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Interactions in aromatic probe molecule loaded poly (N-isopropylacrylamide) hydrogels and implications for drug delivery

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ABSTRACT

Small aromatic molecules are known to interact with poly(N-isopropylacrylamide) (PNIPA) based hydrogels, one of the most frequently employed polymers in temperature induced drug delivery systems. These interactions are poorly understood at the molecular level. In this article we investigate PNIPA both at the macroscopic and at the molecular level using measurements of swelling, differential scanning microcalorimetry (DSC), X-ray powder diffraction (XRD) and solid state ^{1}H NMR methods. The nature and the strength of the interactions affect the efficiency and kinetics of drug delivery. Phenols exert a major influence on PNIPA by reducing its phase transition temperature. The effect depends linearly on the phenol concentration, and is influenced also by the number of phenolic OH groups, as well as their relative positions. The strong interaction between phenol and the polymer that is detected by NMR hinders the crystallisation of phenol when the water is gradually evaporated. The aminoethyl phenol derivative dopamine has a much more limited effect, but in the opposite direction – the transition temperature increases slightly. The strong interaction observed among the dopamine molecules disables the polymer–dopamine interaction and favours crystallization of the dopamine when water is removed. These results reveal that embedding the drugs into polymer matrices for controlled delivery can alter the crystallinity of the stored molecules. As morphology is one of the crucial factors in delivery, this may compromise the rate and the efficiency of release.

1. Introduction

Responsive hydrogels are among the most frequently proposed vehicles for targeted and controlled drug delivery. These smart stimuli-sensitive hydrogels change their physical properties in response to external physical (temperature, mechanical effect, electromagnetic radiation, electric or magnetic field) or chemical stimuli (solvent conditions: composition, dissolved species, pH, ionic strength) [1]. Their ability to store and release drugs puts them at the focus of interest as possible drug eluting systems. Furthermore, hydrogels can protect drug molecules from unfavourable conditions, such as the presence of enzymes or low pH [1]. Since temperature is a highly important parameter in the mammalian body, temperature-sensitive hydrogels have become the most investigated smart polymers [2,3]. The majority of thermosensitive hydrogels investigated in the past decades are synthetic polymers based on poly(N-isopropylacrylamide) (PNIPA) [2–4].

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PNIPA hydrogels exhibit a non-linear volume phase transition (VPT) at a lower critical solution temperature (LCST) around 34 °C, which is close to the natural temperature of the human body [3,5]. On being triggered by stepwise temperature changes PNIPA can exhibit a pulsatile drug release profile [3,6,7].

In terms of kinetics and efficiency of controlled delivery, the nature and strength of the interaction between the drug molecule and the polymer chains are of vital importance. Chemical properties of the guest molecule and potential drug–polymer interactions are crucial in the swelling and release process, but these factors are poorly understood [8,9]. During the loading process free diffusion occurs into and out of the gel matrix, which is usually also related to the swelling of the gel [10,11]. The most common mechanism for discharge is diffusion. When a small molecule interacts with the polymer chains either reversibly or irreversibly, interactions in the gel matrix will determine the rate of release [10]. Interactions between the guest molecule and the gel network can inhibit release by binding of the drug to the polymer chains and/or by altering the swelling properties [8,9].

Molecules with phenolic OH can influence the swelling behaviour of the PNIPA in various ways [12–16]. While some molecules have only a slight effect or no effect at all, other guest molecules can change the transition temperature even at low additive concentrations [16,17]. At a certain concentration (critical concentration) an abrupt collapse of PNIPA may occur already at or below room temperature. The temperature shift depends on the concentration and chemical structure of the additive. Several molecules and ions reduce the LCST [12–16]. Anionic (e.g., sodium dodecyl sulphate) and cationic surfactants (e.g., dodecyl trimethyl ammonium chloride) increase the LCST [18].

In our previous publications the influence of phenol, resorcinol and phloroglucinol, studied by scattering, calorimetric and later by NMR techniques were reported in detail [12–14,19]. It was found earlier that they exhibit an interaction with the polymer chains that depends on the number of the OH-groups [19]. Binding of phenol to PNIPA is mediated by hydrogen bonds between the amide group of the NIPA chain and the hydroxyl group of the phenol molecule [20]. The associative behaviour between phenol and PNIPA was also demonstrated by small-angle neutron scattering (SANS) and solid state NMR techniques [12–14]. By contrast, ^{1}H solid-state NMR results showed that dopamine does not associate with the polymer chains [15].

Here we report novel results that not only encompass all OH-substituted benzene molecules, together with another derivative 4-(2-aminoethyl)benzene-1,2-diol (i.e., dopamine), but also yield an interpretation based on the interactions between PNIPA hydrogels and these biomedically relevant molecules. Phenols are used widely as model molecules for several small aromatic drugs, including tyrosine [20]. Dopamine acts as a hormone and neurotransmitter in the human brain and nervous system. Abnormal levels of this molecule may result in Parkinson's disease and mental disorders [21]. The consequences of our findings on drug delivery vehicles will also be considered.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPA) (99%) and *N,N,N′,N′*-tetramethylethylenediamine (TEMED) (99%) were purchased from Fluka, *N,N′*-methylenebisacrylamide (BA) (99%), ammonium persulphate (APS) (99%) and dopamine hydrochloride (98%) from Sigma–Aldrich, and phenol (99.5%), resorcinol (99%), phloroglucinol (99%), catechol (99%), pyrogallol (99%) and hydroquinone (99%) from Merck. All chemicals were used without further purification. Some of the relevant physico-chemical properties of these aromatic probes, such as solubility in water and pK_a, are listed in Table 1.

2.2. Synthesis of the polymer gel

PNIPA gel films with the molar ratio of [NIPA]/[BA] = 150 were synthesised by mixing 1 M aqueous solution of NIPA (18.75 mL) and 0.1 M solution of BA (1.225 mL) with water (4.9 mL) and TEMED (0.25 μL). After addition of APS (125 μL) to the mixture, polymerisation took place at 20 °C within 24 h. The 2 mm thick gel films were dialyzed in double distilled water and cut into disks of 7 mm (for swelling experiments) and 17 mm (for XRD and NMR techniques), then dried and stored above concentrated sulphuric acid. For calorimetric measurements dry gel disks were powdered (particle size 0.2–1 mm).

2.3. Swelling measurements

Swelling experiments were carried out by equilibrating dry disks in excess aqueous solutions with different initial concentrations (c_0) of the following compounds: phenol, resorcinol (1,2-dihydroxybenzene), phloroglucinol (1,3,5-trihydroxybenzene) and hydroquinone (1,4-dihydroxybenzene) (c_0 = 0–100 mM), catechol (1,2-dihydroxybenzene) (c_0 = 0–175 mM), pyrogallol (1,2,3-trihydroxybenzene) (c_0 = 0–175 mM) and dopamine hydrochloride (c_0 = 0–500 mM) for one week at 20.0 ± 0.2 °C. The dry gel/liquid ratio was 0.012. The equilibrium swelling ratio ($1/\varphi_e$) was determined from the mass balance as:

$$1/\varphi_e = \frac{m_{\mathrm{gel,dry}}/\rho_{\mathrm{gel,dry}} + (m_{\mathrm{gel,swollen}} - m_{\mathrm{gel,dry}})/\rho_{\mathrm{solution}}}{m_{\mathrm{gel,dry}}/\rho_{\mathrm{gel,dry}}} \quad (1)$$

where $m_{\mathrm{gel,dry}}$ and $m_{\mathrm{gel,swollen}}$ are the mass of the dry and the equilibrated gel disks, respectively. The density of the free liquid phase (ρ_{solution}) was taken as 1 g/mL, and that of the dry PNIPA gel ($m_{\mathrm{dry\ gel}}$) is 1.115 g/cm^3 [13]. The reproducibility of the swelling degree of different batches was 1.5–3.5%. The swelling degrees reported here are relative to that measured in pure water.

The aromatic guest uptake n_a (mmol/$g_{\mathrm{dry\ gel}}$), was determined from the initial (c_0) and equilibrium molar concentrations (c_e):

$$n_a = \frac{c_0 V_0 - c_e V_e}{m_0} \quad (2)$$