Two New Types of Copolymer Membranes Controlling Clonidine Zero-Order Release

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ABSTRACT: Two new types of membranes were synthesized by UV curing in our laboratory. The first type of membrane was made of three monomers: 2-hydroxy-3-phenoxypropylacrylate(A), 4-hydroxybutyl acrylate(B), and 2-methyl-2-nitropropyl methacrylate(C1). The second type of membrane was made of the same monomers A and B, and 2-butoxyethyl methacrylate(C2). Permeation properties of clonidine releasing through two new types of copolymer membranes were studied. The effects of the ratios of monomers, the thicknesses of membranes, and the concentration of clonidine on the permeation rates were studied. It was found that both copolymer membranes could control clonidine zero-order release. The permeation rates of the first optimized membrane were linearly dependent on the square root of the drug concentration. The permeation rates of the second optimized membrane had no significant difference when the concentration of clonidine varied in the range of 3.0–5.0 mg mL^{-1}. Furthermore, both optimized membranes were characterized by FTIR, DSC, and SEM. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 3016–3022, 2007

Key words: drug delivery systems; copolymerization; synthesize; membranes; curing of polymers

INTRODUCTION

Transdermal drug delivery (TDD), in comparison to conventional drug delivery methods, such as oral administration and injection, offers an attractive drug administration. TDD eliminates the pain and the possibility of infection associated with injection. TDD does not require patient compliance, avoids gastrointestinal drug metabolism, reduces elimination by liver, and provides sustained release of drug for up to one week. In recent years there has been an increased interest in controlled TDD, which is an efficient technique for drug administration.[1–3]

Clonidine is a widely used antihypertensive drug. Its relatively small molecule, low blood-drug level and high potency make it an ideal candidate for study of TDD systems. It's well known oral clonidine can result in some symptomatic side-effects, such as dry mouth, drowsiness, dizziness, constipation, and sexual dysfunction. Therefore, transdermal administration of clonidine is a useful therapeutic technology in a long-term management of hypertension.[4–7]

Generally speaking, there are two types of technical systems which have been successfully developed in TDD, that is matrix and reservoir systems. The core of both systems is made of polymeric membranes, which are used to control drug release at a constant rate. It is well known that various polymeric membranes can be classified into three types according to the mechanism of release: (1) hydrophobic, nonporous membranes, such as polydimethylsiloxane and ethylene vinyl acetate copolymer; (2) microporous membranes, such as polypropylene; (3) water-swollen, hydrophilic membranes, such as poly(vinyl alcohol)/poly(acrylic acid) blending membrane.[8–14]

Two new types of polyacrylates membranes were photosynthesized by UV radiation in our laboratory. The first type of membrane was made of 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, and 2-methyl-2-nitropropyl methacrylate. The second type of membrane was made of 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, and 2-butoxyethyl methacrylate. The effects of monomers' ratios, membranes' thicknesses and concentration of drug on the permeation rates were investigated. Considered the properties of permeation and plasticity of membranes, the optimized ratios of monomers were decided. Both optimized membranes were further characterized by FTIR, DSC, and SEM. It was found that both membranes controlled clonidine zero-order release.

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EXPERIMENTAL

Materials

2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, 2-methyl-2-nitropropyl methacrylate, and 2-butoxyethyl methacrylate were purchased from Aldrich (USA). Benzoyl peroxide and clonidine hydrochloride were purchased from National Medicine Corporation (CHN). Acetonitrile and methanol were of HPLC grade. All other chemicals were of reagent grade and used as received.

Synthesis of two new types of copolymer membranes

The first type of membrane was made of three monomers, 2-hydroxy-3-phenoxypropylacrylate(A), 4-hydroxybutyl acrylate(B), and 2-methyl-2-nitropropyl methacrylate(C1). The monomers mixed under different weight ratios, A : B : C1 = 5 : 5 : 0; 4.5 : 4.5 : 1, 4 : 4 : 2, 3.5 : 3.5 : 3, 3 : 3 : 4, 2.5 : 2.5 : 5, 2 : 2 : 6, and 1 : 1 : 8. Photo initiator, benzoyl peroxide (5% w/w), was added to the mixture and stirred to dissolve completely. In this process, no other reagents were added to dissolve monomers and initiator since liquid monomers could dissolve solid initiator completely.

The mixture of monomers and initiator was poured onto stainless steel plates and treated under UV radiation (200–400 nm spectra, 3 kW power) for 4.5 min. The distance from plate to the centre of UV lamps was 12 cm. The membranes formed were carefully removed from the stainless plates with scalpel and stored in distilled water. The thicknesses of membranes were measured at several points by digital micrometer and the mean values were obtained.

According to the similar process of the first type of membrane, the second type of membrane was synthesized except that the monomer C1 was replaced by monomer C2, 2-butoxyethyl methacrylate.

Study of clonidine releasing through the copolymer membranes

The permeation properties of clonidine hydrochloride aqueous solution releasing through two types of membranes were studied using modified Franz cell. The copolymer membranes were clamped between donor cell and receptor cell. The cell provided effective area of 0.785 cm^2. The different concentration of clonidine hydrochloride aqueous solution was used as donor solution; phosphate buffer (pH 7.4) was used as receptor solution. The receptor cell was maintained at 37°C and stirred constantly at 200 rpm. At predetermined time intervals, 200 μL solution was taken from receptor cell and replaced with equal volume of fresh phosphate buffer at 37°C. The cumulative amount of clonidine releasing through the copolymer membrane was analyzed by HPLC.[15–17]

HPLC analysis of clonidine

The HPLC system (Waters, USA) consisted of a 1525 binary pump, a 717 autosampler, and a 2487 dual wavelength UV absorbance detector. Data acquisition and processing were dealt with Waters Empower profession software. Mobile phase was a mixture of buffer solution (1.16 g of D-10-camphorsulfonic acid was dissolved in 1000 mL of 0.1*M* sodium acetate, using of D-10-camphorsulfonic acid would contribute to the peak shape of clonidine in the HPLC graph), acetonitrile and methanol in the volume ratio of 6 : 1 : 1. Mobile phase was adjusted to pH 3.0 with phosphate acid, filtered through a 0.45 μm porosity filter and degassed. The liquid chromatographic system was equipped with a 5 μm, 4.6 × 150 mm C8 column (Agilent XDB) with flow rate at 1 mL min^{-1}. Samples injection volume was 20 μL. The wavelength of UV detector was set at 220 nm.

Data analysis

The cumulative amount (Q_t, μg cm^{-2}) of clonidine releasing through the copolymer membranes were plotted versus time T (h). The slope of the linear portion of the plot was presented as the permeation rate J, (μg cm^{-2} h^{-1}). The intercept on the X-axis was taken as the lag time (T_L, h). All the permeation experiments were repeated three times and their mean values with standard deviation were calculated. The data of permeation rates were subjected to one-way analysis of variance (ANOVA) followed by Tukey's post-test to determine the level of significance among various groups. The data were considered to be significant differences at $P < 0.05$.

FTIR analysis of the copolymer membranes

The FTIR spectra of the copolymer membranes were recorded with an Equnox 55 Fourier-transform infrared spectrometer (Bruker, Germany) by a direct transmission method scanning from 4000 to 400 cm^{-1} at a resolution of 2 cm^{-1}. The membranes must be dried in vacuum before analysis.

Differential scanning calorimeter analysis of the copolymer membranes

The glass transition temperature (T_g) of the copolymer membranes were measured on the Pyris 1 dif-

ferential scanning calorimeter (Perkin-Elmer, USA) at a heating rate of 10.0°C min^{-1} from −60.0 to 120.0°C under nitrogen environment. The membranes must be dried in vacuum before analysis.

Scanning electron microscopy analysis of the copolymer membranes

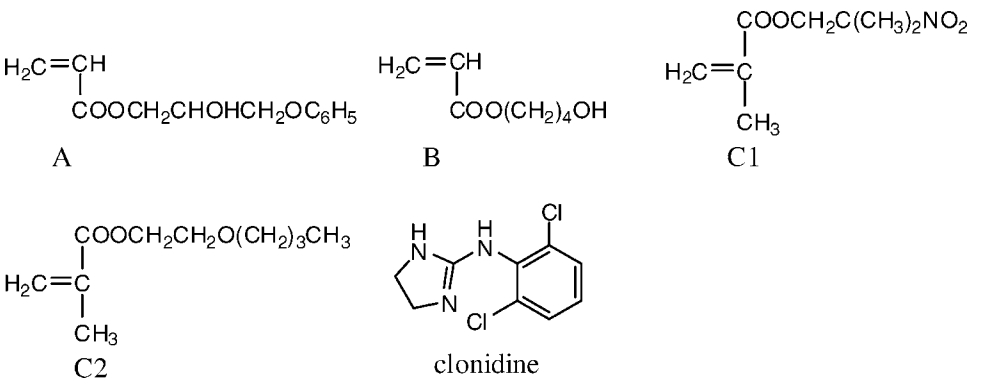
The external morphologies of the copolymer membranes were analyzed using Sirion 200 scanning electron microscopy (Philips, Netherlands) before and after permeation experiments. For SEM analysis, the surfaces of membranes were sputtered with gold in vacuum before viewing under the microscope. The membranes after permeation experiment were washed several times with distilled water to eliminate the residual drug sticking on the surfaces of membranes.

RESULTS AND DISCUSSION

Effects of composition and monomers' ratios on the permeation rates

The concentration of clonidine in donor cell was 3.0 mg mL^{-1}, the thickness of the membrane was 14 μm. The properties of permeation of both copolymer membranes composed of monomers in different ratios were summarized in Tables I and II.

Table I showed that the permeation rates of the first type of membrane increased with monomer C1 feeding. Monomers A and B had hydroxyl groups and long side chains, thus resulting in the compact meshes in the polymer membrane. When monomer C1 was added to polymerized reaction, monomer C1 had short branched chains that contributed to increase the size of meshes in the copolymers. Thus, the size of meshes in the copolymers would increase



with the increase in the ratio of monomer C1, and result in the increase in the permeation rate.

Hydroxyl groups of monomers A and B were helpful to increase plasticity of membrane; thus, the increase in the ratio of monomer C1 would result in the decrease in the plasticity of membrane. It is well known that TDD system required membrane to possess perfect plasticity, including flexibility, and elasticity. Taking into consideration the properties of permeation and plasticity, the first type of membrane made of monomers A, B, C1 in the weight ratio of 4 : 4 : 2 was chosen as the first optimized membrane.

Table II revealed the properties of permeation of the second type of membrane. Take into consideration the properties of permeation and plasticity as similar to the first optimized membrane, the membrane made of monomers A : B : C2 in the weight ratio of 4 : 4 : 2 was chosen as the second optimized membrane.

It was found that the permeation rates of both membranes are linearly dependent on the weight ratio of the monomers C1 and C2, respectively. Figure 1 showed that the variation of the permeation rates with the weight ratio of monomer C1 was greater than that of the monomer C2.

The experiments of clonidine hydrochloride releasing through the membranes had been dealt with

TABLE I
Effects of Monomers' Ratios of the First Type of Membrane on the Permeation Rates

Monomers' ratios A : B : C1	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
5 : 5 : 0	14.701 (0.3418)	0.9922 (0.0016)
4.5 : 4.5 : 1	30.6346 (0.3063)	0.9969 (0.0029)
4 : 4 : 2	43.7423 (0.7814)	0.9961 (0.0012)
3.5 : 3.5 : 3	66.8966 (0.7756)	0.9984 ($9.29*10^{-4}$)
3 : 3 : 4[b]	ND	ND
2.5 : 2.5 : 5[b]	ND	ND
2 : 2 : 6[b]	ND	ND
1 : 1 : 8[b]	ND	ND

[a] The values are presented as mean (S.D.) (n = 3).
[b] The membrane formed was too fragile to perform permeation experiment. ''ND'' stands for ''not determined.''

TABLE II
Effects of Monomers' Ratios of the Second Type of Membranes on the Permeation Rates

Monomers' ratios A : B : C2	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
4 : 4 : 2	34.388 (0.4263)	0.9970 (0.0029)
3.5 : 3.5 : 3	46.428 (0.4401)	0.9938 (0.0080)
3 : 3 : 4	62.3553 (1.0512)	0.9923 (0.0070)
2.5 : 2.5 : 5[b]	ND	ND
2 : 2 : 6[b]	ND	ND
1 : 1 : 8[b]	ND	ND

[a] The values are presented as mean (S.D.) (n = 3).
[b] The membrane formed was too fragile to perform permeation experiment. ''ND'' stands for ''not determined.''

during one day and extended to one week, HPLC analysis of the receptor solution showed that only clonidine peak was detected and no monomers' peaks were detected, which indicated that there were no residual monomers in the membranes. It was significant for the membranes using as controlled release membranes in TDD system without monomers' toxicity and irritant.

Effects of thicknesses of the optimized copolymer membranes on the permeation rates

The first optimized membranes (A : B : C1 = 4 : 4 : 2) with different thicknesses of 14, 20, and 38 μm were synthesized. The effects of thicknesses of the first optimized membrane on the permeation rates were studied. Table III showed that the permeation rates decreased with the increase in thicknesses of the membranes, as expected from Fick's law

TABLE III
Effects of Thickness of the First Optimized Membrane on the Permeation Rates

Membrane thickness (μm)	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
14	43.7423 (0.7814)	0.9961 (0.0012)
20	20.329 (0.7346)	0.9917 (4.50*10^{-4})
38	6.094 (0.0393)	0.9790 (0.0037)

[a] The values are presented as mean (S.D.) (n = 3).

$$J = \frac{1}{A}\frac{dMt}{dt} = P\frac{\Delta C}{L} \quad (1)$$

where $\frac{dMt}{dt}$ is the amount of solute that permeates through the membrane in unit time, A is the permeation area, ΔC is the concentration difference between the donor and receptor side, P is the permeability coefficient, and L is the membrane's thickness.

The permeation rates varied with not only membrane's thickness but also membrane's inner property when the drug released through the membrane. As the inner property of the membrane was different from the properties of drug and receptor layers, a boundary layer developed on either side of the membrane in TDD system. The effect of boundary

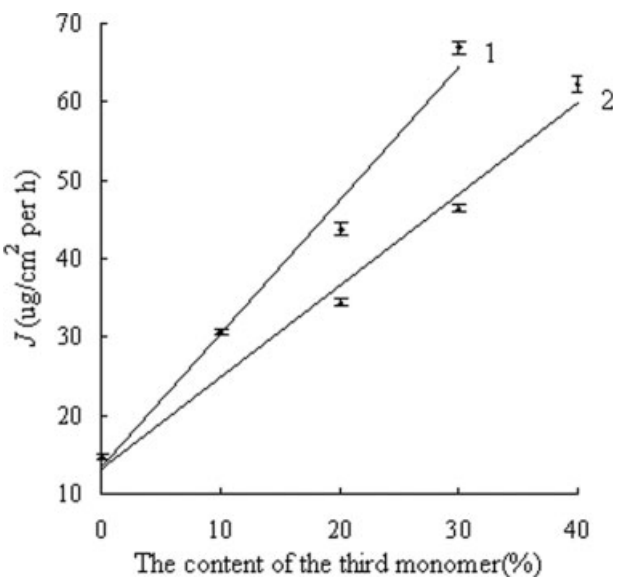


Figure 1 Variation of permeation rates with the contents of monomers: line 1, monomer C1 (correlation coefficient r^2 = 0.9854); line 2, monomer C2 (correlation coefficient r^2 = 0.9866).

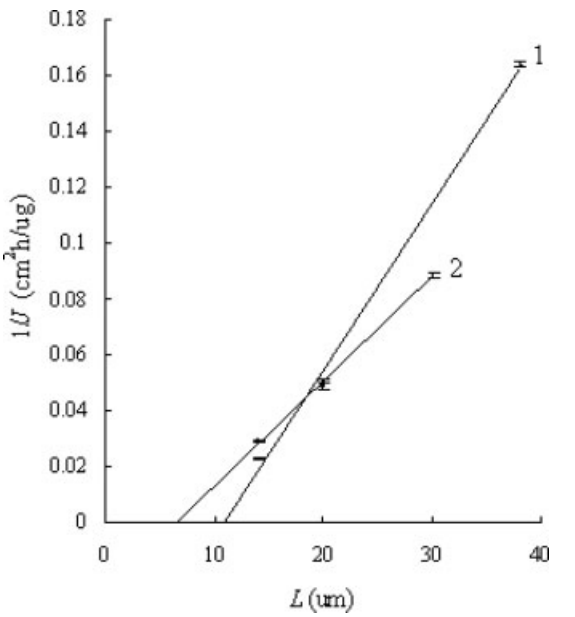


Figure 2 Variation of $1/J$ with thickness of the membranes: line 1, the first optimized membrane, PR_b = 10.88, r^2 = 0.9956; line 2, the second optimized membrane, PR_b = 6.52, r^2 = 0.9972.

TABLE IV
Effects of Thickness of the Second Optimized Membrane on the Permeation Rates

Membrane thickness (μm)	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
14	34.388 (0.4263)	0.9970 (0.0029)
20	20.542 (0.5235)	0.9937 (0.0046)
30	11.2533 (0.1337)	0.9922 (0.0030)

[a] The values are presented as mean (S.D.) (n = 3).

layer resistance on the permeation rate needed to be considered. Eq. (1) can be modified as follows:

$$\frac{1}{J} = \frac{1}{P\Delta C}(L + PR_b) \quad (2)$$

where R_b is the boundary layer resistance.

As reflected from Figure 2, $1/J$ was linearly dependent on L, the intercept on the X-axis was labeled as PR_b. It meant that the desired effect of boundary layer, that is the boundary layer of drug-membrane and the boundary layer of membrane-receptor, had existed.

The effects of different thicknesses (14, 20, and 30 μm) of the second optimized membrane (A : B : C2 = 4 : 4 : 2) on the permeation rates were also studied (Table IV). Figure 2 showed that the value of PR_b of the first optimized membrane was larger than that of the second optimized membrane.

Effects of drug concentration on the permeation rates

The different concentration (0.5, 1.0, 3.0, 5.0, and 7.0 mg mL^{-1}) of clonidine hydrochloride aqueous solution was used as testing drug in the donor cell. The thickness of the first optimized membrane was 14 μm. Table V showed that the permeation rates of the first optimized membrane increased with the increase in the concentration of clonidine. There was almost no occurrence of time lag and burst effect during permeation. This might be attributed to the use of swollen membrane that contained rich hydroxyl groups. The membrane was stored in distilled water until use, so the equilibrium among donor drug, membrane and acceptor solution was instantaneously established.

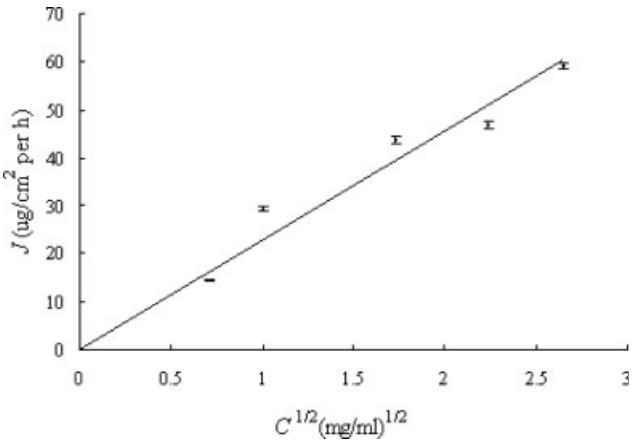


Figure 3 Variation of J with the square root of the drug concentration (correlation coefficient r^2 = 0.9320).

The data of permeation rates and clonidine's concentrations were analyzed, it was found that the permeation rates were proportional to the square root of the concentration of clonidine, and the line passed through the point of origin (Fig. 3). We assumed that the monomer C1, 2-methyl-2-nitropropyl methacrylate, has N=O group, which was hydrophilic; the testing drug, clonidine hydrochloride was dissolved in water; thus, when the drug molecules released through the membrane, the drug molecules had interaction with N=O group of the membranes and resulted in 0.5-order release in the concentration of 0.5–7.0 mg mL^{-1}.

The same permeation experiment was carried out on the second optimized membrane with the thickness of 14 μm. Table VI showed that the permeation rates increased with the concentration of clonidine increasing. Neither time lag nor burst effect was found during permeation. It was found that there were no significant differences in the permeation rates when the concentration of clonidine varied in

TABLE V
Effects of the Concentration of Clonidine on the Permeation Rates through the First Optimized Membrane

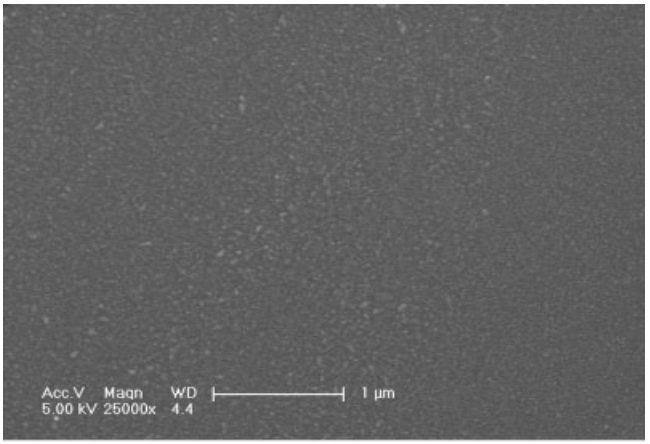
Concentration (mg ml^{-1})	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
0.5	14.5203 (0.1820)	0.9880 (0.0023)
1.0	29.2483 (0.5262)	0.9892 (0.0020)
3.0	43.7423 (0.7814)	0.9961 (0.0012)
5.0	46.8786 (0.7920)	0.9885 (0.0098)
7.0	59.1266 (0.6782)	0.9986 (8.73*10^{-4})

[a] The values are presented as mean (S.D.) (n = 3).

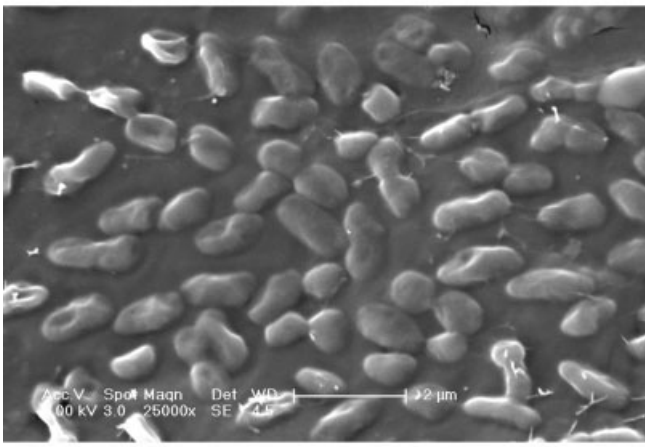
TABLE VI
Effects of the Concentration of Clonidine on the Permeation Rates through the Second Optimized Membrane

Concentration (mg ml^{-1})	Permeation rate, J (μg cm^{-2} h^{-1})[a]	Correlation coefficient (r^2)[a]
0.5	22.842 (0.1568)	0.9945 (0.0022)
1.0	30.247 (0.1938)	0.9980 (9.29*10^{-4})
3.0	34.388 (0.4263)	0.9970 (0.0029)
5.0	34.807 (0.3403)	0.9964 (0.0017)
7.0	47.204 (0.6843)	0.9982 (0.0010)

[a] The values are presented as mean (S.D.) (n = 3).



(a)



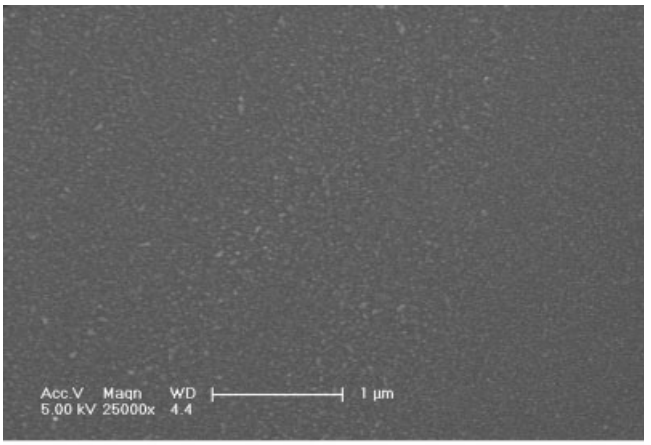
(b)

Figure 4 (a) SEM photograph of the first optimized membrane before permeation experiment (original magnification ×25000). (b) SEM photograph of the first optimized membrane after permeation experiment (original magnification ×25000).

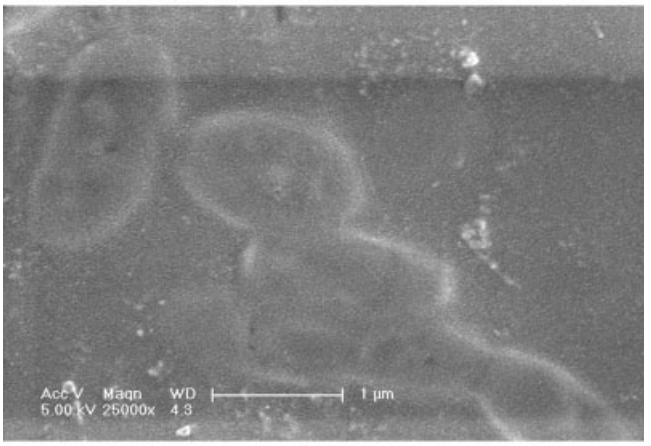
the range of 3.0–5.0 mg mL^{-1} ($P > 0.05$). The possible reason was that drug molecules had interactions with functional groups, such as hydroxyl groups and ester groups, of the membranes. A large number of large and small pores were formed in the membrane when polymerization. When the concentration of drug was below 3.0 mg mL^{-1}, drug molecules have little or no interactions with functional groups of the membrane; thus, drug molecules are released through membranes from small portion of pores in the membrane directly. When the concentration of drug was in the range of 3.0–5.0 mg mL^{-1}, the drug molecules released through the majority pores in the membranes and had interaction with hydrophilic functional groups of the membranes, which retained the drug permeation and led to zero-order release in the concentration of 3.0–5.0 mg mL^{-1}. When the concentration of drug was above 5.0 mg mL^{-1}, the osmotic pressure might overcome the interaction, and drug molecular released from both small and large pores.

Characterization of the optimized copolymer membranes

The FTIR spectra of the first optimized copolymer membrane: 3600–3100 $cm^{-1}(\nu_{OH})$, 2952 $cm^{-1}(\nu_{CH})$, 1598, 1494 and 1456 $cm^{-1}(\nu_{C=C}$, aromatic ring), 758 and 694 $cm^{-1}(\delta_{CH}$, aromatic ring), 1732 $cm^{-1}(\nu_{C=O})$, 1174 and 1244 $cm^{-1}(\nu_{C-O-C})$, 1544 $cm^{-1}(\nu_{N=O})$, 1047 $cm^{-1}(\nu_{C-OH})$. The FTIR of the second optimized copolymer membrane: 3600–3100 $cm^{-1}(\nu_{OH})$, 2954 $cm^{-1}(\nu_{CH})$, 1598, 1496, and 1454 $cm^{-1}(\nu_{C=C}$, aromatic ring), 752 and 694 $cm^{-1}(\delta_{CH}$, aromatic ring), 1733 $cm^{-1}(\nu_{C=O})$, 1174 and 1245 $cm^{-1}(\nu_{C-O-C})$, 1047 $cm^{-1}(\nu_{C-OH})$. We found that the FTIR spectra of both optimized membranes were similar except that



(a)



(b)

Figure 5 (a) SEM photograph of the second optimized membrane before permeation experiment (original magnification ×25000). (b) SEM photograph of the second optimized membrane after permeation experiment (original magnification ×25000).

the first optimized copolymer membrane had the peak at 1544 cm^{-1} which belonged to the N=O stretching in monomer C1.

In the DSC thermogram, the value of glass transition temperature (T_g) of the first optimized membrane was 21.4°C. The T_g value of the second optimized membrane was 4.2°C. These two low T_g values indicated that both of the optimized membranes had strong effects of plasticity, and in accordance with the soft appearances of the membranes.

The SEM photographs of the first optimized membranes before drug permeation experiment showed that the structure of the membrane was homogeneously dense and had no visual pores. The SEM photographs of the first optimized membranes after drug permeation experiment showed a sponge-like, cellular surface (Fig. 4). This result indicated that the drug penetrated through the membrane indeed. The SEM photographs of the second optimized membranes before and after drug permeation experiments were similar to the first optimized membrane (Fig. 5).

CONCLUSIONS

Two new types of membranes controlling clonidine zero-order release were synthesized by UV curing. The first membrane was made of three monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, and 2-methyl-2-nitropropyl methacrylate. The compositions of the second membrane were similar to the first membrane except that the third monomer was replaced by 2-butoxyethyl methacrylate. The permeation rates of both membranes were proportional to the content of the third monomer. The optimized membranes, with good plasticity and perfect permeation, were obtained when three monomers were in the weight ratio of 4:4:2. The permeation rates of the first optimized membrane were proportional to the square root of the concentration of clonidine. The permeation rates of the second optimized membrane were constant when the concentration of clonidine was in the range of 3.0–5.0 mg mL^{-1}. The SEM studies proved that both optimized membranes had a spongy-like structure and drug really released through the membranes. The DSC studies proved that both optimized membranes were soft, and are good candidates for controlled release in TDD. More copolymer membranes are currently under investigation, and the UV curing method might be a new technology for the synthesis of TDD controlled release membranes.

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