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Swelling and diffusion of PNIPA-based gels for localized chemotherapy and hyperthermia

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ABSTRACT

This paper presents the results of an experimental study of the swelling and diffusion of poly(N-iso-propyl-acrylamide) PNIPA-based gels with the potential for applications in bio-micro-electro-mechanical systems (BioMEMS) for localized cancer treatment that involves both chemotherapy and hyperthermia. The swelling due to the uptake of water, rhodamine dye and the cancer drug, paclitaxel, are studied using weight gain experiments that are conducted over a range of temperatures in which hyperthermia can occur during drug delivery. The release of rhodamine dye and paclitaxel is also elucidated by considering their diffusion through the gels. The underlying mechanisms of diffusion and swelling are discussed over a temperature range in which synergistic cancer treatment can be effected by the combined use of hyperthermia and chemotherapy.

1. Introduction

Hydrogels are polymeric gels that consist of an intertwined network of fibers that are held together largely by hydrogen bonds, Van der Waal's forces and cross-linking [1]. In selected cases, they can undergo volume changes in response to multiple environmental stimuli such as pH, temperature and ionic strength [2,3]. Although only a few hydrogels are biocompatible [4], hydrogels can be used to soak up and store cancer drugs [5]. The drugs can then be released in a regulated manner by the controlled application of stimuli, such as temperature, in drug delivery systems and other biomedical applications [6–8].

The use of hydrophilic and hydrophobic co-polymers to control the volume change (de-swelling) temperature of hydrogels has since been reported [9,10]. Hence, one can control the rate and time at which drugs are released using different polymer configurations. In this work, we prepared a series of thermo-responsive co-polymers by free radical mechanism. Acrylamide and Butylmethacrylate are added as copolymers to vary the transition temperatures of PNIPA.

In drug delivery, experimental and theoretical approaches to solute and solvent diffusion through polymeric systems have preceded the use and application of swellable polymers [11–13]. Thus, it is not surprising that recent works have involved studies of diffusion measurements through hydrogels, as this is instrumental in understanding the underlying mechanisms of the transport phenomena of solute or drugs through polymeric gels.

Hyperthermia and Chemotherapy are among the many treatment modalities available for cancer [14]. Prior research [15] has also suggested that synergistic effects can be achieved in cancer therapy by combining the use of chemotherapy and hyperthermia. However, there have not been prior studies on the swelling and diffusion phenomena that can occur in the temperature regime in which synergy can be engineered between these two cancer treatment modalities.

In this paper, we present the results of an experimental study of the swelling and diffusion of paclitaxel and rhodamine dye over temperature range (37, 41, 43, and 45 °C) in which synergy is achievable. A recently developed drug delivery device designed in our lab is used to accomplish controlled drug/rhodamine release and heating. The underlying transport mechanisms are elucidated for drug elution from poly (*n*-isopropylacrylamide) PNIPA-based copolymers with hydrophilic and hydrophobic co-monomers. The implications of the results are then discussed for the localized treatment of cancer.

2. Experimental procedures

2.1. Materials processing

The chemicals, N,N,N′,N′-tetra-methyl-ethylene-diamine (TEMED), ammonium persulfate (APS), N,N′-methylene-bis-acrylamide (MBAAm), Acrylamide (AAm) and Butyl Methacrylate (BMA) were all obtained from Sigma-Aldrich Corporate, St. Louis, MO, and were used as received.

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The PNIPA hydrogel was prepared by free radical polymerization [16,17] and co-polymerization. This was achieved using co-monomer species, such as acrylamide (AAm) (hydrophilic) and Butyl Methacrylate (BMA) (hydrophobic).

Polymerization of the PNIPA hydrogel was carried out in distilled water solution (5 wt.% NIPA) at room temperature (25 °C) for 6 h. This was conducted using the TEMED and APS initiators, and MBAAm cross-linkers in a long cylindrical mold with an outer diameter (OD) of 9.50 mm and a length of 30 cm. The concentrations of TEMED, APS and MBAAm were 5.82 mol%, 1.91 mol% and 1.15 mol%, respectively, based on the NIPA monomer. The transition temperatures, and hence the swelling/de-swelling temperatures, were controlled by adding the co-monomers at different concentrations, as shown in Table 1. When the polymerization was complete, the hydrogels were cut into discs and cylinders. The gels were washed on a daily basis to remove any chemical residue. Subsequently, they were dried in a model 280A Isotemp vacuum oven (Thermo Fisher Scientific Inc., Waltham, Massachusetts) at −68 kPa for 48 h (at 60 °C).

2.2. Transition temperature measurements

The transition temperatures of the hydrogels were measured using Differential Scanning Calorimetry (DSC). This was done using a PerkinElmer Pyres 1 DSC machine (PerkinElmer Inc., Waltham, Massachusetts). About 50 mg of each gel sample was placed in small, hermetically-sealed stainless steel containers that were sealed with rubber O-rings that prevented the evaporation of the water within the gel upon heating. Care was taken during the preparation and handling of the samples to prevent any contact between the containers and exposed skin, which could result in residue on the samples that might affect the heat flux measurements.

2.3. Swelling ratio and water transport measurements

In order to determine the swelling ratios of the different hydrogels (Table 1), the dried gel samples were weighed with a model PI-114N pinnacle series balance (Denver instrument, Arvada, Colorado) at specific temperatures. Weighing was continued until the samples reach equilibrium swelling, i.e. until the weights were constant to within ±1%. Subsequently, each sample was removed from the solution, blotted dry between two pieces of filter paper to remove excess surface moisture, and weighed to determine the masses of the gels [18]. The equilibrium swelling ratio, Q, was calculated as the ratio of the mass of water absorbed to the original dried mass of the gel [19]. It is calculated using the formula:

$$Q = \frac{W_\infty - W_o}{W_o} \tag{1}$$

where W_o and W_∞ are the weights of the dried and swollen hydrogel, respectively.

The swelling kinetics of the gels was also obtained dynamically by measuring the swelling ratios as a function of time at 37 °C. Dried gels were first accurately weighed and placed at 21 °C until equilibrium swelling conditions were reached. The gels were introduced into water at 37 °C. This was done to obtain the gel swelling characteristics under conditions that are relevant to the introduction of the gels into the body from room temperature. At specified times, the gel masses were obtained until their weights remain unchanged to within ±1%. The swelling ratio, Q, was then calculated using:

$$Q = \frac{W_t - W_o}{W_o} \tag{2}$$

where W_t is now the weight of the gel at time, t. The water transport through the gels was obtained by gravimetrically measuring the weight of water absorbed as a function of time. All the experiments were done in triplicates.

Table 1
Gel configuration and their compositions.

Compound	PNIPA		AAm[a]		BMA[b]	
Gel code	Mass (g)	Mol%[c]	Mass (g)	Mol%[c]	Volume (mL)	Mol%[c]
A1	0.7776	100	–	–	–	–
B1	0.7387	95	0.0244	5	–	–
B2	0.6998	90	0.0488	10	–	–
C1	0.7387	95	–	–	0.055	5
C2	0.6998	90	–	–	0.109	10

[a] AAm is a hydrophilic compound.
[b] BMA is a hydrophobic compound.
[c] The mol% was based on the amount of NIPA monomer in the pure PNIPA gel.

2.4. Diffusion measurements

In order to examine the gel release and swelling kinetics, the dried gels were soaked to saturation with rhodamine dye at a specific temperature (37, 41, 43, or 45 °C) for 5 days. This provided sufficient time (as obtained from swelling experiments) for the gels to absorb the dye and swell to equilibrium volumes. The loaded gels were then introduced into test tubes containing 3 ml of distilled water at the same temperature as the soaking temperature. The concentration of dye in each test tube was measured periodically using a UNICO 1200 spectrophotometer (UNICO, Dayton, NJ), operated at a wavelength of 550 nm. The test tube was shaken before each measurement to ensure uniform mixing and about 1 ml of the solution that was taken for each measurement. The 1 ml of solution was returned to the mixed solution after each measurement.

Using the absorbance measurements, concentrations and hence the amount of dye or drug released were obtained. The release was characterized by $\frac{W_t}{W_\infty}$, where W_t is the weight of fluid released at time, t, and W_∞ is the weight of fluid released at infinite time. Using the same procedures described above for rhodamine, the experiments were also performed using paclitaxel to obtain the release characteristics at 37 °C.

3. Results and discussion

3.1. Transition

The results of the transition temperatures measured are shown in Table 2. They clearly show that increasing the quantity of hydrophilic co-monomers increases the transition temperature. Similarly, increasing the hydrophobic co-monomers reduces the transition temperatures of the PNIPA gels.

3.2. Swelling kinetics of gels

In an effort to understand the possible gel response to fluids in the biomedical implant environment, the gel swelling and shrinkage behavior were characterized. Gel collapse and the associated changes in gel volume were also modeled analytically and empirically. The results obtained from the gel swelling experiments are presented in Fig. 1. Rapid de-swelling was observed during the first few hours of exposure to the higher temperature of 37 °C. Such de-swelling is predicted by the Fourier series solution to the equations of gel motion [20–21].

Table 2
Transition temperatures of the hydrogels.

Gel code	Gel composition	Transition temperature[a] (°C)
A1	PNIPA (100%)	34.35
B1	PNIPA-co-AAm (95%–5%)	38.20
B2	PNIPA-co-AAm (90%–10%)	42.55
C1	PNIPA-co-BMA (95%–5%)	33.30
C2	PNIPA-co-BMA (90%–10%)	33.45

[a] Based on DSC measurements.