Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
International Journal of Pharmaceutics 313 (2006) 163–174
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Drug–polymer interactions and their effect on thermoresponsive poly(*N*-isopropylacrylamide) drug delivery systems

D.C. Coughlan, O.I. Corrigan *

School of Pharmacy, Trinity College Dublin, Dublin 2, Ireland

Received 27 September 2005; received in revised form 30 January 2006; accepted 2 February 2006
Available online 3 March 2006

Abstract

Potential interactions between model drugs (benzoates, diltiazem, cyanocobalamin, dextrans) and a thermoresponsive poly(*N*-isopropylacrylamide) (PNIPA) hydrogel and corresponding linear polymer were investigated. The influence of the drugs on the equilibrium swelling level of the hydrogel was examined and drug–hydrogel binding isotherms were established where appropriate. Differential scanning calorimetry (DSC) was used to investigate the influence of the drugs on the lower critical solution temperature (LCST) of the linear polymer solution. Phase solubility studies were preformed to investigate binding. Drug–polymer co-precipitated blends were also prepared and analysed by X-ray diffraction (XRD), thermal analysis and Fourier transform infrared (FT-IR) spectroscopy. Hydrophobic binding was apparent between PNIPA and the aromatic ring/ester side chain of the unionised benzoate. The effect of this binding on hydrogel swelling was clarified in terms of the influence of the binding on the LCST of the system. The drug release rates of the benzoates from the hydrogel were shown to be dependent on drug binding properties. Ionisation of the benzoate prevented such hydrophobic binding, with a weaker salting out effect apparent with sodium benzoate. Significant interactions between diltiazem, cyanocobalamin (Vitamin B12) or the dextrans and PNIPA were not apparent. High concentrations of the hydrophilic drugs did, however, interfere with the magnitude of hydrogel equilibrium swelling. Hydrophobic binding, the salting out effect and the influence of the drugs on hydrogel swelling under non-sink conditions were therefore shown to be important effects which depended on the chemical nature of the drug present.

Keywords: Drug–hydrogel interactions; Thermoresponsive poly(*N*-isopropylacrylamide); Binding Isotherm; Hydrophobic binding; Hydrogel swelling

1. Introduction

Hydrogels are swellable systems that are potentially useful in the design of drug-delivery devices (Lee and Kim, 1991; Shah et al., 1991; Gutowska et al., 1992; amEnde et al., 1995; Ichikawa and Fukumori, 1997; Peppas and Wright, 1998; Qui and Park, 2001; Coughlan et al., 2004). Smart hydrogels, such as thermoresponsive poly(*N*-isopropylacrylamide) (PNIPA)-based hydrogels, have particularly been used to modulate drug release (Gutowska et al., 1992; Ichikawa and Fukumori, 1997; Coughlan et al., 2004). Our previous drug release study from a PNIPA hydrogel (Coughlan et al., 2004) revealed the importance of drug colligative properties when attempting to control the release rate from these systems. Physicochemical properties of the drug such as drug size and solubility were of major importance in the successful ability to turn on and off drug release by modulating the external temperature. The same study (Coughlan et al., 2004) suggested that the chemical nature of the loaded drug influenced the swelling of, and release kinetics from, the PNIPA hydrogel. In particular, the chemical nature of the benzoate drug series [benzoic acid (BA), methyl *p*-hydroxybenzoate (MHB) and propyl *p*-hydroxybenzoate (PHB)] slowed the swelling rate of the hydrogel to a greater degree than that of diltiazem base (DB). The study mentioned does not, however, examine the type or nature of the interactions present between the drugs and the hydrogel. The ability to understand, quantify and predict the observed swelling effects and concomitant effect on release kinetics caused by the loaded drug is desirable. In the case of temperature responsive drug delivery systems, drug–polymer interactions would have implications for the rate of drug release below the lower critical solution temperature (LCST), the magnitude of drug pulse on switching temperature above the LCST and therefore the ability to successfully control drug release characteristics (Coughlan et al., 2004).

* Corresponding author. Tel.: +353 1 6082782; fax: +353 1 6082783.
E-mail address: ocorrign@tcd.ie (O.I. Corrigan).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.02.005

While drug-related factors such as solute size, solubility and loading have been shown to influence the release rate from swellable devices (Coughlan et al., 2004; Shah et al., 1991; Lee and Kim, 1991), the presence and effect of potential drug–polymer interactions on hydrogel swelling and drug release kinetics are not well researched. A limited number of studies on hydrogels (amEnde et al., 1995; Peppas and Wright, 1998; Alvarez-Lorenzo and Concheiro, 2002) have suggested the presence of ionic interactions between the loaded drug used and the polymer chains, therefore influencing the release rate from such systems. For example, amEnde et al. (1995) showed that that the cationic solute oxyprenolol strongly interacted with ionic hydrogels and showed increased hindrance in solute transport of the drug from an anionic solute at high pH. Other studies (Yu and Grainger, 1995; Wu et al., 2005) mention possible hydrophobic binding between the substituents used, although the implication for hydrogel swelling and drug release was not apparent.

The influence of salts (Horne et al., 1971; Eeckman et al., 2001; Saito et al., 2001) and surfactants (Schild and Tirrell, 1991; Kokufuta et al., 1993; Eeckman et al., 2001; Saito et al., 2001) on thermoresponsive polymers has been reported. Flocculation or a 'salting out' effect was shown on the addition of electrolytes, although some salts induced a 'salting in' process, e.g. tetra-alkyl ammonium salts. The 'salting out' process resulted in a decrease in the LCST of thermosensitive polymers while the 'salting in' process increased the transition temperature (Eeckman et al., 2001; Saito et al., 2001). The inorganic ions were not thought to be adsorbed into the polymer network but still affected the phase transition behaviour by disruption of hydrogen bonding (Saito et al., 2001). It was suggested that an increase in the hydrophobic character of PNIPA chains resulted, which consequently lowered the phase transition. Eeckman et al. (2001) showed that both the valence and size of the anion played an important role in the salting out process in respect of PNIPA polymers. The influence of surfactants on the LCST of linear PNIPA-polymers (Schild and Tirrell, 1991; Eeckman et al., 2001; Saito et al., 2001) and crosslinked PNIPA hydrogels (Kokufuta et al., 1993) were also reported. Surfactants caused a decrease or increase in the LCST of PNIPA depending on the hydrophobic chain length and the surfactant concentration (Schild and Tirrell, 1991). In contrast to the salting effect, it was suggested that these surfactants might bind to the polymer (Schild and Tirrell, 1991; Kokufuta et al., 1993; Eeckman et al., 2001; Saito et al., 2001), thereby altering the hydrophilic/hydrophobic balance of the polymer/hydrogel.

Binding between a drug and a hydrogel can potentially alter the drug release characteristics from the hydrogel in two ways. Binding to the hydrogel could directly slow the release rate of the drug due to interactions with the polymer chains, similar to the effect shown by amEnde et al. (1995). Secondly, the binding may affect swelling characteristics and therefore mesh size of the hydrogel, which in turn would have implications for concomitant release rate from that system (Coughlan et al., 2004). The present work therefore examines potential interactions between the model drugs used in our release study (benzoates, diltiazem, cyanocobalamin (Vitamin B12), dextrans) (Coughlan et al., 2004) and poly(*N*-isopropylacrylamide). The type of interactions present between the drugs and the polymeric system were examined. The underlying mechanism involved in any drug–polymer binding was investigated with the aim of understanding and being able to predict the drug release kinetics from these hydrogels.

2. Experimental

2.1. Materials

The various molecular weight dextrans [MW 4300 (D4), 10200 (D10), 43000 (D40), 68800 (D70)], benzoic acid (BA), sodium benzoate (NaB), methyl 4-hydroxybenzoate (MHB), propyl 4-hydroxybenzoate (PHB), cyanocobalamin/vitamin B12 (VB12) (all from Sigma–Aldrich), diltiazem HCl (DHCl) (Seloc PCAS) and diltiazem base (DB) (Elan) were used as received. All other chemicals were of reagent grade as previously described (Coughlan et al., 2004).

2.2. Polymer synthesis

A thermoresponsive PNIPA hydrogel (PNIPA-H) containing 1.15 mol% methylene bisacrylamide as crosslinker was synthesised in aqueous media as previously described (Coughlan et al., 2004). A linear polymer (PNIPA-L) was synthesised in an identical manner to the hydrogel but without the crosslinker. After the polymerisation process, the solution obtained was heated above 50 °C, the precipitated polymer collected by filtration, washed with water at 50 °C and then dissolved in cold water at room temperature. This process was repeated several times to purify the polymer. The collected polymer was then dried in a vacuum oven at 50 °C for 48 h.

2.3. Gel permeation chromatography

The molecular weight of PNIPA-L was determined by gel permeation chromatography, using a method similar to that described by David et al. (2003). Solutions of the polymer and polystyrene standards (2 mg/ml) were prepared in DMF and 100 μl was injected into a system consisting of a Waters Styragel® HR column, a Waters 510 pump and a Waters 410 Differential Refractometer (elution rate 1 ml/min). The internal temperature was set at 40 °C. Millennium® 2010 software was used to integrate the peaks. Samples were injected in triplicate and the elution time compared with a calibration curve to obtain an estimate of the polymer molecular weight.

2.4. Preparation of polymer/drug co-precipitate blends

A solvent casting method (Nair et al., 2001) was used to prepare blends of PNIPA-L and the model drugs. Solutions (10%, w/v) of the appropriate ratios of drug/polymer were prepared in water or ethanol. This solution was poured into a Petri dish and dried under vacuum at room temperature.