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Short communication

A new poly(2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, diethyl maleate) membrane controlled clonidine linear release in the transdermal drug delivery system

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Abstract

Oral clonidine, used as an antihypertensive, can result in some side effects such as dry mouth, drowsiness, dizziness and sedation; thus, clonidine transdermal drug delivery (TDD) was considered. Use of the controlled release membrane was one of the methods in TDD systems to regulate the permeation properties. A new type of copolymer membrane that controlled clonidine linear release in TDD system was synthesized by UV radiation. This membrane consisted of three monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and diethyl maleate. The membrane had both fine permeation properties and perfect physical properties when three monomers were in the weight ratio of 4:4:2; this type of membrane was chosen as an optimized membrane. It was found that the membrane controlled clonidine zero-order release, the permeation rates decreased with the thicknesses of membranes increasing, and the permeation rates were linearly dependent on the square root of the concentration of clonidine. Furthermore, the optimized membranes were characterized by FTIR, DSC and SEM.

Keywords: Transdermal drug delivery (TDD); UV radiation; Clonidine; Controlled release membrane; Polyacrylates

1. Introduction

Oral administration of clonidine, used as an antihypertensive, might result in some adverse effects, including dry mouth, drowsiness, dizziness, constipation and sedation etc. Clonidine is a relatively small molecule with high potency, and a short half-life; thus, a clonidine transdermal drug delivery (TDD) system was considered [1–4].

In conventional medications, such as oral delivery and injection, only the total mass of drug delivered to a patient is controlled. In controlled drug delivery, both the mass and the rate at which the drug is delivered can be controlled. TDD used as

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one of controlled drug delivery systems has many advantages over traditional drug delivery administrations, such as improved systemic bioavailability of the pharmaceutical active ingredients, reduced dose frequency, longer duration of therapeutic action, reduced side effects and the controlled, constant drug delivery profiles [5–7].

In controlled drug delivery systems a membrane is used to moderate the rate of delivery of drug to the body. Generally, there were two types of devices in TDD, matrix and reservoir [8–14]. In the reservoir device the membrane controls permeation of the drug from a reservoir to achieve the drug delivery rate required. In the matrix device the drug is impregnated into the membrane material, and then the drug crosses a membrane by the osmotic pressure produced by the diffusion of water. The membrane in a controlled drug deliver system is called a controlled release membrane. This present study was concerned the controlled release membrane. The microporous membranes reported in the literature [15,16] were used as controlled release membranes, such as polypropylene, polytetrafluoroethylene, polycarbonates, polyvinylchloride, cellulose acetate, cellulose nitrate and polyacrylonitrile. These microporous membranes had similar properties, including porosities from about 0.1 to 0.85, tortuosities from 1 to 10, and thicknesses from 10^{-3} to 10^{-2} cm. The ethylene-vinyl acetate (EVA) membrane was another type of controlled release membranes in controlled drug delivery systems, where an increased content of vinyl acetate comonomers in EVA membrane increased the drug release rate [17–20].

Although various types of controlled release membranes exist, the properties of these membranes were limited and the applications in the transdermal delivery system were also limited. Here we will report a new type of polyacrylates membrane synthesized by UV curing method in our laboratory. Three monomers, 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and diethyl maleate, mixed with photo initiator, benzoyl peroxide, were treated under strong power UV radiation to synthesize the copolymer membrane. The effects of monomers' ratios, membranes' thicknesses and drug concentration on the permeation properties were investigated. Furthermore the membranes were characterized by FTIR, DSC and SEM. The results showed that this new type of membrane could control clonidine zero-order release in the transdermal drug delivery system.

2. Materials and methods

2.1. Materials

2-Hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and diethyl maleate 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.

2.2. Synthesis of copolymer membrane

Three monomers: 2-hydroxy-3-phenoxypropylacrylate (A), 4-hydroxybutyl acrylate (B) and diethyl maleate (C), were mixed in the ratios of which listed in Table 1. Photo initiator, benzoyl peroxide (5% w/w) was added to the mixture and stirred to dissolve completely. In this process, no other solvents were added to dissolve monomers and initiator because liquid monomers could dissolve solid initiator completely.

The mixture was poured onto a stainless steel flat plate and treated under UV radiation for 4.5 min (UV spectrum: 200–400 nm, Power: 3 kW). The distance from the plate to UV lamp was 12 cm. The membranes formed were carefully removed from the plate with scalpel. The membranes were washed with distilled water repeatedly for the purpose of elimination of unused monomers and initiator, and then stored in distilled water. The thicknesses of the membranes were measured at several points by digital micrometer, and the mean values were calculated.

Table 1
Effects of the ratios of monomers on the permeation rates

Monomers ratios A:B:C	Permeation rate J ($\mu g/cm^2$ per h)[b]	Correlation coefficient (r^2)[b]
5:5:0	14.701 (0.3418)	0.9922 (0.00168)
4.5:4.5:1	15.897 (0.0699)	0.9662 (0.01646)
4:4:2	62.430 (0.1636)	0.9984 ($9.291 * 10^{-4}$)
3.5:3.5:3	39.886 (0.5680)	0.9963 (0.00278)
3:3:4	34.961 (0.2780)	0.9921 (0.00227)
2.5:2.5:5	31.047 (0.5326)	0.9962 (0.00343)
2:2:6[a]	ND	ND
1:1:8[a]	ND	ND

[a] The membrane formed was too fragile to perform permeation experiments. "ND" stands for "not determined".
[b] The values are presented as Mean (SD) ($n = 3$).

2.3. Study of clonidine permeation through the copolymer membrane

The permeation properties of clonidine hydrochloride aqueous solution releasing through the copolymer membrane were studied using modified Franz diffusion cell. The copolymer membranes were clamped between donor cell and receptor cell. The cell provided effective area of 0.785 cm^2. Phosphate buffer (pH 7.4) was used as receptor solution. 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. The cumulative amount of clonidine releasing through the copolymer membrane was analyzed by HPLC.

2.4. HPLC analysis of clonidine

The HPLC system (Waters, USA) consisted of a 1525 binary HPLC pump, a 717 plus autosampler and a 2487 dual wavelength UV absorbance detector. Data acquisition and processing was dealt with Waters Empower profession software. Mobile phase was a mixture of buffer solution (1.16 g of D-10-camphorsulfonic acid dissolved in 1000 ml of 0.1 M sodium acetate), acetonitrile and methanol in the volume ratio of 6:1:1, and was adjusted to pH 3.0 with phosphate acid. The liquid chromatograph was equipped with a 5 μm, 4.6×150 mm C8 column (Agilent XDB) with flow rate at 1 ml/min. Samples injection volume was 20 μl. The wavelength of UV detector was set at 220 nm.

2.5. Data analysis

The cumulative amount (Q_t, μg/cm^2) of clonidine releasing through the copolymer membranes was plotted versus time (T, h). The slope of the linear portion of the plot was presented as the permeation rate (J, μg/cm^2 per h). The intercept on the X-axis was taken as the lag time (T_L, h). All the permeation experiments were repeated three times and mean values of the permeation rates 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 $p < 0.05$.

2.6. FTIR analysis of the copolymer membrane

The FTIR spectrum of the copolymer membrane 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 membrane was dried in vacuum before analysis.

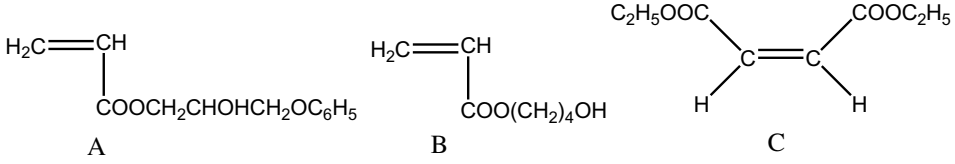
2.7. Differential scanning calorimeter (DSC) analysis of the copolymer membrane

The glass transition temperature (T_g) of the copolymer membrane was measured on the Pyris 1 differential scanning calorimeter (Perkin–Elmer, USA) at a heating rate of 10.0 °C/min from −60.0 to 120.0 °C under nitrogen environment. The membrane must be dried in vacuum before analysis.

2.8. Scanning electron microscopy (SEM) analysis of copolymer membrane

The external morphology of the copolymer membrane was analyzed before and after drug permeation using Sirion 200 scanning electron microscopy (Philips, Netherlands). For SEM analysis, the surface of the copolymer membrane was sputtered with gold in vacuum before viewing under the microscope. The membrane after permeation experiment was washed several times with distilled water for the purpose of elimination of the drug sticking on the surface of the membrane.

3. Results and discussion



3.1. Effects of monomers' ratios on the permeation rates

Membranes made of monomers in the ratios listed in Table 1 were synthesized by UV radiation. The thickness of the membrane formed was 14 μm. The concentration of clonidine was 3.0 mg/ml in the donor cell. Table 1 shows that the permeation rates increased with the increase in the content of monomer C for up to 20%. However, the permeation rates decreased with further increases in the content of monomer C over 20%.

The reason why the permeation rates increased initially was that the monomer C was fed into the mixture. Monomers A and B had hydroxyl groups and long linear chains. The compact meshes in the polymer membranes were formed when monomers A and B were fed into the polymerized reaction. Monomer C had short branched chains that were helpful in increasing the size of the mesh and resulted in the permeation rate increasing at the beginning.

As we know hydroxyl groups contribute to plasticity of membrane and plasticity has some advantages for the controlled release membrane, including reducing the brittleness, improving flow, imparting flexibility, increasing toughness and strength, resisting tearing and impacting. In a word, plasticity is of benefit drug permeation. Monomer C lacks hydroxyl groups and has a cis-structure. Its cis-structure made the membrane rigid when the content of monomer C was over 20%, which would decrease the plasticity and result in the permeation rates decreasing.

For above-mentioned reasons, the membrane made of monomers in the ratio of A:B:C = 4:4:2 had both fine permeation properties and perfect plasticity, this type of membrane was chosen as an optimized membrane for further characterization.

Moreover, permeation properties were studied for one day and extended to one week, HPLC analysis discovered that no monomers' peaks were detected. It showed that there were no residual monomers in the copolymer membrane.

3.2. Effects of the optimized copolymer membrane's thickness on the permeation rates

The optimized copolymer membranes (A:B:C = 4:4:2) with different thickness (14, 20 and 36 μm) were synthesized. The concentration of clonidine was 3.0 mg/ml in the donor cell. Table 2 showed that the permeation rates decreased with the increase in the thicknesses of the optimized membranes, as expected from Fick's law

Table 2
Effects of the thickness of the optimized membrane on the permeation rates

Membrane thickness (μm)	Permeation rate J (μg/cm^2 per h)[a]	Correlation coefficient (r^2)[a]
14	62.430 (0.1636)	0.9984 ($9.291 * 10^{-4}$)
20	28.326 (0.9536)	0.9958 (0.00278)
36	9.203 (0.2871)	0.9745 (0.00307)

[a] The values are presented as Mean (SD) ($n = 3$).

$$J = \frac{1}{A}\frac{\mathrm{d}Mt}{\mathrm{d}t} = P\frac{\Delta C}{L}, \tag{1}$$

where J is the permeation rate, $\mathrm{d}Mt/\mathrm{d}t$ is the amount of solute that permeates through the membrane in unit time, A is the permeation area, ΔC is the concentration difference between donor and receptor sides, P is the permeability coefficient, and L is the membrane's thickness.

Because the drug releasing through the membrane in vitro in the transdermal drug delivery system was controlled by diffusion, the permeation rate varied with both membrane's thickness and membrane's inner property. The effect of thickness of the membrane on the permeation rate was studied. 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 the TDD system when the membrane was contacted with drug and receptor layers and held tightly. Eq. (1) can be modified to Eq. (2), as follows:

$$\frac{1}{J} = \frac{1}{P\Delta C}(L + PR_{\mathrm{b}}) \tag{2}$$

where R_{b} is taken as the boundary layer resistance.

As reflected from Fig. 1, $1/J$ was linearly dependent on L, the intercept on the X-axis was taken as

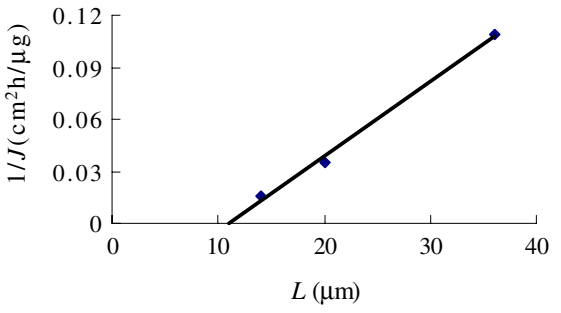


Fig. 1. Variation of $1/J$ with thickness (L) of the optimized membrane ($r^2 = 0.9953$).

PR_b, and the value of PR_b was 10.86. This value meant that the desired effect of boundary layer, i.e. the boundary layer of drug-membrane and the boundary layer of membrane-receptor, had occurred.

3.3. Effects of drug concentration on the permeation rates

The concentration of clonidine in the donor cell was 0.5, 1.0, 3.0, 5.0 and 7.0 mg/ml, respectively. The optimized copolymer membranes (A:B:C = 4:4:2) with the same thickness (14 μm) were synthesized. Table 3 depicted that the permeation rates increased with the increase in the concentration of clonidine, and there was almost no occurrence of time lag and burst effect. This might be attributed to the use of swollen membrane that contained rich hydroxyl groups and had been stored in distilled water until use. The equilibrium seemed to be instantaneously established.

The data of permeation rates and clonidine concentration were analyzed, it was found that the permeation rates were proportional to the square root of the drug concentration, and the line passed through the point of origin (Fig. 2). This relationship between permeation rates and clonidine concentration was similar to Higuchi's model which assumed the permeation rates decreased in proportion to the square root of time. We assumed that partial amount of the drug with 7.0 mg/ml in the donor cell impregnated into the membrane and diffused from the membrane at first, the drug in the donor cell became exhausted and the concentration of drug reduced to 5.0 mg/ml. Then the drug with 5.0 mg/ml impregnated into the membrane and diffused from the membrane too, further resulted in the concentration of drug in the donor cell lowered to 3.0 mg/ml. Drug with other concentration, including 1.0 and 0.5 mg/ml, diffusion from the membrane repeated the above process. Thus, although the permeation rates of drug with different concentrations were by no means constant, the permeation rates could be easily varied by incorporating more or less drug.

Table 3
Effects of the concentration of clonidine on the permeation rates

Concentration (mg/ml)	Permeation rate J (μg/cm^2 per h)[a]	Correlation coefficient (r^2)[a]
0.5	16.693 (0.2425)	0.9915 (0.0031)
1.0	38.157 (0.4614)	0.9985 (0.00165)
3.0	62.430 (0.1636)	0.9984 ($9.291 * 10^{-4}$)
5.0	90.164 (0.4991)	0.9969 ($9.609 * 10^{-4}$)
7.0	103.623 (0.8032)	0.9963 ($9.073 * 10^{-4}$)

[a] The values are presented as Mean (SD) ($n = 3$).

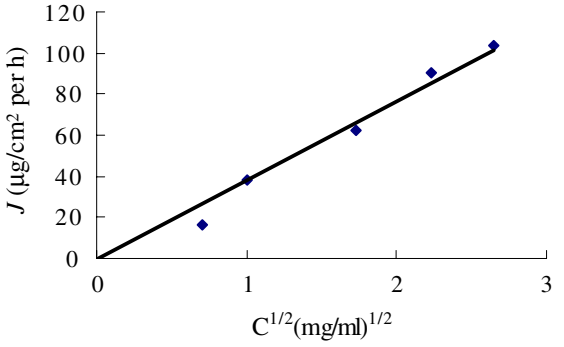


Fig. 2. Variation of J with the square root of the concentration ($r^2 = 0.9711$).

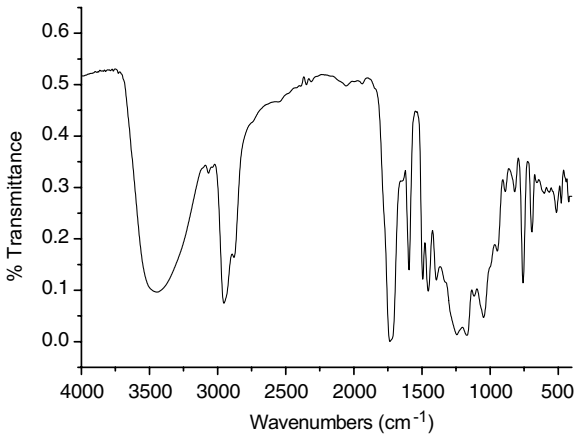


Fig. 3. FTIR of the optimized copolymer membrane.

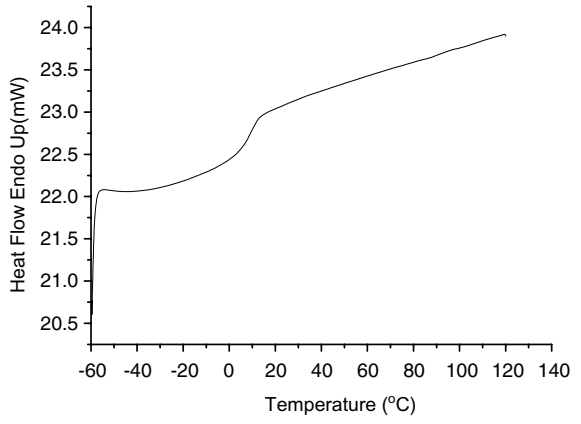


Fig. 4. DSC characterization of the optimized copolymer membrane.

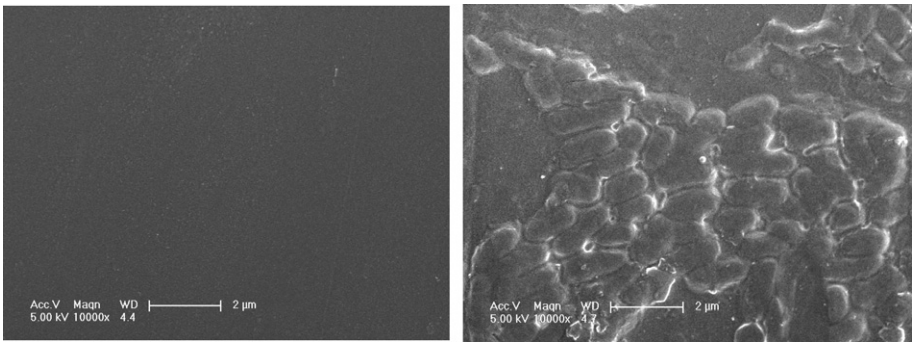


Fig. 5. Left: SEM photograph of the optimized copolymer membrane before drug permeation (original magnification 10000×). Right: SEM photograph of the optimized copolymer membrane after drug permeation (original magnification 10000×).

3.4. Characterization of the optimized copolymer membrane

In the FTIR spectrum, peaks at the 3600–3100 cm^{-1} region were due to the OH stretching, 2952 cm^{-1} was due to the CH stretching, and the peaks at 1595, 1494, 1454, 758 and 692 cm^{-1} were originated from the aromatic ring. The very strong peak at 1735 cm^{-1} was due to the C=O stretching in acrylate, the less intense peaks at 1170 and 1244 cm^{-1} were designated to the C–O–C stretching in acrylate, 1047 cm^{-1} was due to the C–O(H) stretching (Fig. 3).

In the DSC thermogram, the glass transition temperature (T_g) was 8.8 °C, this low value indicated that the membrane had strong effect of plasticity, and in accordance with soft appearance of the membrane (Fig. 4).

The SEM photograph of the membrane before drug permeation showed that the surface of the membrane was homogeneously dense and had no visual pores. The SEM photograph of the membrane after drug permeation showed a sponge-like, cellular surface (Fig. 5). This result indicated that the drug penetrated through the membrane indeed.

4. Conclusions

A new type of membrane controlling clonidine zero-order release was synthesized by UV curing. This membrane was made of three monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and diethyl maleate. All of the membranes made of monomers in the different ratios could control clonidine zero-order release. When the above-mentioned monomers were in the ratio of 4:4:2, the membrane had both fine permeation property and perfect plasticity; thus, this type of copolymer membrane was chosen as an optimized membrane. The permeation rates were proportional to the square root of concentration of clonidine when an optimized membrane was used. The permeation rates decreased with the increase in the thicknesses of membranes. SEM analysis showed that the surface of the membrane had been changed because of clonidine permeation. DSC analysis reflected that the membrane had fine plasticity and might become a candidate as controlled release membrane because of its soft appearance. More copolymer membranes are under investigation in our laboratory. It is possible that this new type of membranes could be employed as controlled release membranes in transdermal drug delivery systems.

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