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Thermally Driven Hydrogel Actuator for Controllable Flow Rate Pump in Long-Term Drug Delivery

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4.1 Introduction

'Smart' hydrogels can change their volume by a large fraction in response to many stimuli, such as temperature, pH, ions concentration, solvent composition and light irradiation. This environmental sensitivity plays an important role in achieving new technological and scientific applications.

Hydrogels used as osmotic pumps were introduced in the 1970s. They allowed the development of new drug delivery systems, such as those used for the therapies of the gastrointestinal tract. Easy to regulate long-term devices with a very simple mechanical design could be commercially convenient with respect to those using complex electro-mechanical systems.

In this chapter the use of a thermally activated hydrogel actuator for the realization of long-term drug delivery systems able to control the drug flow rate following defined tasks is investigated. In the first part, the material properties of the thermally sensitive hydrogel, whose network is constituted by cross-linked poly(vinyl-methyl-ether) (PVME) molecules, are outlined; the dynamic properties of a designed drug delivery system using such a hydrogel as the driving actuator are then derived.

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4.2 Materials and Methods

The hydrogel has been synthesized by means of free radical polymerization of PVME [1] by γ–radiation. A PVME–sodium alginate emulsion was obtained by mixing a 30% (by weight) PVME aqueous solution with a 1% sodium alginate water solution. Then, the emulsion was cross-linked by means of Ca^{2+} ions in a 1 M calcium chloride ($CaCl_2$) bath solution and submitted to γ–radiation of 0.91 M rad/h for 24 hours. The final PVME hydrogel samples were cut in the form of parallelepiped of various dimensions and left to equilibrate in a bath of de-ionized water at room temperature.

The sample's equilibrium dimensions were measured by means of a stereo microscope as a function of temperature in a bath of de-ionized water, while the length–time behaviour of hydrogel samples submitted to free swelling experiments was detected by means of a Hall effect isotonic transducer connected to a computer acquisition data system.

4.3 Hydrogel Actuator

The kinetic equation of motion of a hydrogel matrix is available in the frame of biphasic models [2, 3] and for simple cases it is possible to obtain the explicit time dependence of the spatially distributed strain of the gel [4–7, 9]. To obtain the relevant properties of the PVME actuator, it is necessary to know the material constants that define the kinetics of the hydrogel readjustment.

In addition to the material constants, the hydrogel readjustment depends also on geometrical factors such as its shape and porous structure [8]. Our PVME actuator has a macroporous structure where the fluid is enclosed in pores, whose walls comprise a homogeneous gel given by the PVME polymer network and whose intermolecular spaces are filled by the water (interstitial fluid). The macroporous structure of our PVME gel makes the dynamics of the global actuator dependent by the physical length characterizing the pores and by their shape. In the PVME material made of connected cells of pseudo-spherical shape, the physical length is the mean thickness 'a' of the thin walls of the pores.

From the equations of motion that describe the accommodation of thin gel layers [6, 9], the characteristic time (τ) of the mechanical readjustment is proportional to the square of the wall thickness ('a') and inversely proportional to the gel diffusion coefficient (D), following the relation:

$$D = \mu/f \tag{4.1}$$

where μ is the shear elastic modulus of the gel and f is its friction coefficient, which in a neutral gel is given by the inverse of its hydraulic permeability [2, 7].

One of the simplest ways to determine the gel diffusion coefficient (D) is by means of free swelling experiment [5–7]. Since our actuator is driven by means of temperature changes, the free swelling kinetic is coupled to the heat transmission one, that is, it is mainly due to thermal diffusion and interstitial fluid convection.

By observing that the time readjustment due to positive and negative temperature jumps does not change appreciably, it is possible to conclude that the mechanical response time of the PVME gel readjustment is much bigger than the one characterizing the thermal kinetics. The reason is that the thermal flow due to the interstitial fluid convection is of opposite sign in the gel shrinking with respect to the one in the swelling process. If the thermal kinetics were the limiting factor, a clear hysteresis would appear between the hydrogel contraction and expansion process.

By posing that the mechanical readjustment of the hydrogel is much slower than the thermal transmission kinetics, it possible to assume a quasi-instantaneous change of temperature of the whole actuator before starting the mechanical relaxation of the gel.

4.3.1 Thermo-Mechanical Gel Dynamics

To describe the spatially distributed strain of the PVME gel system, the THB equation of motion [5] can be used. Even if is an oversimplified version of the Biot's poroelastic model [7], it adequately describes the diffusion kinetics of gel matrices [3, 5–7] and reads:

$$f\,\partial U_i/\partial t = \partial \sigma_{ij}/\partial x_j \tag{4.2}$$

where U_i is the displacement vector of a gel element and $f = (K_{11} - K_{12}\,K_{21}\,/\,K_{22})^{-1}$ is the gel friction coefficient (where K_{ij} are the electro-osmotic Onsager coefficients [7]); σ_{ij} is the gel stress tensor that in the linear approximation reads:

$$\sigma_{ij} = k\,\varepsilon_{\alpha\alpha}\,\delta_{ij} + 2\mu(\varepsilon_{ij} - \varepsilon_{\alpha\alpha}\,\delta_{ij}/3) + \alpha\delta_{ij} \tag{4.3}$$

where k and μ are, respectively, the bulk and the shear elastic moduli of the gel, α is the chemically or thermally induced stress at zero strain for isotropic materials and δ_{ij} is the Kroneker delta; $\varepsilon_{\alpha\alpha}$ is the gel dilatation, given by the trace of the strain matrix ε_{ij}:

$$\varepsilon_{ij} = (\partial U_i/\partial x_j + \partial U_j/\partial x_i)/2$$

In the case of an uncharged polymer network (i.e. $K_{12} = K_{21} = 0$), the friction coefficient results: $f = (K_{11})^{-1}$ [7], where K_{11} is the gel hydraulic permeability.

Generally speaking, the material parameters in Equation (4.1) and Equation (4.2) are functions of the physical variables of the material (e.g. temperature, strain itself, etc.) as well as of the chemical ones (e.g. pH, ionic strength and type of solvent). Because the dependence of the material parameters on the mechanical deformation is weak, μ, k and f can be assumed constants in the thermal gel readjustment, where the temperature is held constant for $t > 0$. Moreover, since the temperature change can be approximately assumed uniform over the sample, the thermal stress (α) is only a function of time.

Given $\alpha_{(T,\,t \le 0)} = \alpha_0$, the application of a sudden change of temperature (Δt) at time $t = 0$ that is held constant as a function of time, leads to the following thermal stress function:

$$\alpha_{(t)} = \alpha_0 + \theta_{(t)}\,(\alpha_{(T+\Delta T)} - \alpha_0)$$

By choosing the null reference thermal stress state at $t > 0$ so that:

$$\alpha_{(t>0)} = \alpha_{(T+\Delta T)} = 0$$

the following isobtained:

$$\alpha_{(T,\,t)} = (1 - \theta_{(t)})\alpha_{0\,(T)}$$

where $\theta_{(t)}$ is the unit step function.

Hence, the application of a temperature step change is equivalent to freeing the gel sample, at time equal zero by the stress $-\alpha_{0\,(T)}$, and letting it move toward the equilibrium volume, such as in a free swelling experiment.

In the case of thermal stimulation, it is possible to perform free deswelling experiments depending on the sign of temperature change.

By introducing Equation (4.2) in Equation (4.1), and by taking the divergence of both members and inserting the incompressibility of solid and liquid constituents, the equation of motion finally reads [7]:

$$f\,\partial\,\varepsilon_{\alpha\alpha}/\partial t = (k + 4\mu/3)\partial^2\varepsilon_{\alpha\alpha}/\partial x_i\,\partial\,x_i \tag{4.4}$$

When the gel sample has the shape of a thin quasi-planar layer, assuming the z-axis is perpendicular to the gel layer plane, Equation (4.2) can be simplified as follows [6, 9]:

$$\partial\varepsilon_{xx}/\partial t = D\,\partial^2\varepsilon_{xx}/\partial z^2 \tag{4.5a}$$

$$\partial\varepsilon_{yy}/\partial t = D\,\partial^2\varepsilon_{yy}/\partial z^2 \tag{4.5b}$$

$$\partial\varepsilon_{\alpha\alpha}/\partial t = D_b\,\partial^2\varepsilon_{\alpha\alpha}/\partial z^2 \tag{4.5c}$$

where $D = \mu/f$ and $D_b = (k + 4\mu/3)/f$.

The spatio-temporal solutions for the strains ε_{xx} and ε_{zz} are [9]:

$$\varepsilon_{xx} = \frac{4\varepsilon_0}{\pi}\sum_{n=1}^{\infty}\left(\frac{(-1)^n}{2n+1}\right)\exp\left[\frac{(2n+1)^2 t}{\tau}\right]\cos\left(\frac{(2n+1)z\pi}{a}\right) \tag{4.6a}$$

$$\varepsilon_{zz} = \varepsilon_{\alpha\alpha} - 2\varepsilon_{xx} = \frac{4\varepsilon_0}{\pi}\sum_{n=1}^{\infty}\left(\frac{(-1)^n}{2n+1}\right)\cos\left(\frac{(2n+1)z\pi}{a}\right) \left\{3\exp\left[\frac{(2n+1)^2 t}{\tau_b}\right] - 2\exp\left[\frac{(2n+1)^2 t}{\tau}\right]\right\} \tag{4.6b}$$

where $\tau = a^2/\pi^2 D$ and $\tau_b = a^2/\pi^2 D_b$ are the characteristic time constants for the 'shear' and 'bulk' diffusional gel readjustment, ε_0 is the initial uniform strain of the sample with respect the final one (at $t = \infty$) assumed as reference ($\varepsilon_\infty = 0$) and 'a' is the gel layer thickness at $t = \infty$. Moreover, since $D_b > D$, it follows that $\tau_b < \tau$

From Equations (4.6a) and (4.6b), the length $L_{(t)}$ and the thickness $a_{(t)}$ of the gel are obtained as a function of time, respectively, to read [9]:

$$L_{(t)} = L_\infty \left\{1 + \varepsilon_{xx\,(Z=0)}\right\} = L_\infty \left\{1 + \frac{4\varepsilon_0}{\pi} \sum_{n=1}^{\infty} \left(\frac{(-1)^n}{2n+1}\right) \exp\left[\frac{(2n+1)^2 t}{\tau}\right]\right\} \tag{4.7a}$$

$$a_{(t)} = a\left\{1 + 2\int_0^{a/2} \varepsilon_{zz}\right\} = a\left\{1 + \frac{8\varepsilon_0}{\pi^2} \sum_{n=1}^{\infty} \left(\frac{(-1)^n}{2n+1}\right) \left\{3\exp\left[\frac{(2n+1)^2 t}{\tau_b}\right] - 2\exp\left[\frac{(2n+1)^2 t}{\tau}\right]\right\}\right\} \tag{4.7b}$$

Given the above kinetics for the pore walls and assuming the global macroscopic gel dimension quasi-isomorphic to the pore diameter, and hence to the pore wall circumference, the gel actuator length will approximately follow the time law given by Equation (4.7a).

For $t > 9\tau$ in Equation (4.7a) the slower exponential relaxation prevails, so that the PVME actuator length reads:

$$L_{(t)} \cong L_\infty \left\{1 - \frac{4\varepsilon_0}{\pi} \exp\left[\frac{t}{\tau}\right]\right\} = L_\infty \left\{1 - \frac{4\varepsilon_0}{\pi} \exp\left[\frac{\pi^2 D}{a^2} t\right]\right\} \tag{4.8}$$

By fitting the exponential length relaxation of the PVME samples it possible to obtain the characteristic time (τ) and the gel diffusion coefficient (D).

4.3.2 Experimental Results

The dependence of the PVME response time constant, $\tau = a^2/\pi^2 D$, as a function of the temperature is reported in Figure 4.1. By introducing the temperature dependence of the

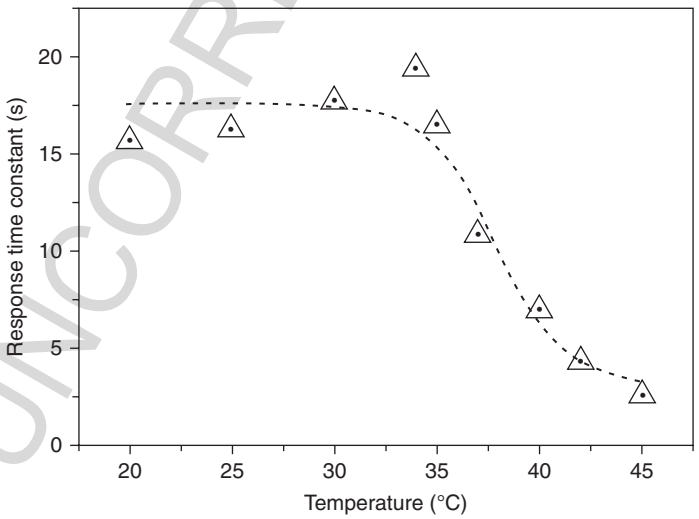

Figure 4.1 *Readjustment time constant of the PVME gel as a function of temperature.*

pore wall thickness, $a = \alpha f(T)$, where $f(T) = L_{(T)}/L_{(T=20°C)}$ as reported in Figure 4.2, the normalized diffusion coefficient, D/α^2, shown in Figure 4.3 is obtained. The data refer to thermal free swelling experiments at different temperatures by applying a thermal sudden jump of 2 °C.

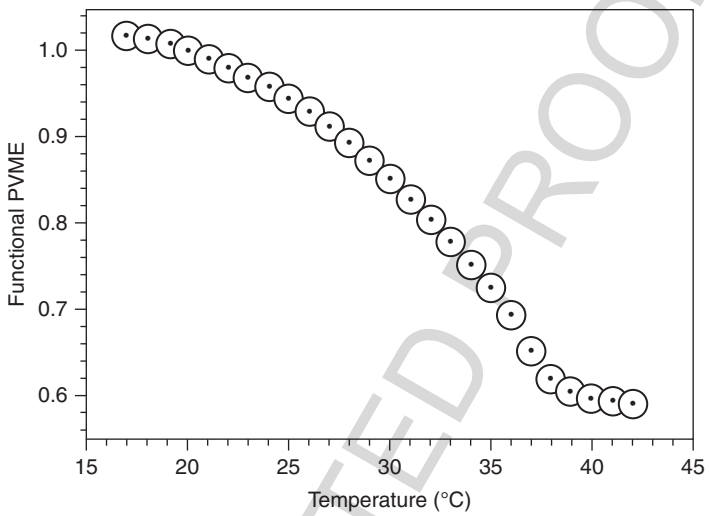

Figure 4.2 *The equilibrium length $L_{(T)}$ of the PVME gel normalized by one at T = 20 °C as a function of temperature.*

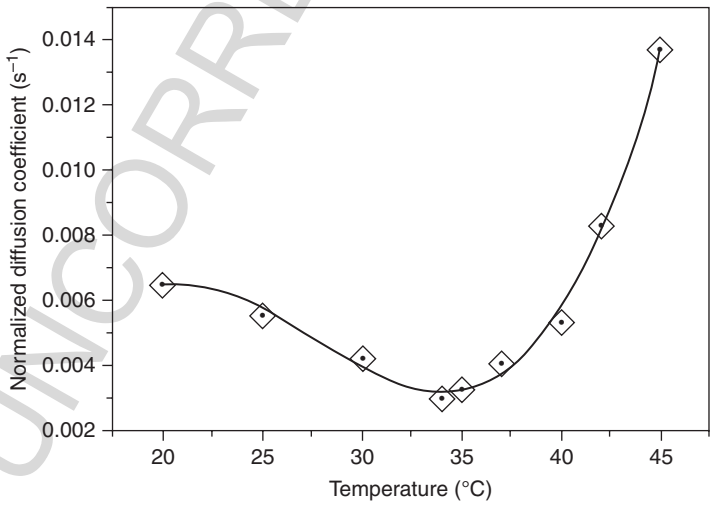

Figure 4.3 *The shear diffusion coefficient D/α^2 of the PVME gel matrix as a function of temperature.*

By using the relationship that links the Young's elastic modulus (E) to the bulk (k) and to the shear (μ) elastic moduli that reads:

$$\mu = E(3/(9 - E/k))$$

since, in gels, it is usual for $k > E$ [1, 6, 8], it follows that:

$$^{3}/_{8}\ E < \mu < {}^{1}/_{3}\ E$$

Therefore, by measuring the Young's elastic modulus (E) of the PVME by means of independent force–elongation experiments, reported in Figure 4.4, it is possible to evaluate the shear elastic modulus of the material, reported in Figure 4.5, with a precision of about 5 %. Once the shear elastic modulus has been determined, the friction coefficient (f) can be obtained from the relation: $D = \mu/f$ reported in Figure 4.6. It is interesting to note that the shear elastic modulus (μ) and the friction coefficient (f) show the typical dispersion sigmoid and bell shape, respectively.

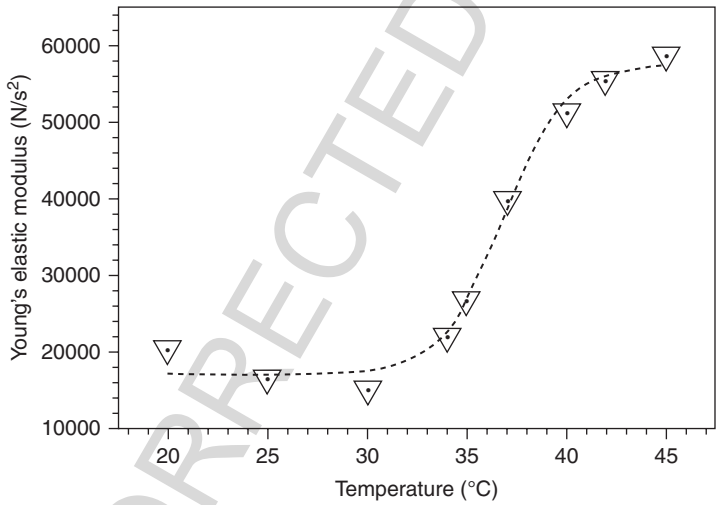

Figure 4.4 *The Young's elastic modulus (E) of the PVME gel as a function of temperature.*

The force generated by a PVME gel strip of a known sectional area, is a consequence of the thermal stress ($\alpha_{(T)}$) of Equation (4.3). Actually, the effect of the thermal stress ($\alpha_{(T)}$) is to change the free gel rest length and, therefore, it is possible to obtain the isometric force generation of a PVME actuator, with zero stress on the lateral surfaces, by means of the equilibrium PVME length measured as a function of the temperature shown in Figure 4.2 with the Young's gel modulus reported in Figure 4.4.

By posing that the PVME actuator exerts zero force at 36 °C, the stress generated by its temperature change is reported in Figure 4.7.

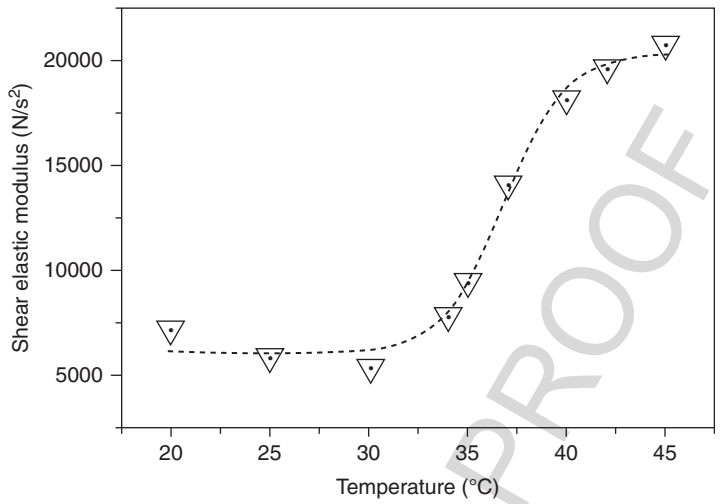

Figure 4.5 *The shear elastic modulus (μ) of the PVME gel as a function of temperature.*

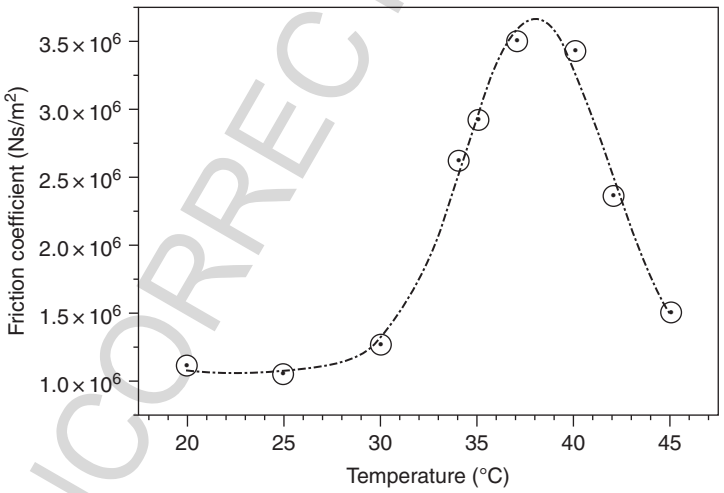

Figure 4.6 *The fluid–matrix friction coefficient (f) of the PVME gel as a function of temperature.*

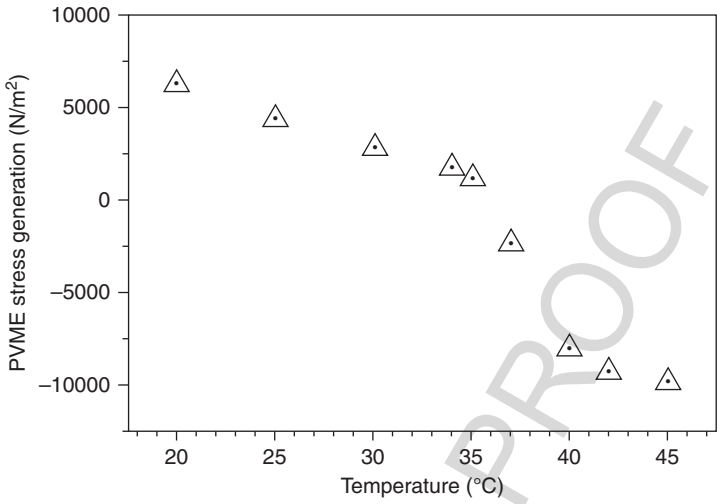

Figure 4.7 *The generated stress of the PVME gel actuator as a function of temperature when its zero force point is chosen at T = 36°C.*

4.4 Pump Functioning

The schematic drawing of a controllable pump for long-term drug delivery is shown in Figure 4.8. An internal spring is regulated for the maximal drug release that is achieved at the lowest device temperature (body temperature of 36 °C). Then, to lower the drug flow as requested, the temperature of the actuator must be appropriately raised by means of the thermal heating of the resistors.

Since cooling of the PVME cell happens spontaneously and the lost heat power is fixed, while the heating power can be regulated by the electrical energy dissipated into the resistors, the heating–cooling cycle is not symmetric. Therefore, if the PVME contraction can be practically as fast as desired, its relaxation time is fixed and slow. This fact limits the application of the PVME gel motor (as all thermally driven mechanisms such as shape memory alloys) to phenomena that do not have very fast kinetics.

The use of Peltier's cells that actively cool the gel mover can lead to a faster relaxation response of the actuator and increase of drug delivery.

An internal programming unit able to take into account of the thermal and mechanical inertia of the whole pumping system will definitely improve the timely regulated drug outflow.

4.5 Conclusion

In this present chapter it has been shown how a thermally controlled hydrogel actuator can be used to let a drug infusion pump execute a time-defined tasks.

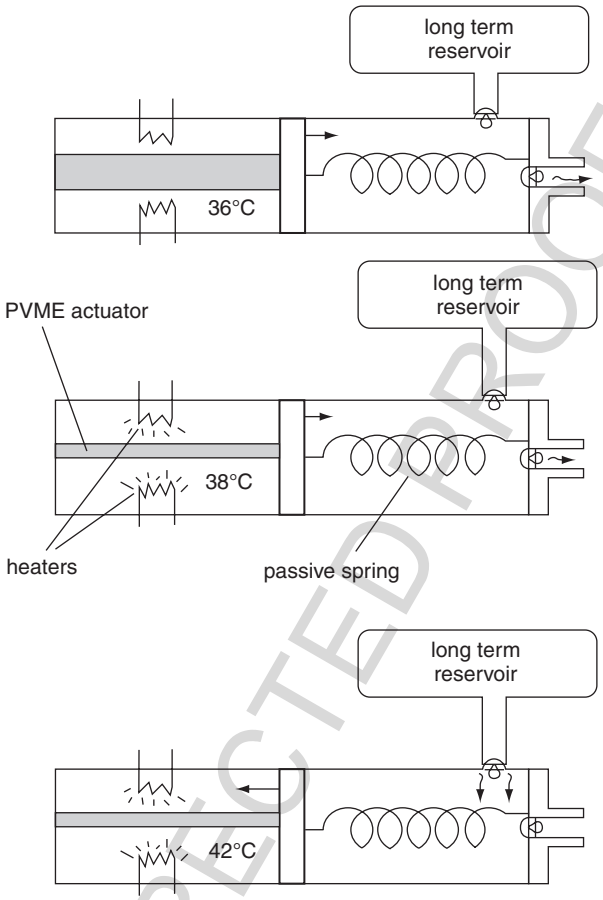

Figure 4.8 *Schematic drawing of a controllable pump for long-term drug delivery.*

By using a biphasic model, the characteristics of the hydrogel mover (as force density and time response) are explicitly defined together with their functional dependence by the geometrical and material parameters.

The macroporous structure of the 'hydrogel motor' allows a quick contractile response to temperature changes regardless of its dimension.

The use of thermoelectric cooling units can shorten the thermal cooling and the elongation time of the actuator.

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Chapter 4

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