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Diffusional transport modulation through reversible bilayer membranes

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A new approach to attaining time invariant diffusional flux through bilayered membranes with reversible barriers has been demonstrated. The barrier has been formed by exploiting the phenomenon of volume transition in polymers. The novelty of the approach is that such bilayers can be formed *in situ*. A theoretical analysis shows how the desired diffusional behaviour can be achieved. The validity of the concept, as well as the quantitative predictability of the theoretical analysis, is demonstrated by experimentation on model systems. A potential application is highlighted.

1. Introduction

Diffusion of a low molecular weight solute through a rubbery polymer is generally fickian. As a result, the diffusional flux decreases with time. Yet there are situations, especially in the area of drug delivery systems, where it is desirable to ensure that the diffusional flux does not change with time. An understanding of the physics and mathematics of diffusion in polymers has been exploited in the past to design systems, where the flux could indeed remain constant. Such attempts have involved manipulation of the device geometry (Rhine *et al.* 1980), use of non-uniform solute profiles (Lee 1984), diffusion-swelling coupling (Shah *et al.* 1990; Vyavahare *et al.* 1992), etc.

This paper illustrates a new approach to attaining time invariant diffusional flux through bilayered membranes with collapsible barriers. These can be designed on the basis of an understanding of the kinetics of swelling and deswelling of pH sensitive hydrogels. The novelty of the approach is that such bilayers can be formed *in situ* and the diffusional behaviour can be manipulated at will depending on the external stimuli. The versatility of such systems is experimentally demonstrated through model systems. A potential application is illustrated.

2. Diffusion through a bilayered membrane

We consider the problem of diffusion of a solute through a bilayered membrane depicted schematically in figure 1. Here a polymer core of half length L is surrounded by a barrier of thickness δ_B. The concentration of the solute in the core is $C_2(x,t)$,

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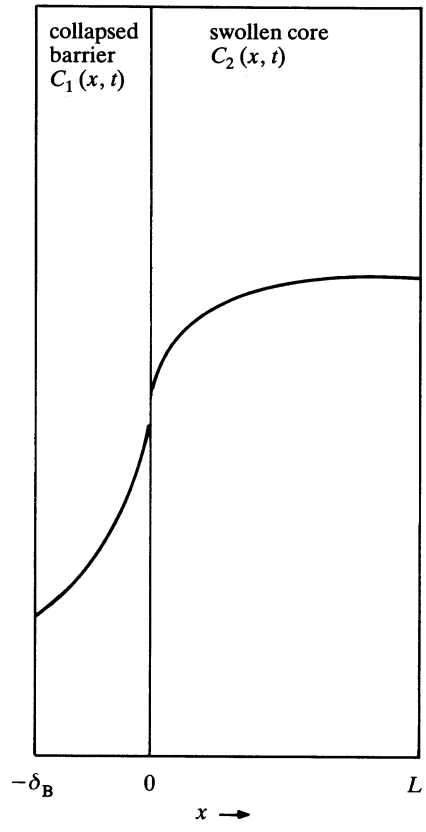


Figure 1. Diffusional transfer across a bilayer membrane.

whereas that in the barrier layer is $C_1(x,t)$. The diffusivity of the solute in the polymer core (D_2) is different than that in the barrier layer (D_1). The appropriate balance equations then follow as

$$\partial C_1/\partial t = D_1 \partial^2 C_1/\partial x^2, \tag{1}$$

$$\partial C_2/\partial t = D_2 \partial^2 C_2/\partial x^2, \tag{2}$$

with the initial conditions

$$C_1 = C_{10}, \quad t = 0, \quad -\delta_B < x < 0, \tag{3}$$

$$C_2 = C_{20}, \quad t = 0, \quad x > 0, \tag{4}$$

and the boundary conditions

$$\partial C_2/\partial x = 0, \quad x = L, \quad t \geqslant 0, \tag{5}$$

$$D_1 \partial C_1/\partial x = D_2 \partial C_2/\partial x, \quad x = 0, \quad t > 0, \tag{6}$$

$$C_1 = KC_2, \quad x = 0, \quad t > 0, \tag{7}$$

$$C_1 = 0, \quad x = -\delta_B, \quad t \geqslant 0. \tag{8}$$

Here K is the partition coefficient for the solute between the barrier layer and the polymer core. Equation (8) implies absence of any external mass transfer resistance

and a large bulk volume. We now assume that the barrier layer thickness is much smaller than that of the polymer core. In this case we can approximate the geometry in figure 1 as a semi-infinite slab and replace the boundary condition (5) by

$$\partial C_2/\partial x = 0, \quad x \to \infty, \quad t \geqslant 0. \tag{9}$$

Further, the flux of the solute released is given by,

$$M_t = \int_0^t \left(-D_1 \frac{\partial C_1}{\partial x}\right)_{x=-\delta_B} \mathrm{d}t. \tag{10}$$

We solved equations (1)–(10) analytically to obtain the ratio of the solute released at a given time (M_t) to that of the total solute released (M_∞) as

$$\frac{M_t}{M_\infty} = \frac{C_{10}\sqrt{(4D_1 t)}}{(C_{10}\delta_B + C_{20} l)} \left\{ \sum_{n=0}^{\infty} \left[\beta^n \operatorname{ierfc}\left(\frac{2n\,\delta_B}{\sqrt{(4D_1 t)}}\right) + \frac{2}{\alpha}\beta^{n+1} \operatorname{ierfc}\left(\frac{(2n+1)\,\delta_B}{\sqrt{(4D_1 t)}}\right) - \beta^{n+1} \operatorname{ierfc}\left(\frac{(2n+2)\,\delta_B}{\sqrt{(4D_1 t)}}\right)\right]\right\}, \tag{11}$$

where

$$\alpha = \frac{C_{10}}{KC_{20} - C_{10}}(1 - K\sqrt{(D_1/D_2)}), \tag{12}$$

$$\beta = \left(\frac{1 - K\sqrt{(D_1/D_2)}}{1 + K\sqrt{(D_1/D_2)}}\right). \tag{13}$$

Although equation (11) is rigorous, it cannot be used directly for the design of a bilayer system. We can make further approximations to get a physical insight into the role of the transport parameters for designing systems for controlling the rate of diffusion.

For a thin barrier layer containing no drug initially, we assume that the pseudo steady-state profile is established immediately in the barrier. By replacing equations (6), (7) and (8) by

$$D_2 \partial C_2/\partial x = (D_1 K/\delta_B) C_2 = \upsilon C_1 \quad \text{at} \quad x = 0, \quad t > 0, \tag{14}$$

we obtain

$$\frac{M_t}{M_\infty} = \frac{2}{L}\sqrt{\left(\frac{D_2 t}{\pi}\right)} + \frac{D_2}{\upsilon L}\exp\left(\frac{\upsilon^2 t}{D_2}\right)\operatorname{erfc}\left[\sqrt{\left(\frac{\upsilon^2 t}{D_2}\right)}\right] - \frac{D_2}{\upsilon L}, \tag{15}$$

where

$$\upsilon = D_1 K/\delta_B$$

for

$$t \gg D_2 \delta_B^2/D_1^2 K^2, \tag{16}$$

it then follows that

$$M_t/M_\infty = ((2/L)\sqrt{(D_2/\pi)})\,(\sqrt{t} - (\sqrt{(D_2\pi)}/2\upsilon)). \tag{17}$$

Here the fractional release of the solute is proportional to the square root of time, which is the fickian behaviour.

On the other hand for an approximate range

$$D_2 \delta_B^2/20 D_1^2 K^2 < t < D_2 \delta_B^2/7 D_1^2 K^2. \tag{18}$$

We obtain,

$$M_t/M_\infty \approx (KD_1/\delta_B L)\, t. \tag{19}$$

It is readily seen now that the overall fractional release of the solute is directly proportional to time and the diffusional flux is independent of time.

We will now demonstrate as to how in a polymeric hydrogel, transport parameters could be manipulated to satisfy either inequality (16) or inequality (18) and obtain bilayered membrane systems showing a uniquely desired diffusional behaviour.

3. Experimental details

4-methyl-7-hydroxy coumarine methacrylate (MOCM) was synthesized by the condensation of 4-methyl-7-hydroxy coumarine and methacryloyl chloride. 4-carboxy styrene was synthesized as described by Broos *et al.* (1978). Sodium styrene-4-carboxylate (SSC) was prepared by treating 4-carboxy styrene (0.11 M) with sodium hydroxide (0.1 M) in methanol.

Bulk copolymers of HPMA with MOCM and HPMA with SSC were prepared by bulk polymerization in test tubes. Polymerization was carried out using *t*-butyl hydroperoxide as an initiator. This was done at 50 °C initially for 6 h and then at 60 °C for 18 h. When polymerization was complete, polymer rods were obtained by breaking the glass tubes. Discs of 1.6 cm diameter and 0.09–0.11 cm thickness were cut on the lathe.

Polymeric discs for release studies were extracted in water for one day to remove any traces of unconverted monomers. P(HPMA–MOCM) discs for release studies were soaked in 4% theophylline in aqueous 0.05 N sodium hydroxide solution till equilibrium swelling was reached, P(HPMA–SSC) discs for release studies were soaked in 1% solution of theophylline and metronidazole in water. All the release studies were carried out from swollen polymers at 37 °C. Concentration of theophylline and metronidazole released was monitored by the absorbance of the release medium on a Shimadzu 240 UV-vis spectrophotometer at 272 nm and 319 nm respectively.

Diffusion coefficients of metronidazole from the swollen polymer matrices were experimentally determined using the procedure reported by Yasuda *et al.* (1968).

Partition coefficients were determined experimentally by placing drug free polymeric discs of known weight in 25 cm^3 of distilled water containing a known concentration of metronidazole at 37 °C for 48 h. The drug concentration before and after partitioning was measured and used to calculate the partition coefficient (K_{sp}) of metronidazole from the solution to the polymer phase using the relation

$$K_{sp} = V_p C_e / V_s (C_i - C_e). \tag{20}$$

Here V_s and V_p denote the volumes of elution solution and of polymeric disc respectively. Similarly C_i and C_e denote the initial and equilibrium concentration of the drug in the solution respectively. Forty-eight hours were adequate to ensure equilibrium. The partition coefficient, K between the barrier and the core polymer can then be obtained as the ratio of K_{sp} for the core polymer to that for the deswollen polymer.

As it is difficult to find out the solubilities in polymers, the solubility of metronidazole in monomers was estimated spectrophotometrically at 37 °C, by saturating the monomer solution with metronidazole.

Barriers were formed by treating the swollen hydrogel discs for the desired time intervals with 0.1 N sulphuric acid or simulated gastric fluid.

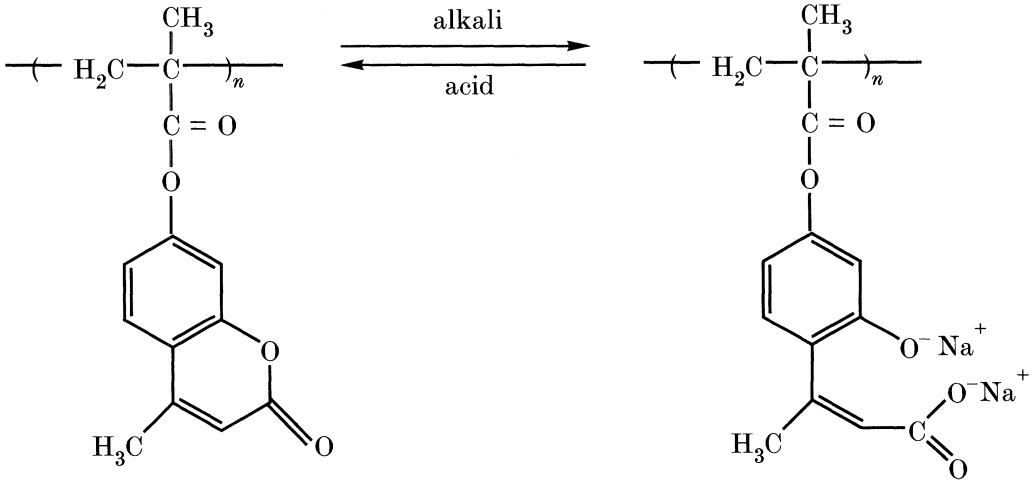
4. Results and discussion

(*a*) *Creation of a reversible bilayered membrane*

When a swollen polymer, possessing stiff chains and/or ionizable groups, is subjected to a change in pH, temperature, etc., it can deswell by a discontinuous volume phase transition (Tanaka 1987). This subject has attracted the attention of a number of researchers in recent years. We ourselves have undertaken studies to understand the molecular level phenomena occurring during such volume transitions (Badiger *et al.* 1991) and have also exploited such transitions to design systems for separation of macromolecules from aqueous solutions (Badiger *et al.* 1992). Here we exploit the phenomenon in a slightly different way.

Hydrogels, which interact with the medium, have been explored in the literature (Hoffman 1987). If these hydrogels are pH sensitive, this sensitivity could be exploited to create barrier layers. When a hydrogel is immersed in an acidic medium, collapse of the surface layer takes place. The thickness of this collapsed layer, which now forms the barrier layer, can be controlled by controlling the time of immersion. If the pH is again changed to the alkaline range, this barrier layer will swell. We thus have a way to create reversible barriers, where the thickness δ_B (shown in figure 1) can be controlled at will. For designing specific systems, we consider hydrogels made of 2-hydroxyl propyl methacrylate (HPMA), which undergo swelling in water. To form a reversible barrier, we must incorporate monomers that interact with the medium. A suitable system to consider is the copolymer of HPMA with 4-methyl-7-hydroxy methyl coumarine methacrylate (MOCM). The basis for the choice of this copolymer needs an explanation.

Coumarines undergo ring opening in the presence of sodium hydroxide to yield sodium coumarinate. Acidification leads to relactonization to yield coumarine and not coumarinic acid (Murray *et al.* 1982). Thus, when a polymer containing coumarine in the pendent chain namely P(HPMA–MOCM) is immersed in the alkaline medium, coumarine ring opens up to produce COO^- and OH^- ions which leads to the enhanced swelling of the polymer:



MOCM
hydrophobic

hydrophilic

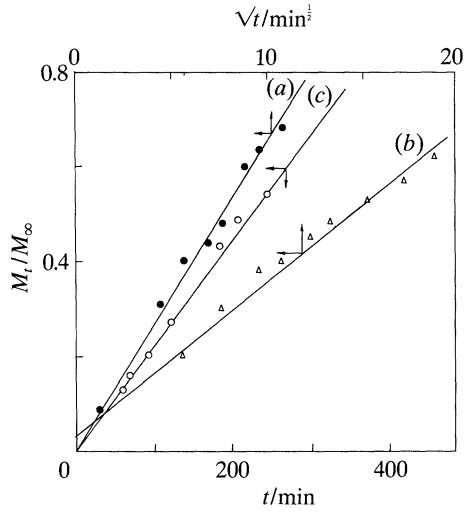


Figure 2. Diffusional release from P(HPMA–MOCM) (*a*) Fully swollen hydrogel, hydration 74%. (*b*) Completely deswollen hydrogel, hydration 16%. (*c*) Acid treated polymer with bilayer.

When the swollen polymer is brought in contact with the acidic medium for a limited time period, the swollen polymer in the surface layer will undergo relactonization and will collapse to form the barrier layer.

Recently the swelling characteristics of the hydrogels based on the copolymers of 2-hydroxy ethyl methacrylate (HEMA) and sodium styrene carboxylate (SSC) (namely P(HEMA–SSC)) and the diffusional release of drugs as a function of pH were reported by us (Shah *et al.* 1991). The structure of styrene carboxylic acid is analogous to that of *p*-methyl benzoic acid ($pK_a = 4.37$). Further when polymerized, the vinyl unsaturation in the monomer, which would otherwise lower the pK_a value of the monomer in comparison to *p*-methyl benzoic acid, disappears. The polymer P(HPMA–SSC) is therefore expected to exhibit similar transition in the pH range 4–6. Thus a swollen hydrogel based on the copolymer of sodium styrene 4-carboxylate would undergo deswelling in the pH range 4–6.

Having controlled δ_B through such chemical means, it is readily seen that with the manipulation of diffusion coefficients in the swollen core (D_2) and in the barrier layer (D_1), we could use equations (16) and (18) to design systems, where the diffusional flux is invariant with time.

(*b*) *Experimental validation*

The release of theophylline from the equilibrium swollen P(HPMA–MOCM) hydrogel having degree of hydration 74% is shown in figure 2*a*. We see that M_t varies as $\sqrt{t}$ and the release follows fickian diffusion. The release of theophylline from the hydrogel, which has undergone complete deswelling (figure 2*b*) in the acidic medium also follows fickian diffusion. Obviously, the release rate of theophylline from the deswollen matrix of lower degree of hydration (namely 16%) is considerably lower.

When the swollen hydrogel is immersed in 0.5 N sulphuric acid for a short time

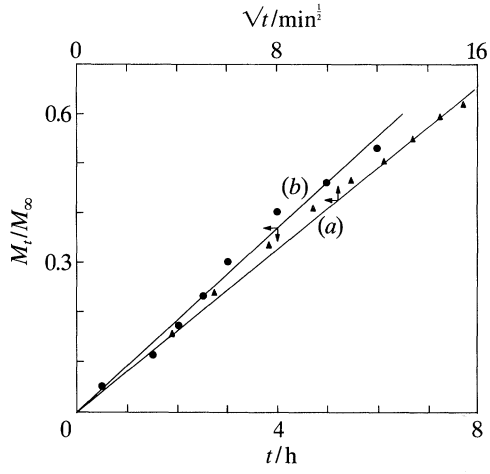


Figure 3. Diffusional release of metronidazole from swollen P(HPMA–SSC) hydrogels. (*a*) Hydration 74%; (*b*) immersed in 0.1 N H_2SO_4 for 30 min.

period (2 h), the hydrogel in the surface layer undergoes volume phase transition to form a barrier layer on the surface. The hydrogel now consists of a core having a degree of hydration of 74% and a barrier layer of degree of hydration of 16%. We see from figure 2*c* that M_t varies as t now and the rate of diffusion of theophylline from such a system is indeed constant.

We have thus shown qualitatively that either fickian diffusion or diffusion rate, which is invariant with time can be obtained by designing the bilayer systems. A limitation of the system P(HPMA–MOCM) is that the coumarine undergoes ring opening at pH $\approx$ 10. Instead, the polymer could be so designed as to undergo swelling/deswelling under physiological conditions, such systems could find applications in the design of drug delivery systems in the gastrointestinal tract. It would be further desirable to quantify the release rates from such systems using the physico-chemical properties of the bilayered systems based on the theoretical considerations presented in section 2. We have investigated the system P(HPMA–SSC) in more detail.

HPMA was copolymerized with sodium styrene carboxylate (2% by weight). The degree of hydration of the polymer in water is 74% since sodium styrene carboxylate is in the ionized state. Under acidic conditions, the polymer undergoes deswelling as the carboxylate anion is converted to the carboxylic acid. Degree of hydration of the polymer in the deswollen state is 11%. It is therefore anticipated that such a hydrogel, when swollen to equilibrium in water and exposed to dilute acid to form a barrier layer, would lead to the diffusion of solute at a constant rate. In contrast, the hydrogels based on P(HPMA–MOCM) need to be exposed to alkali (pH $\approx$ 10) to open the coumarine ring and bring about consequent swelling.

The release of metronidazole from P(HPMA–SSC) hydrogel is shown in figure 3, we see that M_t now varies as $\sqrt{t}$ (figure 3*a*). The release of metronidazole from the hydrogel swollen to equilibrium in water and subsequently immersed in 0.1 N H_2SO_4 for 30 min is shown in figure 3*b*. The fractional solute release is now linear with time and the release rate is constant.

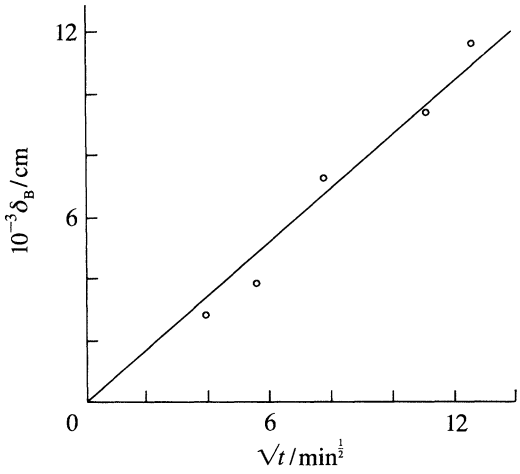


Figure 4. Kinetics of deswelling of P(HPMA–SSC) hydrogels in simulated gastric fluid. Thickness of the barrier layer against the square root of time of immersion.

(*c*) *Physiological relevance of the system*

The principle of barrier formation and the diffusional release of a solute at constant rate from the reversible bilayer membranes can be exploited for the delivery of drugs in the gastrointestinal tract. The polymers presently used as enteric coatings prevent the release of drugs in the stomach. The polymers dissolve at the intestinal pH and release the drug. If the barrier formation could be brought about under the acidic conditions prevalent in the stomach, (pH = 1.5) the release of the drug in the intestinal region, (pH $\approx$ 7) would proceed at constant rate. Because D_1 and D_2 are determined by the choice of the drug and the equilibrium swelling of the polymer in the collapsed and the swollen state, the release rate of the drug would depend upon the thickness of the barrier layer δ_B.

δ_B can be controlled by manipulating the duration of immersion of the swollen hydrogel in the acidic medium. The kinetics of collapse of hydrogels has been reported to be fickian (Gehrke & Cussler 1989). If this were so, the thickness of the barrier layer would be linear with respect to the square root of time. To check if the collapse of the hydrogel was also fickian in the present case P(HPMA–SSC) hydrogels swollen to equilibrium in water were immersed in the simulated gastric fluid for varying time intervals and the thickness of the barrier layer was measured. The results shown in figure 4 confirm that the deswelling is indeed fickian in nature. It is thus possible to manipulate the thickness of the barrier layer at will.

The bilayered hydrogels formed in above experiments were then immersed in simulated intestinal fluid (pH = 7.2) and the release of metronidazole was monitored. The results shown in figure 5 illustrate that the release of metronidazole in all the cases is linear with time.

(*d*) *Quantitative validation*

We will now show that the diffusional phenomena experimentally demonstrated by us can be quantitatively validated through the model calculations done by us. To achieve this, various physicochemical parameters were determined for the systems independently. These were, $D_1 = 7 \times 10^{-9}$ cm^2 s^{-1}, $D_2 = 1.14 \times 10^{-7}$ cm^2 s^{-1}, and $K =$ 0.794. The thicknesses of the barrier layers were experimentally determined as shown

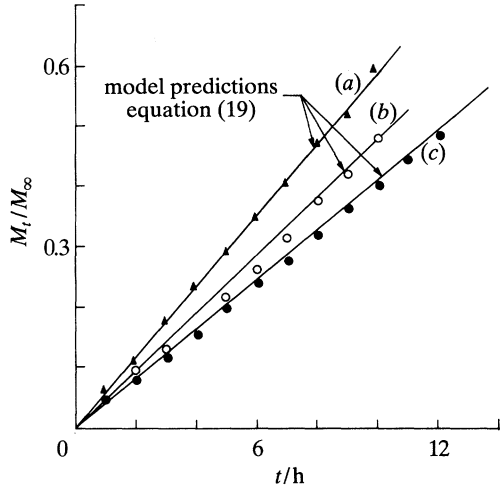


Figure 5. Diffusional release of metronidazole in simulated intestinal fluid from P(HPMA–SSC) bilayer membrane formed by immersion in simulated gastric fluid for (*a*) 1.5 h, (*b*) 2 h and (*c*) 2.5 h.

in figure 4. With this we find that the inequality (18) is satisfied for this set of experiments and hence the rate of diffusional release will be given by equation (19). The theoretical predictions based on equation (19) are seen to be in good agreement with the experimental data in all the cases. Although the release of the drug was carried out from the slab geometry, the rate of release from the microspheres is also expected to remain constant, as the surface area, across which the release takes place, remains constant.

5. Conclusions

This communication illustrates as to how the volume phase transition in polymers can be exploited to design reversible bilayer systems. The deswelling process has been shown to be fickian in nature. The thickness of the barrier layer can thus be manipulated *a priori*. The conditions under which the diffusional release of a solute from such systems can take place at a constant rate have been arrived at theoretically and validated experimentally with model systems. A possible application of such systems in oral drug delivery is illustrated.

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