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## A novel approach for the control of drug release rate through hydrogel membrane II. Thermodynamic modeling of the partition control scheme

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### ABSTRACT

In advanced drug delivery systems, drug permeation rate is the key parameter that governs performance. Among the factors that influence the permeation rate, partition effect is presently given less attention. In the first part of this study [L. Shang, S. Zhang, H. Du, S. S. Venkatraman, A novel approach for the control of drug release rate through hydrogel membrane. I. Effect of drug immobilization on drug release rate by copolymerization method. *Eur. J. Pharm. Biopharm.* 68 (2008) 715–723], a scheme was proposed to alter the drug release rate through controlling the partition behavior by immobilizing drug molecules in the membrane. It was hypothesized that the immobilized drug contributes to the total chemical potential of all drug molecules, resulting in a reduction in the partition coefficient. In this paper, the working mechanism of the control scheme is studied through thermodynamic modeling on the assumption that substances in the system are dependent upon one another (rather than independent as they are usually treated). Experimental results provide satisfactory verification of the model. With this model, drug permeation rate can be quantitatively tailored.

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### 1. Introduction

Polymeric membranes are found in many biomedical applications, such as kidney dialysis [2] and advanced drug delivery systems (ADDs) [3–6]. One of the fundamental issues in applying membranes in those biomedical fields is to control the permeation rate of macromolecules (e.g. proteins, peptide, DNA) through the membrane. Drug delivery is a combination of material science, pharmaceuticals and biology [7]. Adoption of different types of membranes has made it possible to release drug in an optimal fashion according to the nature of a disease [8]. As design of ADDs evolves more towards biology and emphasizes on system miniaturization down to nanometer scale [9], it is worth re-examining the unsolved issues of precise control of drug release rate from the materials angle.

In general, the permeation mechanism of non-porous polymeric membranes can be described by solution-diffusion model [10], whereby the permeating molecule from one compartment (donor) dissolves in the membrane (measured by partition coefficient) and then diffuses along a concentration gradient to the other side of the membrane to dissolve in the other compartment

(receptor) (Fig. 1). Depending on the properties of the material used for the membrane, the permeation mechanism could be complicated by membrane swelling [11] and erosion [12]. Different models have been developed to predict the permeation rate of both simple and complex systems [13,14,15] and intensive research efforts are devoted to study the relationship between permeability (defined as the product of diffusivity and partition coefficient) and intrinsic material properties of the membrane. Although many parameters are found important (pore size, geometry, permeating molecule–membrane interactions [15]), they can be generalized by two basic factors: diffusivity and partition coefficient. Both factors play equally important roles in determining permeation rate, but in control of the permeation rate, diffusivity has been viewed as a dominating factor since 1980s [16,17] whereas partition behavior is usually taken as a by-product at a given diffusivity. This has been so because partition coefficient is a quantity governed by thermodynamic properties of the permeating molecule, thus difficult to control [18–21] and, diffusivity and partition coefficient are usually correlated.

Our preliminary experimental results [1] have shown that the partition coefficient can be controlled by immobilizing a certain amount of drug molecules in the membrane while retaining diffusivity of the free drug of the same type. One of the potential applications of this control scheme is for hydrogel-based pulsatile ADDs, which requires sharp change in the drug permeation rate

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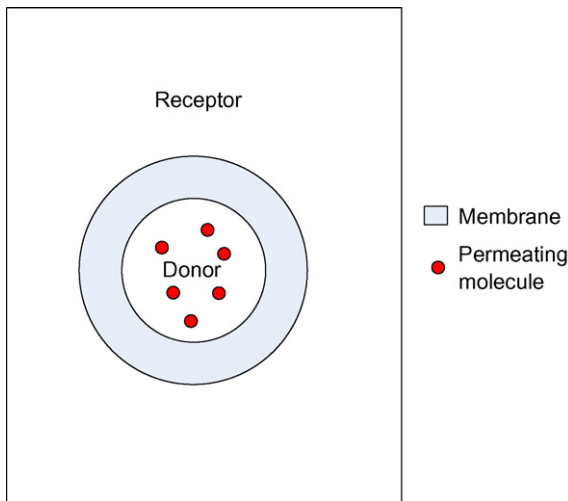


Fig. 1. A schematic diagram of donor-membrane-receptor system.

when the device is triggered on and off to better mimic the physiological release profile of certain hormones. In such systems, a substantial difference in release rate between the 'on' and 'off' states is desirable to release the drug at an effectively high rate during 'on-state' to exert therapeutic effect and an acceptably low rate during 'off-state' to minimize side-effects. However, in conventional systems, the switching between 'on' and 'off' is controlled by gel swelling [22]. Because of the nature of the hydrogels used in such systems, a high swelling ratio at 'on-state' is often accompanied by a measurable swelling ratio at 'off-state', which results in drug leakage. Reduction in drug leakage during 'off-state' was clearly observed in our previous study [1], however, the effect of drug immobilization on 'on-state' is still not clear to date. Furthermore, although the control scheme was proved to be effective, its working mechanism still remains as a hypothesis.

Encouraged by the preliminary success [1], in this work a more complete picture of the effect of drug immobilization on both 'on' and 'off' states will be studied. The working mechanism of the control scheme will be examined by modeling the partition behavior under the hypothesized working mechanism. With the model, membrane permeation rate in ADDS can be quantitatively controlled.

## 2. Model development

The hypothesized mechanism of the partition control scheme is that the immobilized drug molecules contribute to the total chemical potential of the drug molecules of the same type in the membrane but are not free to be released. As a result, the amount of drug moving from the donor into the membrane, to balance its chemical potential in the donor, is reduced thereby reducing the permeability [1]. The challenge to model the partition effect under this hypothesis is that a change in the amount of one component in the system does not only affect the distribution of that component, but also affect the others, whereas in conventional thermodynamics, it is usually assumed that different components can be added in or withdrew from the system independently.

In conventional thermodynamics, the definition of chemical potential (Eq. (1)) is based on an ideal situation: the change in Gibb's free energy due to one component is independent to others, therefore in the differentiation operation (Eq. (1), all other components

can be kept constant:

$$\mu_i = \left( \frac{\partial G}{\partial n_i} \right)_{T,P,n_j} \quad (1)$$

where  $G$  is Gibb's free energy,  $n_i$  is the amount of component  $i$ ,  $V$  is volume and  $P$  is pressure. The subscripts indicate that temperature, pressure and the amount of all other components are maintained constant.

Although Eq. (1) is theoretically sound, we propose that dependence shall be considered in some practical situations whereby a change in one component inevitably causes a change in the other. The infinitesimal expression of Gibb's free energy equation (Eq. (2)) is re-configured in the following way to handle the 'dependent' case: in a general scenario two dependent substances (A and B) in the membrane are grouped together, represented by a combined chemical potential ( $\mu_{M,grouping}$ ), and total concentration in the membrane ( $C_{M,grouping} = C_{M,A} + C_{M,B}$ ), where  $C_{M,A}$  and  $C_{M,B}$  are the concentration of A and B in the membrane, and they are dependent; subscript  $M$  denotes membrane. Mathematically the above description writes:

$$dG = -SdT + VdP + (\mu_{M,A} dC_{M,A} + \mu_{M,B} dC_{M,B}) + \sum_{i=3} \mu_i dC_i \quad (2)$$

and

$$\mu_{M,grouping} dC_{M,grouping} = \mu_A dC_A + \mu_B dC_B \quad (3)$$

where  $S$  is entropy.

Hence the combined chemical potential is

$$\mu_{M,grouping} = \mu_{M,A} \left( \frac{dC_{M,A}}{dC_{grouping}} \right)_{T,P,n_{i>2}} + \mu_{M,B} \left( \frac{dC_{M,B}}{dC_{grouping}} \right)_{T,P,n_{i>2}} \quad (4)$$

and let

$$\alpha = \left( \frac{dC_{M,A}}{dC_{M,grouping}} \right)_{T,P,n_{i>2}} \quad \text{and} \quad \beta = \left( \frac{dC_{M,B}}{dC_{M,grouping}} \right)_{T,P,n_{i>2}} \quad (5)$$

At chemical potential equilibrium, it is assumed that the combined chemical potential in the membrane is balanced by the chemical potential of substance A in the donor:

$$\mu_{M,grouping} = \mu_{D,A} \quad (6)$$

Subscript  $D$  denotes donor. Substituting the expressions for chemical potential into the above equation:

$$\mu_{M,0} + RT \ln(\gamma_{M,grouping} C_{M,grouping}) = (\mu_{M,0} + RT \ln(\gamma_{M,A} C_{M,A}))\alpha + (\mu_{M,0} + RT \ln(\gamma_{M,B} C_{M,B}))\beta = \mu_{D,0} + RT \ln(\gamma_{D,A} C_{D,A}) \quad (7)$$

where  $\mu_0$  is the reference chemical potential,  $\gamma$  is activity coefficient.

Therefore, the concentration ratio of substance A in membrane and donor is

$$\frac{C_{M,A}}{C_{D,A}} = \left[ \frac{\exp((\mu_{D,0} - \mu_{M,0})/RT) \gamma_{D,A}}{C_{D,A}^{\alpha-1} \gamma_{M,A}^{\alpha} (\gamma_{M,B} C_{M,B})^{\beta}} \right]^{1/\alpha} \quad \text{for } C_{M,B} > 0 \quad (8)$$

Now consider the partition control scheme: let A stand for the free drugs, and B for the immobilized ones of same type as A. Assuming the donor is an infinite source of A, thus  $C_{D,A}$  is constant. The concentration ratio derived in Eq. (8) is therefore the partition

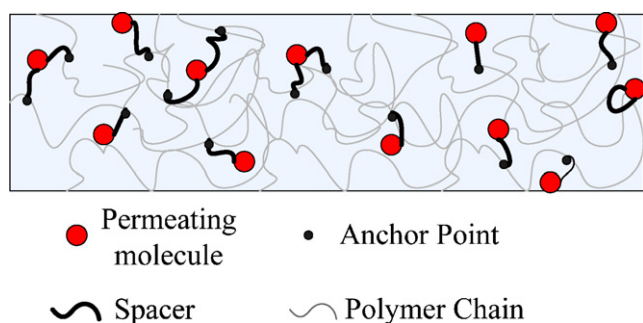


Fig. 2. Membrane with immobilized permeating molecules.

coefficient of free drugs ( $K_{\text{eff}}$ ):

$$K_{\text{eff}} = \left[ \frac{\exp((\mu_{D,o} - \mu_{M,o})/RT)\gamma_{D,\text{free}}}{C_{D,\text{free}}^{\alpha-1} \gamma_{M,\text{free}}^{\alpha} (\gamma_{M,\text{immob}} C_{M,\text{immob}})^{\beta}} \right]^{1/\alpha} \quad \text{for } C_{M,\text{immob}} > 0 \quad (9)$$

where  $\mu_{D,o}$ ,  $\mu_{M,o}$ ,  $R$ ,  $T$  and  $\gamma_{D,\text{free}}$  are constants at a given donor condition, and the activity coefficients of the free and the immobilized molecules in the membrane are related through:

$$\gamma_{M,\text{immob}} = b\gamma_{M,\text{free}} \quad (10)$$

This is because the free drugs constantly undergo random movement in the membrane, but when they are immobilized through a spacer (Fig. 2) they can move in a similar fashion as free drug molecules only within a distance defined by the length of the spacer. Factor  $b$  takes this restriction into account. Inserting Eq. (10) into Eq. (9) gives rise to

$$K_{\text{eff}} = \left[ \frac{\exp((\mu_{D,o} - \mu_{M,o})/RT)\gamma_{D,\text{free}}}{C_{D,\text{free}}^{\alpha-1} \gamma_{M,\text{free}} (bC_{M,\text{immob}})^{\beta}} \right]^{1/\alpha} \quad \text{for } C_{M,\text{immob}} > 0 \quad (11)$$

Eq. (11) is applicable to predict the partition coefficient of a drug when a certain amount of the drug of the same type is immobilized in the membrane.

### 3. Materials and methods

#### 3.1. Materials

The monomers used for the pH-sensitive hydrogel were polyethylene glycol monomethacrylate (PEGMA, EG repeating unit molecular weight 400; Polysciences, Warrington, PA), and 2-(diethylamino)ethyl methacrylate (DEAEMA, Sigma). Tetraethylene glycol diacrylate (TEGDA, Sigma) was used as crosslinking agent and the photo initiator used was 2,2-dimethoxy-2-phenyl acetophenone (DMPA, Sigma). Bovine Serum Albumin (BSA, Sigma) was chosen to be the model drug in this study. Acryloyl chloride (Merck) was used for protein functionalization and immobilization to the hydrogel. Phosphate-buffered saline (PBS, Sigma) was used as buffer solution. All the chemicals were used as received.

#### 3.2. Hydrogel membrane synthesis

PEGMA (4 g) and DEAEMA (2 ml) were mixed with ethanol (1 ml). Crosslinking density was set to be 1% per mole of monomer (PEGMA + DEAEMA). The monomer mixture was stirred over night. Just before synthesis, 3% (w/w) (total monomer) DMPA were added

into the solution and stirred for two hours. The monomer mixture was put in an ultrasonic bath for 10 min to remove dissolved oxygen. 100  $\mu\text{l}$  monomer was then pipetted between two silane-treated glass slides, which were separated by 200  $\mu\text{m}$  spacer. The system was then exposed to UV light (Crosslinker, 365 nm) for 2 min on each side at the intensity of 3  $\text{mW}/\text{cm}^2$ . The synthesized membranes were soaked in deionized (DI) water for a week to remove un-reacted proteins and monomers. The soaking water was changed daily to ensure freshness.

#### 3.3. BSA and membrane functionalization

BSA (50 ml) solution of desired concentration was prepared in deionized water. Different amounts of acryloyl chloride (Table 1) were then added and the solution was stored at 4  $^{\circ}\text{C}$  for 2 h. Acrylate groups were covalently bound to the nitrogen atoms of the peptide bonds in the BSA molecule after this process. To introduce C=C bonds to the synthesized membrane for protein immobilization, 100  $\mu\text{l}$  acryloyl chloride was added into 50 ml DI water and 10 pieces of synthesized membranes were soaked in it. The beaker was kept at 4  $^{\circ}\text{C}$  for 24 h.

#### 3.4. Loading of functionalized BSA (F-BSA) and immobilization

After functionalization of BSA and the membrane, the functionalized membranes were soaked in the F-BSA solution for three days to allow the F-BSA to load into the membranes. In the chamber of UV crosslinker, 100  $\mu\text{l}$  of the 20 mg/ml DMPA solution (dissolved in ethanol) was applied to the surface of F-BSA loaded membranes and then the UV polymerization was initiated. The procedure was repeated on both sides of the membrane, so that the BSA was immobilized. The BSA immobilized membranes were soaked in DI water at about 4  $^{\circ}\text{C}$  with the water changed daily to remove un-immobilized BSA.

#### 3.5. X-ray photoelectron spectroscopy (XPS)

The success of protein immobilization in the hydrogel membrane was characterized by XPS (Kratos AXIS Ultra) with monochromatic Al K $\alpha$  (1486.71 eV) X-ray radiation (15 kV and 10 mA). The atomic concentration was calculated by the build-in software of the XPS system. Samples used for XPS measurements were vacuum dried after the soaking process (the soaking process is as described in: *Loading of functionalized BSA (F-BSA) and immobilization*).

#### 3.6. Protein permeation

pH 7.4 and 6.5 corresponded to the 'off-state' and 'on-state' of the system, respectively, as suggested in the swelling experiment (results not shown). So the effect of protein immobilization on the 'off-state' leakage was studied at pH 7.4 and the effect on 'on-state' was studied at pH 6.5. The membranes used for the protein permeation experiment were equilibrated in PBS of desired pH for at least 2 days. The permeation experiment was conducted using a pair of

Table 1

Amount of acryloyl chloride used for protein functionalization at different protein concentration

Bovine serum albumin (mg/ml)	Acryloyl chloride ( $\mu\text{l}$ )
5	40
10	80
20	160
40	320

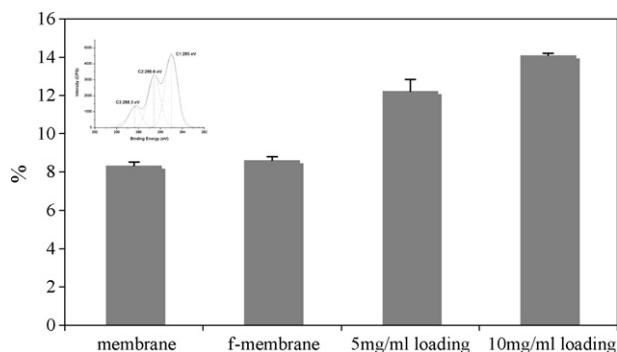


Fig. 3. The atomic percent of carbon atoms in amide group of the membrane at different loading concentrations of functionalized protein.

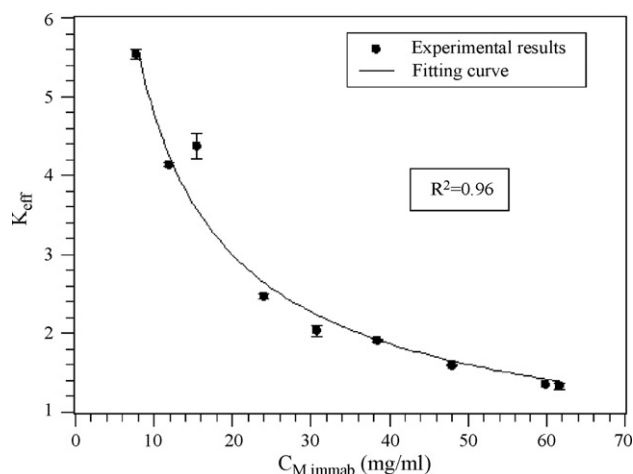


Fig. 4. The black dots are the average of effective partition coefficients ( $K_{eff} = K/K_{steric}$ ), calculated from the experimentally measured data ( $K$ ) of three independent experiments, and  $K_{steric}$  is calculated based on Eq. (2) of ref. [1]. The error bar is the standard deviation of the measured data. For curve fitting,  $\gamma_{M,free}$  is regarded as a constant in the interested concentration range. The curve fitting was performed by a freeware run under Mac OS 10.5: qtiplot.

home-made side-by-side diffusion cells with an inner diameter of 1 cm. The diffusion cell consists of two glass chambers with a volume of 3 ml each. To determine the effective diffusion coefficient of solute, precisely weighed BSA was dissolved in PBS of desired pH and stored at 4 °C before use. Samples that were equilibrated at that pH were used for the permeation experiment. Two milliliters of 5 mg/ml BSA solution was loaded into the donor chamber and 2 ml fresh PBS of the same pH was loaded into the receptor chamber. Receptor solution was completely taken out at predetermined

interval for measurement and fresh solution of the same volume was refilled into the receptor and restart timing. Donor solution was also changed at the end of each interval to guarantee infinite source condition. The sampling interval chosen was 0.5, 1, 1.5, 2, 2.5 and 3 h. The amount of released BSA in the receptor solution was measured using a UV–vis spectrophotometer (Shimadzu UV-2450) at 278.5 nm, the concentration was obtained from a standard curve calibrated at 278.5 nm. The permeation for each type of membrane at a given pH value was repeated three times.

The flux entering the receptor was calculated by

$$F = C_R V_R / (At) \quad (12)$$

where  $C_R$  and  $V_R$  are the receptor protein concentration and receptor volume, respectively,  $A$  is the effective area for diffusion, and  $t$  is time.

The diffusivity of the solute in the membrane and the partition coefficient was calculated from the permeation experimental data by [23,24]:

$$\ln(t^{0.5} F_t) = \ln \left\{ 2C_{eff} \left( \frac{D}{\pi} \right)^{0.5} \right\} - \frac{L^2}{4Dt} \quad (13)$$

where  $F_t$  is the flux at time  $t$ ,  $L$  is the thickness of the membrane,  $D$  is the diffusivity of the solute in the hydrogel membrane, and  $C_{eff}$  is the effective drug concentration (the concentration of un-immobilized drug) at the donor side of the membrane, which was used for partition coefficient calculation according to the following relationship:

$$K_{eff} = \frac{C_{eff}}{C_D} \quad (14)$$

where  $C_D$  is the drug concentration in the donor chamber.

## 4. Results and discussion

### 4.1. Characterization of protein-immobilized membrane

Because 23.55% of total carbon in BSA is in amide groups (as measured by XPS for BSA powders), which is higher than that of the membrane (8.33%), therefore the proportion of carbon atoms in amide groups shall increase after protein immobilization. The characterization peak of the amide group is at 288.3 eV [25], and it is found that the atomic concentration of C 1s in amide group increases as the membrane being functionalized and protein being immobilized (Fig. 3). It proves that BSA has been successfully immobilized in the membrane by the three-step procedure. Since the functionalization of drug molecules is based on amide groups of proteins, the immobilization method can be applied to different protein therapeutic agents.

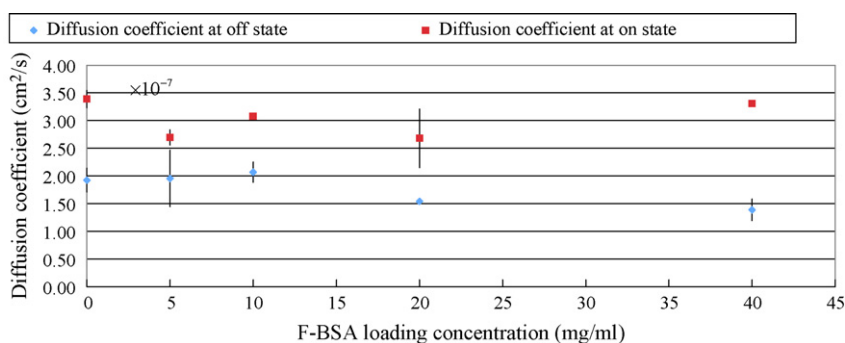
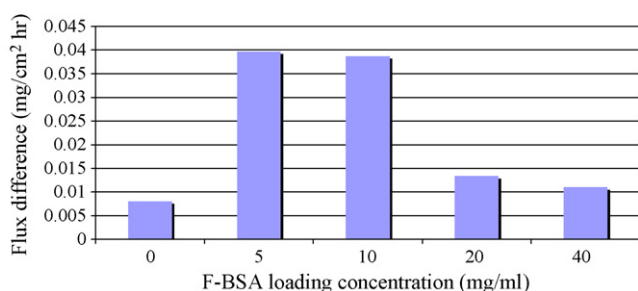


Fig. 5. Diffusion coefficient comparison at on state (pH 6.5, solid squares in the figure) and off state (pH 7.4, solid circles in the figure) at different loading concentration of functionalized bovine serum albumin (F-BSA).



**Fig. 6.** The change in drug release flux between on and off states at different loading levels of functionalized bovine serum albumin (F-BSA). Flux difference = flux at on state-flux at off state. Since mean value is used, no error bar is applicable to this result. A high difference is desirable for device design.

#### 4.2. Model verification and working mechanism of the control scheme

The permeation experiments showed that the partition coefficient decreased as immobilization level increased, and the fitting curve by Eq. (11) agreed well with experimental results (Fig. 4). The fitting parameter  $b$  was found to be 0.054,  $\alpha = 0.595$  and  $\beta = 0.405$ . Since  $b$  depends on the immobilization agents used, a long and flexible spacer will make the immobilized drug molecules behave more like a free drug molecule, therefore enhance the sensitivity of the control scheme (less amount of drug is needed to be immobilized for a desirable reduction in partition coefficient). Meanwhile the diffusion coefficient was not affected by immobilization (Fig. 5), suggesting that partition behavior of the drug can be separately controlled by the proposed scheme.

Since the assumption of the model is the hypothesized working mechanism of the control scheme, a good agreement between the model and experimental results confirms that the working mechanism of the control scheme is the same as previously stated in Section 2.

#### 4.3. Effect of drug immobilization on both 'on' and 'off' states

By immobilizing a certain amount of the drug molecules in the membrane, the difference in drug permeation rates between the 'off-state' and the 'on-state' can be greatly increased (Fig. 6), so that with the same gel-swelling capability, a substantially lower amount of drug is leaked during 'off-state' with a particular 'on-state' release rate. This is because with the same amount of BSA being immobilized, its concentration in the membrane is smaller during 'on-state' (due to higher water content) hence the reduction effect on the partition coefficient due to drug immobilization is weaker compared to 'off-state', resulting in an increase in the change of release rate when the system is switched on and off. However, as immobilization increases, the partition coefficient-immobilization curve (Fig. 4) tends to be less steep, this is why at high immobilization levels the change in the release rate during switching is reduced. Hence the amount of immobilization shall be carefully chosen for the optimal operation (biggest change in release rate when the system is switched on and off).

#### 4.4. Discussion on other potential applications of the control scheme

Another potential application of the partition control scheme is for core-shell micro/nano-spheres with a drug-loaded core and a rate-controlling shell [26]. Instead of selecting material and composition for the shell to realize the desirable release rate, a general shell material and composition can be used to address biocompati-

bility and targeting issues, and the release rate can be engineered by immobilizing a certain amount of the drug molecules in the shell. The advantage of the control scheme is that it allows for greater design flexibility: for example, biocompatibility and mechanical integration of the device can be addressed without considering the release characteristics at the membrane design phase; rather the desired release profile can be engineered after the membrane is synthesized. Because the proposed partition control scheme is based on thermodynamic behavior of permeating molecules, it is generally applicable to non-porous membranes when their permeation rate is to be precisely controlled.

## 5. Conclusions

The experimental data agree well with the hypothesized working mechanism of the partition control scheme: the immobilized drugs contribute to the total chemical potential of all drug molecules of the same type (both free and immobilized ones), resulting in a reduction in the amount of free drug dissolved in the membrane, hence a decrease in partition coefficient and permeation rate.

Quantitative control of drug permeability is now feasible through drug molecule immobilization. The amount of immobilization needed for a required permeation rate can be calculated from

$$K_{\text{eff}} = \left[ \frac{\exp((\mu_{D,o} - \mu_{M,o})/RT)\gamma_{D,\text{free}}}{C_{D,\text{free}}^{\alpha-1}\gamma_{M,\text{free}}(bC_{M,\text{immob}})^{\beta}} \right]^{1/\alpha} \quad \text{for } C_{M,\text{immob}} > 0$$

where  $K_{\text{eff}}$  is the partition coefficient of free drugs;  $\mu_{D,o}$  and  $\mu_{M,o}$  are the reference chemical potentials in the donor and membrane, respectively;  $\gamma_{D,\text{free}}$  and  $\gamma_{M,\text{free}}$  are the activity coefficients of free drugs in the donor and membrane, respectively;  $C_{D,\text{free}}$  is the free drug concentration in the donor and  $C_{M,\text{immob}}$  is the concentration of immobilized drug in the membrane;  $R$  is the gas constant and  $T$  is the temperature;  $\alpha$ ,  $\beta$  and  $b$  are fitting parameters.

This partition control scheme offers an avenue to tailor the drug release profile of membrane-based advanced drug delivery systems with greater flexibility: i.e. the difference in drug permeation rates between the 'off-state' and the 'on-state' can be increased and drug release profile can be modified after the membrane is synthesized.

### Nomenclature

$A$	effective area for diffusion (cm <sup>2</sup> )
$b$	fitting parameter introduced in Eq. (10)
$C$	concentration (mg/cm <sup>3</sup> )
$C_{\text{eff}}$	the effective drug concentration of free drugs in the membrane
$D$	diffusivity (cm <sup>2</sup> /s)
$F_t$	the flux entering the receptor at time $t$ (mg/(cm <sup>2</sup> h))
$G$	Gibb's free energy (joule)
$K_{\text{eff}}$	the partition coefficient defined by the ratio of free drug concentration in the membrane and the donor
$L$	thickness of the membrane (cm)
$n_i$	the amount of component $i$ in the system (mole)
$P$	pressure of the system under consideration (Pa)
$R$	the gas constant (J/(K mole))
$S$	entropy of the system (J/K)
$t$	time (second in the calculation of diffusivity, hour in the calculation of flux)

$T$	temperature (K)
$V$	volume of the system under consideration ( $\text{cm}^3$ )
<b>Symbols</b>	
$\alpha$	fitting parameter defined in Eq. (5)
$\beta$	fitting parameter defined in Eq. (5)
$\gamma$	activity coefficient
$\mu$	chemical potential (joule per mole as in Eq. (1), joule per concentration otherwise)
$\mu_{M, \text{immob}}$	the chemical potential of immobilized drugs in the membrane
<b>Subscripts</b>	
A, B, C	three different type of substances
D	donor
free	free drugs
immob	immobilized drugs
M	membrane
R	receptor

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