



Quaternary polymethacrylate–magnesium aluminum silicate films: Water uptake kinetics and film permeability



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ARTICLE INFO

Article history:

Received 15 January 2015

Received in revised form 21 April 2015

Accepted 17 May 2015

Available online 21 May 2015

Keywords:

Quaternary polymethacrylate

Eudragit RS/RL

Magnesium aluminum silicate

Film permeability

Water uptake

Diffusion coefficient

ABSTRACT

The aim of this study was to investigate the impact of the addition of different amounts of magnesium aluminum silicate (MAS) to polymeric films based on quaternary polymethacrylates (QPMs, here Eudragit RS and RL). MAS contains negatively charged $-\text{SiO}^-$ groups, while QPM contains positively charged quaternary ammonium groups. The basic idea is to be able to provide desired water and drug permeability by simply varying the amount of added MAS. Thin, free films of varying composition were prepared by casting and exposed to 0.1 M HCl and pH 6.8 phosphate buffer. The water uptake kinetics and water vapor permeability of the systems were determined gravimetrically. The transport of propranolol HCl, acetaminophen, methyl-, ethyl- and propylparaben across thin films was studied using side-by-side diffusion cells. A numerical solution of Fick's second law of diffusion was applied to determine the apparent compound diffusion coefficients, partition coefficients between the bulk fluids and the films as well as the apparent film permeability for these compounds. The addition of MAS resulted in denser inner film structures, at least partially due to ionic interactions between the positively charged quaternary ammonium groups and the negatively charged $-\text{SiO}^-$ groups. This resulted in lower water uptake, reduced water vapor permeability and decreasing apparent compound diffusivities. In contrast, the affinity of the investigated drugs and parabens to the films substantially increased upon MAS addition. The obtained new knowledge can be helpful for the development of novel coating materials (based on QPM–MAS blends) for controlled-release dosage forms.

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1. Introduction

Polymeric films offer a great potential as coating materials for pharmaceutical dosage forms for controlled drug delivery (Maroni et al., 2013; Siepmann and Siepmann, 2013) or aiming at taste masking or moisture protection (Joshi and Petereit, 2013). Various parameters, including the polymer properties and the type of preparation method can affect the resulting system performance, e.g., drug release patterns in the gastro-intestinal tract. However, in practice it can be difficult to identify the required film coating

composition and preparation procedure to provide desired system characteristics. An interesting strategy to overcome this hurdle is to use blends of two types of polymers: by simply varying the polymer: polymer blend ratio broad spectra of film coating properties can be provided (Siepmann et al., 2008). Alternatively, a polymer can be blended with a clay to achieve this goal (Pongjanyakul et al., 2005; Khunawattanakul et al., 2010). Importantly, molecular interactions of the polymer chains with the clay compounds can occur, which can effectively alter the physicochemical properties of the composite films (Khunawattanakul et al., 2010; Caridade et al., 2013).

Quaternary polymethacrylate (QPM) is a positively charged polymer that is widely used as coating material for pharmaceutical dosage forms. Eudragit RS 30D and Eudragit RL 30D are examples for two commercial QPM products. These are aqueous polymer dispersions (solids content = 30%). In Eudragit RS 30D and Eudragit RL 30D, the QPM contains 5 and 10% w/w quaternary ammonium groups (here abbreviated 5 QPM and 10 QPM). QPM is an insoluble,

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but swellable polymer. The quaternary ammonium groups play an important role for its hydration, attracting water into the system: thus, the swelling of 10 QPM is more pronounced than the swelling of 5 QPM (Akhgaria et al., 2006), resulting in a higher permeability for many drugs and consequently faster release. The swelling of QPM is a priori independent of the pH of the release medium, but can strongly depend on the type and concentration of ions in the bulk fluid (Bodmeier et al., 1996; Sun et al., 2001). Limitations for the use of QPMs as film formers include their considerable sticking tendency encountered during the coating process (Wesseling et al., 1999) and potentially unsuitable drug permeability (Lehmann, 1997). To adjust desired drug release rates, blends of 5 QPM and 10 QPM can be used. For instance, Amighi and Moës (1995) successfully applied this strategy, but the high sticking tendency during the coating process remains. Alternatively, a naturally occurring anionic polymer can be added to QPM, such as pectin or sodium alginate. The positively charged QPM can interact with the anionic polymer via electrostatic interactions. The complexation of QPM with pectin was for example shown to reduce the swelling of the films and retard pectin leaching out of the systems (Semdé et al., 1998). Incorporation of sodium alginate into QPM films resulted in increased film strength, decreased film tackiness, and retardation of drug transport across thin films (Khuantham and Pongjanyakul, 2014).

Magnesium aluminum silicate (MAS), a natural smectite clay, is composed of a central octahedral sheet of aluminum or magnesium and double external silica tetrahedron layers (Alexandre and Dubois, 2000), also called silicate layers. Importantly, the surfaces of the silicate layers exhibit negative charges (containing numerous $-\text{SiO}^-$ groups). MAS is water-insoluble, but can hydrate in water. It is widely used in pharmaceuticals, for example as a diluent, suspending agent or stabilizing agent (Kibbe, 2000). Negatively charged MAS can interact with positively charged polymers, such as chitosan. This offers the possibility to effectively alter the physicochemical properties, mechanical properties and drug permeability of composite films (Khunawattanakul et al., 2010). Moreover, MAS can form complexes with positively charged drugs, e.g., nicotine (Suksri and Pongjanyakul, 2008) and propranolol HCl (Rojtanatanya and Pongjanyakul, 2010). Such drug–MAS complexes have been reported to provide improved thermal properties and to result in more sustained drug release.

In a previous study, the impact of adding MAS to QPM films on the resulting mechanical properties and tackiness of the composite films was studied (Rongthong et al., 2013). The electrostatic interactions between QPM and MAS were shown to lead to the formation of exfoliated and intercalated nanocomposite films, resulting in improved thermal stability and reduced tackiness of the films. Also, wet QPM–MAS films exhibited higher mechanical strength in acidic and neutral media. However, yet it is unknown how the addition of MAS to QPM films affects the water uptake and drug permeability of these systems, which are two key properties for their use as advanced coating materials. Therefore, the objective of the present study was to investigate the water uptake kinetics of QPM–MAS films of various compositions upon exposure to 0.1 M HCl and pH 6.8 phosphate buffer and to monitor changes in the systems' permeability for different types of drugs and parabens.

2. Materials and methods

2.1. Materials

Aqueous dispersions of 10 QPM (Eudragit RL 30D) and 5 QPM (Eudragit RS 30D) were purchased from Roehm Pharma (Darmstadt, Germany). Magnesium aluminum silicate (MAS) (Veegum HV) was obtained from R.T. Vanderbilt Company (Norwalk, CT,

USA). Diethyl sebacate was purchased from Aldrich Chemistry (Dorset, England). Propranolol HCl and acetaminophen were purchased from Changzhou Yabang Pharmaceutical (Jiangsu, China) and Praporn Dasut (Bangkok, Thailand), respectively. Methylparaben and ethylparaben were purchased from Sigma–Aldrich (Tokyo, Japan). Propylparaben was obtained from Fluka (Dorset, England). All other reagents and solvents were of analytical grade.

2.2. Preparation of thin, free films

QPM and QPM–MAS films were prepared using a casting method. MAS aqueous dispersion (4% w/v) was prepared with hot water and kept at room temperature overnight. Twenty grams aqueous QPM dispersion (30%, w/w polymer solids content) were mixed with 0.9 g diethyl sebacate (acting as a plasticizer) and stirred for 30 min. Appropriate amounts of the MAS aqueous dispersion were added to these aqueous, plasticized QPM dispersions to achieve the following QPM–MAS ratios: 4:0, 4:0.1, 4:0.25, 4:0.5, and 4:0.75 (w:w). These QPM–MAS dispersions were further stirred for 30 min, then adjusted to 150 mL with distilled water and shaken in a water bath at 75 oscillations min^{-1} for 24 h at 37 °C. The dispersions were subsequently cast onto Teflon plates (17 × 18 cm) and dried at 50 °C for 48 h in an oven. Afterwards, the films were peeled off the plates and kept in a desiccator at room temperature prior to the measurements. The thickness of the films was measured with a thickness gauge.

2.3. Water uptake studies

Dynamic changes in the water contents of thin, free films upon exposure to 0.1 M HCl and pH 6.8 phosphate buffer were monitored gravimetrically. QPM and QPM–MAS films were cut into pieces of approximately 1 × 1 cm, which were exposed to the media in a horizontal shaker, kept at 37 °C. At pre-determined time points, film samples were withdrawn and weighed after careful removal of excess surface water by blotting with a filter paper (wet weight = W_{wet}). The film pieces were subsequently dried at 50 °C to constant weight (W_{dry}) in an oven. The water contents of the films at each time point were calculated as follows:

$$\text{water content (\%)} = \left(\frac{W_{\text{wet}} - W_{\text{dry}}}{W_{\text{wet}}} \right) \times 100\% \quad (1)$$

2.4. Determination of the water vapor permeability

Circular films pieces (1 cm in diameter) were placed onto (open) 5 mL glass vials, containing 3.5 g silica gel beads. The films were fixed with screw lids, the surface area available for water permeation per film was 0.58 cm^2 . The vials were placed in a desiccator containing a saturated aqueous sodium chloride solution (providing 75% relative humidity). The desiccator was kept in a room at 26 °C, 55 ± 3% relative humidity (Pongjanyakul et al., 2005). The weight changes of the vials were monitored gravimetrically during 120 h. The water vapor permeability coefficient (WVP coefficient) was determined from the slope of the straight line obtained when plotting the cumulative amount of water vapor permeated through a film as a function of time, using the following equation (Pongjanyakul et al., 2005):

$$\text{WVP coefficient} = \frac{\text{rate} \times d}{A \times \Delta P_v} \quad (2)$$

where rate is the water permeation rate (=cumulative amount of water permeated through the film per time); d is the mean thickness of the film; A is the surface area available for water vapor

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