International Journal of Pharmaceutics 460 (2014) 63–72

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Modification of quaternary polymethacrylate films using sodium alginate: Film characterization and drug permeability

Natnicha Khuathan, Thaned Pongjanyakul *

Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

ARTICLE INFO

Article history:
Received 1 September 2013
Received in revised form 18 October 2013
Accepted 29 October 2013
Available online 6 November 2013

Keywords:
Quaternary polymethacrylate
Sodium alginate
Molecular interaction
Film permeability
Mechanical properties

ABSTRACT

The aims of this study were to investigate the molecular interaction of quaternary polymethacrylate (QPM) in aqueous-dispersion form with sodium alginate (SA) and to characterize the physicochemical properties, mechanical properties, and drug permeability of the QPM–SA films. The results demonstrated that QPM can interact with SA via electrostatic force, leading to the formation of flocculate particles in the dispersions. Transparent QPM–SA films were prepared using a casting/solvent evaporation method. The positively charged quaternary ammonium groups of QPM can interact with the negatively charged carboxyl groups of SA, which was observed using ATR-FTIR spectroscopy. This interaction caused a change of thermal properties, an increase in film strength, and a decrease in film tackiness. The puncture strength of the wet films in acidic media increased as the amount of SA was increased, but the flexibility of the films decreased. The wet films still presented good strength and flexibility in neutral pH when using 2.5–6.3%w/w SA because of their lower water uptake in such media. The incorporation of SA into QPM films was able to reduce drug permeability but increase drug diffusivity in acidic media. In contrast, the drug diffusivity decreased with the addition of a small amount of SA into the films when using a neutral medium. This phenomenon can be attributed to the effect of pH on the water uptake of the film and the ionization of the SA in the microenvironment of the films. These findings suggest that SA can modify the characteristics of QPM films, and QPM–SA films present a strong potential for application as a film coating material for modified-release tablets.

1. Introduction

Preparation of thin polymeric films is very important for pharmaceutical manufacturing, particularly film coating for solid dosage forms such as tablets and pellets. The coated films on such dosage forms can mask the unpleasant taste and odor of drugs, and protect drugs from degradation caused by light and moisture (e.g. oxidation and hydrolysis) (Nagai et al., 1997). In addition, film coating can provide sustained drug release, and protect the drugs from acid degradation in the gastrointestinal tract (Wu et al., 1997). Materials that are commonly used for these purposes are synthetic polymers, such as hydroxypropyl methylcellulose (Cao et al., 2004; Sangalli et al., 2004), and polymethacrylates (Moustafine et al., 2012). In addition, natural polymers, such as chitosan (Koizumi et al., 2001; Nunthanid et al., 2002), and sodium alginate (SA) (Pongjanyakul et al., 2005; Lai et al., 2011) have been previously employed as tablet-coating materials for the modified release of drugs.

Quaternary polymethacrylate (QPM), a polymer that is synthesized from acrylic and methacrylic esters, has been widely employed as a film coating material in pharmaceutical dosage form (Lehmann, 1997). QPM is available in aqueous-dispersion form as the commercial products, Eudragit® RS30D and Eudragit® RL30D, which contain 5 and 10% quaternary ammonium groups (5QPM and 10QPM), respectively (Lehmann, 1997). These copolymers contain positively charged quaternary ammonium groups that have chloride ions as counter ions in their structures (Fig. 1a). The 5QPM films provide a lower swelling property and drug permeability than the 10QPM films (Knop, 1996). Mixing the 5QPM and 10QPM dispersions can modify the drug permeability of the resultant films, but the mixed films are still limited by a narrow range of film permeability (Bodmeier and Paeratakul, 1990). Furthermore, QPM films have poor mechanical properties. This can be increased by the incorporation of water-soluble or water-insoluble plasticizers to improve the flexibility of the films (Bodmeier and Paeratakul, 1993). Moreover, anionic hydrophilic polymers, such as pectin (Semdé et al., 2000), which interact with QPM via electrostatic force, can reduce the hydration and swelling of QPM films, resulting in the retardation of drug diffusion across the film.

SA, a negatively charged biopolysaccharide, is extracted from brown seaweed. It is composed of alternating blocks of 1–4 linked

* Corresponding author. Tel.: +66 43 362092; fax: +66 43 202379.
E-mail address: thaned@kku.ac.th (T. Pongjanyakul).

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http://dx.doi.org/10.1016/j.ijpharm.2013.10.050

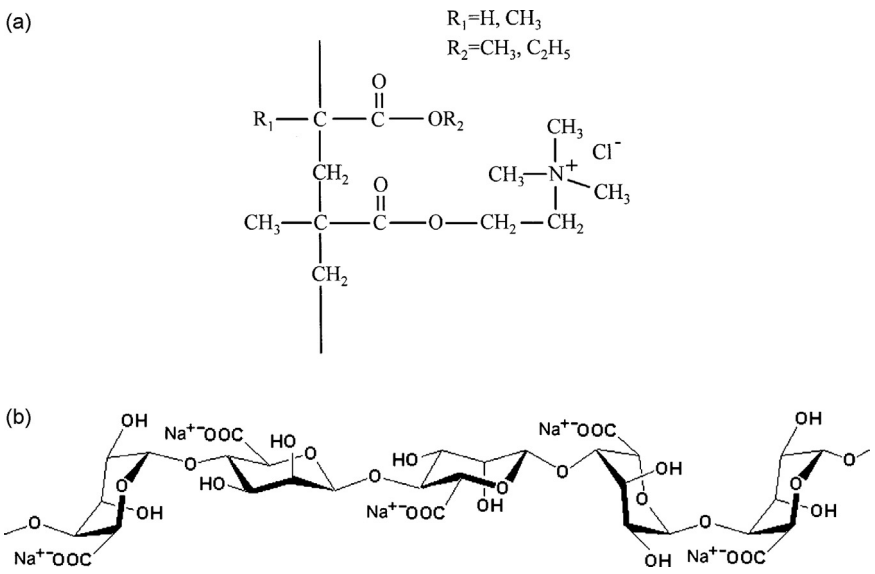

Fig. 1. Molecular structures of QPM (a) and SA (b).

α-L-guluronic and β-D-mannuronic acid residues, as shown in Fig. 1b. SA is regarded as an excellent polysaccharide for use in drug-delivery systems because of its unique biocompatibility, biodegradability, and non-toxicity. For these reasons, it has been widely used as an excipient in pharmaceutical dosage forms (Rowe et al., 2006) and can be used to fabricate drug delivery systems such as matrix dosage forms (Liew et al., 2006; Sriamornsak et al., 2007), film-coated dosage forms (Sriamornsak and Kennedy, 2006), beads (Lee et al., 1999), and controlled-release capsules (Pongjanyakul and Puttipipatkhachorn, 2007). In addition, SA can interact with positively charged chitosan to form polyelectrolyte complexes (Takahashi et al., 1990; Lawrie et al., 2007). Recently, a report has been published concerning the interaction between SA and cationic polymers with dimethylamino groups (Moustafine et al., 2005). The complexes obtained were used to prepare a matrix tablet for colon drug delivery (Moustafine et al., 2009). For these reasons, SA is an interesting material and has potential for modifying the characteristics and drug permeability of QPM films.

Therefore, the aim of this work was to study the effect of SA on the characteristics of QPM dispersions and films. The particle size and zeta potential of the QPM–SA dispersions with various SA contents were examined before film casting. The QPM–SA films were prepared using a casting/solvent evaporation method. The characteristics of the films such as thickness, surface and matrix morphology, thermal behavior, molecular interaction between QPM and SA, mechanical properties, tackiness, and drug permeability, were investigated. Propranolol HCl (PPN) was used as a model drug in this study. QPM–SA films could potentially be used in tablet film coatings intended to modify drug release.

2. Materials and methods

2.1. Materials

QPM in aqueous-dispersion form (Eudragit® RL 30D) was purchased from Röhm Pharma GmbH (Darmstadt, Germany). SA (Manugel® DMB) was obtained from ISP Thailand Ltd. (Bangkok, Thailand). Diethyl sebacate and PPN were purchased from Aldrich Chemistry (Dorset, UK) and Changzhou Yabang Pharmaceutical Co., Ltd. (Jiangsu, China), respectively. All other reagents and solvents were of analytical grade and used as received.

2.2. Preparation of QPM–SA dispersions

SA dispersion (2%w/v) was prepared by dispersing SA powder (2 g) in deionized water. The volume of the dispersion was adjusted to 100 ml, and the obtained SA dispersion was stored at room temperature overnight for full hydration. The QPM dispersion (30%w/w polymer solid content) was weighed to obtain a QPM amount of 4 g. After that, 2%w/v SA dispersion in a volume of 0, 5, 12.5, 25.0, or 50.0 ml was measured and mixed with the QPM dispersion to achieve a SA content of 0, 2.5, 6.3, 12.5, or 25.0%w/w based on the QPM content, respectively. The SA dispersion was slowly poured into the QPM dispersion, and the mixture was stirred using a magnetic stirrer. The 100-ml final volume was adjusted using deionized water. The obtained QPM–SA dispersions were stirred at room temperature for 30 min and then incubated in a water bath at 37 °C with shaking at 75 oscillations min^{-1} for 24 h.

2.3. Characterization of QPM–SA dispersions

2.3.1. Particle size determination

The particle size of dispersed phase of the QPM and QPM–SA dispersions was determined using a laser-diffraction particle-size analyzer (Mastersizer2000 Model Hydro2000SM, Malvern Instruments Ltd., UK). The samples were mixed in 70 ml of deionized water in a sample dispersion unit and stirred at a rate of 50 Hz for 30 s before the determination. The volume-weighted mean diameter was recorded.

2.3.2. Zeta potential measurement

The zeta potential of the QPM, SA and QPM–SA dispersions was measured using a laser Doppler electrophoresis analyzer (Zetasizer Model ZEN 2600, Malvern Instruments Ltd., UK) at a temperature of 25 °C. The samples were diluted to obtain appropriate concentrations (count rates >20,000 counts s^{-1}) prior to the measurement.

2.3.3. Viscosity determination

The viscosity of the QPM and QPM–SA dispersions was measured using a small sample adapter of Brookfield digital rheometer (Model DV-III, Brookfield Engineering Labs Inc., Stoughton, MA) at 37 ± 1 °C. Average and standard deviation of three data of the single point viscosity at a shear rate of 27.2 s^{-1} were reported.