-5}\, \text{s}^{-1}$. During the first phase, the film was wetted and the drug release was slow. After the film wetting, PPZ was able to be released from the film at an increased rate (Korhonen et al., 2015). In the case of RLPO-PVP-PPZ, the process was linear for up to the first 90 minutes with a rate constant of $1.44\times10^{-5}\, \text{s}^{-1}$ and after that between 90 and 400 minutes, the rate constant was estimated as $2.21\times10^{-5}\, \text{s}^{-1}$. During the first phase, PVP was released allowing a faster film wetting and PPZ release than observed with the RLPO-PPZ film (Korhonen et al., 2015). Thus, the change in the refractive index was a combination of dissolution of PVP and PPZ. During the second phase, it is reasonable to assume that only PPZ was released with an increased release rate when compared to RLPO-PPZ film.
The PPZ concentrations of the dissolution media were analyzed after the reflectometric experiment was stopped, i.e. at 480 min. It was found that with RLPO-PPZ, the concentration was 38.2 ± 2.9 µg/ml which corresponded to 0.013 ± 0.001 mg/cm² and 0.48% of PPZ released (Figure 2). In the case of RLPO-PVP-PPZ, the PPZ concentration was 96.6 ± 23.4 µg/ml which corresponded to 0.032 ± 0.008 mg/cm² and 1.5% of PPZ released (Figure 2). This shows the solubilizing effect of PVP, since the PPZ concentration was much higher with RLPO-PVP-PPZ. In addition, this shows that the reflectometric method was able to detect small drug concentrations. As one can assume that the refractive index increases linearly as a function of the content of the dissolved substances, the amount of PPZ can be estimated from the reflectometric measurement curve on the case of RLPO-PPZ film, i.e. an increase of 0.0095 in the refractive index corresponds to 1% of PPZ release. However, the presented method monitors the common effect of all dissolving substances on the refractive index of the release medium. In many cases (as with formulation RLPO-PPZ in this study), the only dissolving substance is the drug. Sometimes however, as with RLPO-PVP-PPZ, there may be also be other dissolving components in the formulation and these cases the simultaneous effect of them on the refractive index of the medium is measured. In this study the effect of fast dissolving PVP may be excluded after the initial period of dissolution, after which the change in the refractive index was solely caused by the dissolution of PPZ. It is the task for future studies to resolve how the individual dissolution processes of two different dissolving substances could be distinguished.

It should be noted that when the films are in contact with buffer solution, film swelling may occur (Nollenberger and Albers, 2013), thus changing the distance between the sample surface and the prism. We visually inspected all of the sample surfaces after the 8 hour test and concluded that RLPO-PPZ and RLPO-PVP samples showed only minimal swelling, unlike the RLPO-PVP-PPZ film in which swelling was apparent. However, the effect of swelling on the RI measurement was found to be insignificant.

In these measurements, the laser’s wavelength was 632.8 nm. All the materials involved were transparent in the visible spectral range, which means that the use of other light sources / wavelengths is possible in that spectral range. However, many buffer solutions and film chemicals absorb light in the UV spectral range, and when operating in UV-range, the refractive index is modulated by the light absorption.

The buffer solution was stationary during the test. Thus all the dissolving chemicals were present to affect the development of the refractive index (cumulative mode). The system also allows us to introduce a small flow for the buffer solution. The flow removes dissolved substances, clearing off the space on the sensor for new released drugs to be detected. This transient mode makes it possible to study layered samples in a more realistic fashion. The approach will be examined in the future.

The utilization of the proposed method is based on the assumption that the buffer solution and the dissolved substances have different refractive indices. Obviously, large index differences are more easily observed than
smaller ones. The choice of the buffer solution makes it possible to fine-tune the sensitivity of the system. The sensitivity of the setup is also determined by the area illuminated by the laser beam on the prism surface and the location of the illuminated area respect to the sample film. By making the illuminated area smaller and placing it closer to the film, the sensitivity can be enhanced. The diameter of laser beam was 3 mm and it covered an ellipsoidal area of approximately 3x4 mm on the prism surface. As a consequence this sensing area was 1/10 of sample disk area.

The reflectance data can also be used to monitor drug release. However, the reflectance has non-linear dependence on the dissolved drug concentration.

3.2. In vitro drug release studies

The drug release measured in the side-by-side diffusion cells is shown in Figure 3. From the figure, it can be seen that PPZ was released faster from RLPO-PVP-PPZ than from RLPO-PPZ. The release followed Higuchi kinetics, i.e. was linear with respect to the square root of time between 5 and 480 min with RLPO-PPZ ($r^2 = 0.9971$) and between 15 and 480 min with RLPO-PVP-PPZ ($r^2 = 0.9932$). The corresponding drug release rate constants were $15.99 \mu g cm^{-2} s^{-1/2}$ and $21.70 \mu g cm^{-2} s^{-1/2}$, respectively. The cumulative amounts of PPZ released at 480 min were $0.32 \pm 0.05 mg/cm^2$ and $0.40 \pm 0.09 mg/cm^2$, which corresponded to 12% and 19% of PPZ released, respectively. These amounts are much higher than obtained with the reflectometric set-up (Figure 2). When comparing the two methods (Figures 2 and 3), it can be concluded that both methods were able to distinguish the differences in drug release between the different films. However, the drug release rates and kinetics are different due to the differences in the hydrodynamics of the different measurement set-ups (Missaghi and Fassihi, 2005) and the fundamental differences in what the two methods actually measure, i.e. the reflectometric method measures changes in the refractive index produced by all dissolving materials. Although the surface area of the film in contact with the medium was slightly larger in the reflectometric set-up (i.e. 1.13 cm$^2$) compared to that of the in vitro method (0.64 cm$^2$), the amounts of drug released were much smaller in the reflectometric set-up, since the buffer volume was small (0.38 ml), there was no mixing of the medium and the medium was not changed during the measurements, i.e. sink condition most probably didn’t prevail during the whole duration of the measurement. Instead, in the in vitro method, the buffer (3ml) was mixed and replaced with a fresh liquid at every sampling point. Furthermore, the refractive index and the drug release efficiency are both dependent on temperature. The RI and side-by-side diffusion cell measurements were conducted at different temperatures, namely 20.5°C and 32°C, respectively. However, the purpose of this study was to demonstrate the feasibility of the RI measurement in the present application mainly by observing the shape/trend of RI-curve (not converting the RI unit to that estimated in the side-by-side diffusion cell test).

4. Conclusions
In this study, a traditional optical reflection measurement method was developed for real-time monitoring of drug dissolution from thin EUDRAGIT® RL PO poly(ethyl acrylate-co-methyl methacrylate-co trimethylammonioethyl methacrylate chloride) films. The measurement unit was a round glass plate onto which the studied films were sprayed. Drug release was monitored by measuring the changes in the refractive index of the phosphate buffer medium. The method was able to detect the distinctive drug release characteristics of the different film formulations and measure relatively small drug concentrations. Thus, it was demonstrated that this method can provide valuable information about the drug release from thin polymeric films in low liquid volume surroundings; these correspond better than the traditional dissolution testing methods to the physiological conditions present at the site of administration.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Tables

References


Figure Caption

**Figure captions**

Figure 1. Schematic drawing of the measurement setup. The change in the refractive index due to dissolution is monitored by the internal reflection mode.

Figure 2. Film dissolution depicted (average ± sd, n=3) by the refractive index of liquid in the flow cell. The black line represents measurements of an empty cell i.e. glass substrate without any film. The length of the error bar indicates the standard deviation of measurements, which, for clarity, are displayed only at eight selected points. The inset shows the refractive index as a function of time for up to 100 min.

Figure 3. Perphenazine release (average ± sd, n=6) from the RLPO-PPZ and RLPO-PVP-PPZ films in pH 7.4 measured in side-by-side diffusion cells.
Figure 2

Refractive index over time for different films:
- RLPO-PVP
- RLPO-PPZ
- RLPO-PVP-PPZ
- No film

1.5% of PPZ released
0.49% of PPZ released
Table 1. The thin film formulations containing EUDRAGIT® RL PO (RLPO), polyvinylpyrrolidone (PVP) and perphenazine (PPZ) prepared in this study.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Amount of RLPO wt %</th>
<th>Amount of PVP wt%</th>
<th>Amount of PPZ wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLPO-PVP</td>
<td>10</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>RLPO-PPZ</td>
<td>10</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>RLOP-PVP-PPZ</td>
<td>10</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>