Release Kinetics of Benzoic Acid and Its Sodium Salt From a Series of Poly(N-Isopropylacrylamide) Matrices with Various Percentage Crosslinking

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ABSTRACT: Swelling and concomitant drug-release kinetics from a series of poly (N-isopropylacrylamide) (PNIPA) matrices were examined. Scanning electron microscopy indicated a decrease in polymer pore/mesh size above the lower critical solution temperature (LCST) with increasing percentage crosslinker. The release of sodium benzoate (NaB) or benzoic acid (BA) were investigated above and below the LCST of the gels and compared to the drug-loaded gel-swelling rates. The release rate of NaB increased with increasing percentage crosslinker above the LCST in contrast to a decrease in release rate with increasing crosslinker seen previously with nonthermoresponsive hydrogel systems. As the percentage crosslinker increased, there was therefore a decrease in the ability to thermally control the release of this small model drug. In contrast to the crosslinker-dependent pattern apparent with NaB, drug-PNIPA hydrophobic binding controlled the swelling rate of BA-loaded hydrogels. As a result, all the BA-loaded systems showed similar diffusion controlled swelling and release patterns, effectively independent of the inherent-swelling rates of the hydrogels. The crosslinking content of the hydrogel and the physicochemical nature of the loaded drug were therefore shown to be important in thermal control of drug release from PNIPA hydrogels.
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INTRODUCTION

Swellable systems such as hydrogel matrices are potentially useful as drug delivery devices.[1–5] Hydrogels may be synthesized by the covalent crosslinking of polymer chains but may also be formed by hydrogen bonding, van der Waals interactions, or physical entanglement of the polymer chains.[5] The level of covalently bound crosslinker incorporated into a hydrogel is one of the most important factors that influences hydrogel swelling.[2] Increasing the level of crosslinker is potentially a useful method of increasing the mechanical strength of the hydrogel[6] and altering the swelling rate and extent, as demonstrated with acrylamide-based gels.[7] The level of hydrogel swelling is dependent on the type of crosslinker and monomer used as well as the method of polymerization.[7]

The importance of crosslinking content in controlling the mesh/pore size and therefore the rate of drug release from nonthermoresponsive swellable systems has previously been demonstrated.[8–10] As the crosslinking ratio increased, the mesh size decreased at the molecular level, therefore decreasing the free volume available for solute transport. A reduction in the rate of drug

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release was shown due to a reduction in the solute diffusion coefficient.[10,11] Temperature responsive hydrogels that contain crosslinkers formed by covalent bonds can potentially act as on–off drug delivery systems that respond to an external temperature change.[1–5,12] Such delivery systems may be used as subdermal implants for noncontinuous drug delivery and have been advocated as a way of targeting solid tumors. Temperature responsive hydrogels generally contain nontemperature responsive crosslinkers such as N,N′-methylenebisacrylamide (MBA)[1] or ethylene glycol dimethacrylate.[12] The influence of crosslinker content in poly(N-isopropylacrylamide) (PNIPA) gels on drug-release kinetics has not been systematically examined to date.

The effect of drug physicochemical properties on the swelling kinetics of, and drug release from, a thermoresponsive PNIPA hydrogel, having 1.15 mol% MBA, was recently examined.[1] The chemical nature of the chosen drug was shown to significantly influence the swelling properties of these hydrogels. In the case of unionized benzoates (methyl p-hydroxybenzoate, propyl p-hydroxybenzoate) and benzoic acid (BA), the mechanism of such an effect on swelling was shown to be a hydrophobic-binding interaction between these benzoates and PNIPA.[13] The unionized form of the benzoates bound to PNIPA, thereby depressing the lower critical solution temperature (LCST) of the hydrogel and accounting for the solubility-dependent swelling and release patterns.[1,13] In contrast to the binding effect with the unionized benzoates, the sodium salt of BA (sodium benzoate, NaB) did not directly interact with PNIPA,[13] but caused an osmotically induced increase in hydrogel-swelling rate.[1]

In light of the benzoate–PNIPA binding described,[1,13] the current study, using a series of thermoresponsive hydrogels with increasing percentage crosslinker, examines the release kinetics of NaB and BA from the gels. In order to further our understanding of thermoresponsive control of drug release, this mechanistic study explores the release of this acid/salt pair from the series of PNIPA gels, where the rate and level of swelling varies within the series. Previous drug-release studies from PNIPA hydrogels[1,3,4,12,13] have neither investigated drug release from gels with varying swelling kinetics nor the interplay between the drug and the swelling matrix in such systems. This study therefore examines such a scenario, focusing on the release of the drug and concomitant-swelling rate of the matrix at two different temperatures. The chosen drugs, which differ in their solubility and PNIPA-binding capacity,[13] represent a salt (NaB, solubility in phosphate buffer pH 6.8 at 37°C: 399.6 mg/mL) and its acid (BA, 9.6 mg/mL).[1] In addition to examining the effect of matrix swelling and the chemical nature of the drug on release kinetics, the small molecular size of BA/NaB (molecular diameter ~4.2 Å)[1] makes them useful markers for evaluating the ability of the series of hydrogels to control drug release by change of external temperature. The drug-loaded matrices described have been developed with the aim of providing a better understanding of thermoresponsive drug delivery systems and the mechanisms of drug release from such systems.

METHODS

Materials

BA and NaB (Sigma–Aldrich, Ireland) were used as received. All other chemicals were of reagent grade.[1] A series of PNIPA matrices (PNIPA-H) were synthesized in aqueous media as previously described[1] using various percentages of MBA as the crosslinker [PNIPA-H1 (1.15 mol%), PNIPA-H2 (2.22 mol%), PNIPA-H3 (5.68 mol%), PNIPA-H4 (11.17 mol%)].

Glass Transition Temperature

The glass transition temperatures (T_g) of the polymers were determined using 5–10 mg dried samples ($n = 3$) run in an open pan using a Mettler Toledo 821^e Differential Scanning Calorimeter (DSC). The samples were initially heated to 180°C at 10°C/min, cooled to 25°C at 20°C/min followed by heating to 260°C at 10°C/min. The first heating cycle was to remove all residual moisture/solvent and erase the effect of previous thermal history. The glass transition temperature was taken as the midpoint of the inflection.

Equilibrium-Swelling Studies

Equilibrium swelling of the hydrogels at various temperatures was examined in phosphate buffer (PB) pH 6.8 (isotonic).[1] Following initial equilibration of the hydrogels at 22°C, the temperature of the media was increased daily to allow equilibrium swelling at that particular temperature.