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European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 429–434
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Poly(2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, dibutyl maleate) membrane controlled clonidine zero-order release

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Received 14 February 2006; accepted in revised form 8 November 2006
Available online 19 November 2006

Abstract

Poly(2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate, dibutyl maleate) membrane was synthesized by UV curing method in our laboratory for the first time. When above-mentioned monomers were in the weight ratio of 4:4:2, the membrane not only had perfect permeation property but also had excellent plasticity, so the membrane made from monomers in the ratio of 4:4:2 was chosen as an optimized membrane. The optimized membrane provided perfect linear permeation properties in clonidine transdermal drug delivery system. The permeation rate decreased in proportion to the thickness of membrane. When the concentrations of clonidine were in the range of 0.5–7.0 mg/ml, the permeation rate was proportional to the square root of clonidine concentrations. The optimized membrane was characterized by FTIR, DSC and SEM.

Keywords: Transdermal drug delivery systems; UV curing; Clonidine; Controlled release membranes; Polyacrylates

1. Introduction

Clonidine is a widely used antihypertensive drug. Oral administration of clonidine may cause many adverse effects, such as dry mouth, drowsiness, dizziness, constipation and sedation. Clonidine has small molecular structure, low blood drug level and high potency, so clonidine administered transdermally was considered [1–4].

The advantages of transdermal drug delivery include avoidance of first-pass gastrointestinal and hepatic metabolism, the potential for enhanced efficacy and/or decreased side effects resulting from improved delivery kinetics of lower total doses, and superior patient compliance because of decreased dosing frequency. Therefore there has been an increased interest in the transdermal drug delivery system in recent years, which is an efficient and profitable drug administration [5–7].

Generally speaking, there are several types of technical systems which have been successfully developed in transdermal drug delivery, such as matrix and reservoir systems [8–17]. In reservoir system, an inert membrane encloses the drug to be released; the drug diffuses through the membrane at a finite, controlled rate. The membrane is so-called controlled release membrane. The present study concerns the controlled release membrane. As reported in patents and the famous clonidine patch named Catapres-TTS [18,19], there were microporous membranes that controlled the constant dosage rate in the system. These microporous membranes might be formed from polymers such as polypropylene, polytetrafluoroethylene, polycarbonates, polyvinylchloride, cellulose acetate, cellulose nitrate and polyacrylonitrile. These microporous membranes had porosities from about 0.1 to 0.85, tortuosities from 1 to 10 and thicknesses from 10^{-3} to 10^{-2} cm.

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doi:10.1016/j.ejpb.2006.11.005

The types of microporous membranes were various, but the properties of membranes were limited and the applications in the transdermal delivery system were limited. Our laboratory hoped other types of membranes were synthesized to enrich the membrane controlled system. A new type of polyacrylate membrane was synthesized by UV curing method in our laboratory. Three monomers' mixture, 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and dibutyl maleate mixed with initiator benzoyl peroxide, was cured by strong power UV ray to synthesize the copolymer membrane. The effects of monomers' ratios, membrane thicknesses and drug concentrations on the permeation properties were investigated. Furthermore, the membrane was characterized by FTIR, DSC and SEM. It was found 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 dibutyl maleate were purchased from Aldrich (USA). Three monomers must be purified by vacuum distillation before UV curing in order to eliminate the effect of inhibitors on photosynthesis. 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 the copolymer membrane

Three monomers: 2-hydroxy-3-phenoxypropylacrylate(A), 4-hydroxybutyl acrylate(B) and dibutyl maleate(C), were mixed in different ratios as 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 since liquid monomers could dissolve solid initiator completely.

The mixed solution in different monomers' ratios was poured onto a stainless steel flat plate and treated under UV ray for 4.5 min (UV spectrum: 200–400 nm, 3000 W). The distance from plate to UV lamps 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, then stored in distilled water. The thicknesses of the membranes were measured at several points by digital micrometer, and the mean values and standard deviation were calculated.

2.3. Study of clonidine release through copolymer membrane

The permeation properties of clonidine hydrochloride aqueous solution through copolymer membrane were studied using vertical glass diffusion cells (modified Franz 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 the receptor cell and replaced with equal volume of fresh phosphate buffer at 37 °C. The cumulative amount of clonidine released through the copolymer membrane was analyzed by HPLC.

2.4. Study of sorption water experiments of copolymer membranes

The copolymer membranes were stored in distilled water for one week. The weight of the membrane absorbing water completely was measured after water covering on the surface of the membrane was absorbed gently by filter paper. Then the membrane was dried in vacuum oven for 72 h at 80 °C. The weight of the dried membrane was measured. The value of the sorption water rate was calculated as per the following equation

$$R = \frac{W_s - W_d}{W_d} \times 100$$

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

Monomers ratios A:B:C	Permeation rate (J, μg/cm^2/h)[b]	Correlation coefficient (r^2)[b]	Sorption water rates (%)[b]
5:5:0	14.701 (0.3418)	0.9922 (0.0016)	3.044 (0.076)
4.5:4.5:1	33.636 (0.5400)	0.9984 (5.13×10^{-4})	2.182 (0.061)
4:4:2	56.825 (0.6909)	0.9961 (0.0033)	2.034 (0.071)
3.5:3.5:3	35.104 (0.7178)	0.9995 (2.08×10^{-4})	1.825 (0.063)
3:3:4	34.804 (0.7798)	0.9956 (0.0055)	1.124 (0.043)
2.5:2.5:5	26.382 (0.5882)	0.9916 (0.0053)	0.467 (0.020)
2:2:6[a]	ND	ND	ND
1:1:8[a]	ND	ND	ND

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

where R is the sorption water rate, W_s is the weight of the membrane absorbing water and W_d is the weight of dried membrane.

2.5. 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. Sample injection volume was 20 μl. The wavelength of UV detector was set at 220 nm.

2.6. Data analysis

The cumulative amount (Q_t, μg/cm^2) of clonidine released through the copolymer membrane 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/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 their mean value with standard deviation was calculated. The data of permeation rate 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 $p < 0.05$.

2.7. FTIR analysis of copolymer membrane

The FTIR spectra 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 membranes were dried in vacuum before analysis.

2.8. Differential scanning calorimetric (DSC) analysis of 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.

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

The external morphology of the copolymer membrane was analyzed before and after permeation experiment using Sirion 200 scanning electron microscope (Philips, Netherlands). For SEM analysis, the surfaces of corresponding membrane were sputtered with gold in vacuum before viewing under the microscope. The membranes after permeation experiment were washed several times by distilled water.

3. Results and discussion

3.1. Effects of monomers' ratios on the permeation rates

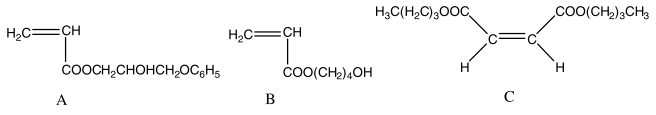
Membranes made from monomers in different ratios were synthesized by UV radiation. All of the membranes' thicknesses were 14 μm. The concentration of clonidine was 3.0 mg/ml in donor cell. The permeation rates of membranes with different composition are summarized in Table 1. The results showed that the permeation rates increased with the increase in the content of monomer C up to 20%. When the content of monomer C was over 20%, the permeation rates decreased with the increase in the content of monomer C. Moreover, there were no significant differences when the ratios of monomers A, B and C were 4.5:4.5:1, 3.5:3.5:3 and 3:3:4.

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

It was known that hydroxyl groups contributed to plasticity of membrane and plasticity contributed to drug permeation. Monomer C was lacking a hydroxyl group and was of *cis*-structure. When the content of monomer C was over 20%, its *cis*-structure made the membrane rigid which would decrease the plasticity and result in the permeation rates decreasing. Table 1 shows that the sorption water rates of the copolymer membranes decreased with the monomer C content increasing.

For above reasons, the membrane with the ratio of A:B:C = 4:4:2 not only had fine permeation properties but also had excellent plasticity, and was chosen as optimized membrane for further experiments.

Permeation properties were studied during one day and extended to one week, HPLC analysis results discovered that no monomers' peaks were detected. It showed that there were no residual monomers in the copolymer membrane. So the copolymer membrane was safe to skin without monomers' toxicity and irritant.



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

The optimized copolymer membranes (A:B:C = 4:4:2) with different thicknesses (14, 20 and 26 μm) were synthesized. The concentration of clonidine was 3.0 mg/ml in the donor cell. The effects of the thickness of the optimized membranes on the permeation rates were studied. Table 2 shows that the permeation rates decreased with the increase in the thickness, as expected from Fick's law

$$J = \frac{1}{A}\frac{\mathrm{d}Mt}{\mathrm{d}t} = P\frac{\Delta C}{L} \quad (1)$$

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, and ΔC is the concentration difference between donor and receptor sides, P is the permeability coefficient and L is the membrane 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 thickness and membrane inner property. As the membrane inner property was different from the properties of drug and receptor layers, a boundary layer developed on either side of the membrane in the system when the membrane was contacted tightly with drug and receptor layers. Eq. (1) can be modified to Eq. (2), as follows:

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

where R_{b} is described 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 PR_{b}, and the value of PR_{b} was 10.02. This value meant that the effect of boundary layer, i.e., the boundary layer of drug-membrane and the boundary layer of membrane receptor, was observed.

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

Membrane thickness (μm)[a]	Permeation rate (J, μg/cm^2/h)[a]	Correlation coefficient (r^2)[a]
14 (0.2241)	56.825 (0.6909)	0.9961 (0.0033)
20 (0.2832)	24.612 (0.5287)	0.9919 (0.0110)
26 (0.1634)	14.681 (0.1850)	0.9835 (0.0085)

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

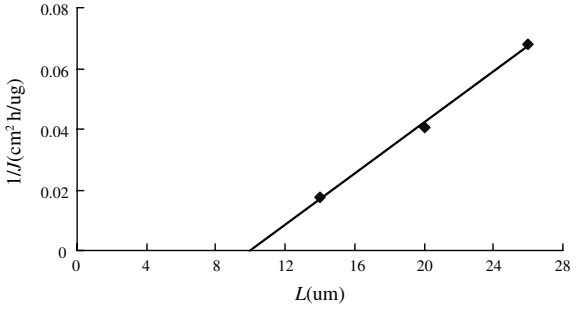


Fig. 1. Variation of $1/J$ with thickness of the optimized membrane ($r^2 = 0.9974$).

3.3. Effects of drug concentration on the permeation rates

The concentration of clonidine in 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 depicts 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 because the membrane containing many hydroxyl groups was stored in distilled water until use, and the equilibrium seemed to be instantaneously established.

The reason why 0.5 mg/ml clonidine was chosen as the lowest tested concentration was that the concentration of clonidine in the blood varied between 0.1 and 15 ng/ml, usually between 0.2 and 3 ng/ml, depending upon the person being treated [18]. In order to maintain the concentration of clonidine in the blood at a therapeutic level, substantially constant rates varied between 0.1 and 100 μg/h, usually between 0.2 and 70 μg/h. When the concentration of clonidine was 0.5 mg/ml in the present study, the permeation rate was 21.874 μg/cm^2 h. The value of the effective permeation area was 0.785 cm^2, so the constant rate was 17.17 μg/h just locating in the range of 0.2–70 μg/h. Taking into consideration the difference between drug solution and drug reservoir, the permeation rates in the drug reservoir were slower than the permeation rates in the drug solution. Higher concentrations of the drug in the solution, i.e., in the range of 1.0–7.0 mg/ml, were studied.

The data of permeation rates and clonidine concentrations were analyzed. It was found out 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 concentrations was alike Higuchi's model which assumed the permeation rates decreased in proportion to the square root of time; thus, we assumed that the drug with high concentration, such as 7.0 mg/ml, dissolved in the polymer and diffused from the polymer. When the concentration of 7.0 mg/ml became exhausted, the concentration became low, such as 5.0 mg/ml, and the drug with low concentration began to be depleted. Other lower

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

Concentration (mg/ml)	Permeation rate (J, μg/cm^2/h)[a]	Correlation coefficient (r^2)[a]
0.5	21.874 (0.3000)	0.9917 (0.0012)
1.0	33.992 (0.2040)	0.9927 (0.0056)
3.0	56.825 (0.6909)	0.9961 (0.0033)
5.0	65.388 (0.4195)	0.9974 (0.0023)
7.0	90.339 (0.8854)	0.9951 (0.0034)

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

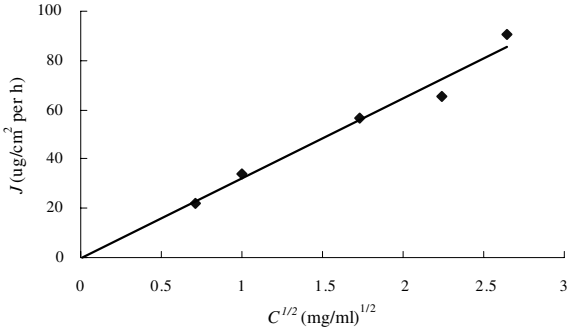


Fig. 2. Variation of J with the square root of the concentration ($r^2 = 0.9740$).

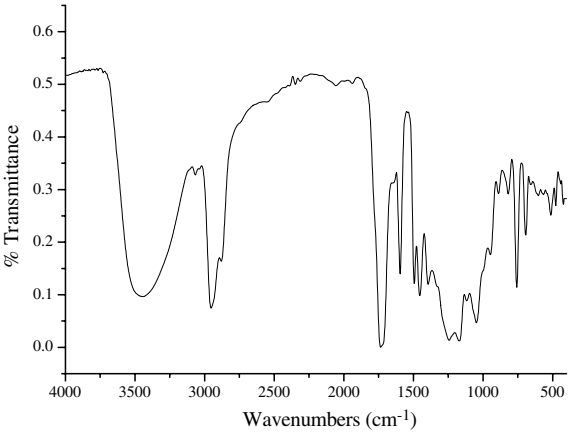


Fig. 3. FTIR of the optimized copolymer membrane.

concentrations of drug in the range of 3.0–0.5 mg/ml varied as the above process. Thus, although the permeation rates with different concentrations of drug were by no means constant, the permeation rates could be easily varied by incorporating more or less drug.

3.4. Characterization of optimized copolymer membrane

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

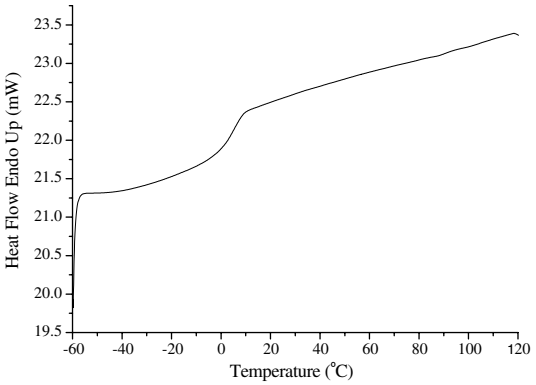


Fig. 4. DSC characterization on the optimized copolymer membrane.

In DSC thermogram, the glass transition temperature (T_g) was 4.4 °C, this low value indicated that the membrane had a strong plasticizing effect, and accorded with the membrane's soft appearance (Fig. 4).

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

4. Conclusions

A new type of membrane was photosynthesized by UV radiation in our laboratory. The membrane was made from three monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and dibutyl maleate. When the membrane was made from different ratios of monomers, all of the membranes with different compositions could

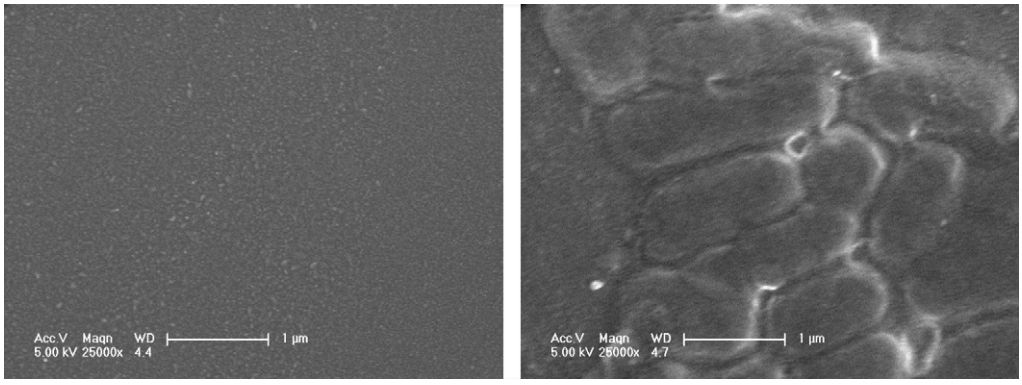


Fig. 5. Left: SEM photograph of the optimized membrane before drug release experiment (original magnification 25,000×). Right: SEM photograph of the optimized membrane after drug release experiment (original magnification 25,000×).

control clonidine zero-order release. When three monomers listed above are in the ratio of 4:4:2, the synthesized copolymer membrane was chosen as an optimized membrane because of its fine permeation and plasticity properties. This optimized membrane was similar to the microporous membrane reported in the literature on the aspect of the release properties, such as constant dosage release. However this synthesized membrane had more advantages than microporous membrane. This synthesized membrane could change the ratios of compositions and the thicknesses of membranes to achieve different permeation rates, and the permeation rates were linearly dependent on the square root of the concentrations of clonidine. The SEM studies showed that the membrane had spongy formation and clonidine released through the membrane. The membrane also showed fine physical properties from the DSC study. This new type of membrane was hopeful to be used as controlled release membranes in the transdermal drug delivery system.

Acknowledgements

The authors are highly thankful for the support of School of Pharmacy, and Analysis and Testing Centre at Shanghai Jiaotong University.

References

[1] D. Schenk, W. Fischer, Transdermal systems for the release of clonidine, U.S. Patent 2004208917 (2004).
[2] P. Huber, W. Fischer, Transdermal systems for the delivery of clonidine, U.S. Patent 2004028726 (2004).
[3] P. Huber, K.T. Bostedt, Transdermal system for the administration of clonidine, Eur. Patent 1103260 (2001).
[4] X.L. Gong, X.H. Lei, Compound transdermal nicotine–clonidine paster for giving up smoking, C.N. Patent 1,239,656 (1999).
[5] R. Langer, Transdermal drug delivery: past progress, current status, and future prospects, Adv. Drug Deliv. Rev. 56 (2004) 557–558.
[6] B.J. Thomas, B.C. Finnin, The transdermal revolution, Drug Discov. Today 9 (2004) 697–703.
[7] A. Naik, Y.N. Kalia, R.H. Guy, Transdermal drug delivery: overcoming the skin's barrier function, Pharm. Sci. Technol. Today 3 (2000) 318–326.
[8] Y.S.R. Krishnaiah, V. Satyanarayana, P. Bhaskar, Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers, Int. J. Pharm. 247 (2002) 91–102.
[9] V.S. Mare, P.V. Bharti, P.R. Vavia, Acrylate terpolymer in fabrication of medicated skin patches, Polym. Adv. Tech. 14 (2003) 466–474.
[10] C. Valenta, B.G. Auner, The use of polymers for dermal and transdermal delivery, Eur. J. Pharm. Biopharm. 58 (2004) 279–289.
[11] O. Sanli, G. Asman, Release of diclofenac through gluteraldehyde crosslinked poly(vinyl alcohol)/poly(acrylic acid) alloy membrane, J. Appl. Polym. Sci. 91 (2004) 72–77.
[12] S.C. Shin, J. Kim, M.K. Yoon, I.J. Oh, J.S. Choi, Transdermal delivery of triprolidine using TPX polymer membrane, Int. J. Pharm. 235 (2002) 141–147.
[13] D.N. Tipre, P.R. Vavia, Acrylate-based pressure sensitive adhesive in fabrication of transdermal therapeutic system, Polym. Adv. Technol. 14 (2003) 502–507.
[14] A.N.L. Rocha, T.N.C. Dantas, J.L.C. Fonseca, M.R. Pereira, Permeation of drugs in chitosan membranes, J. Appl. Polym. Sci. 84 (2002) 44–49.
[15] S.C. Shin, S.Y. Byun, Controlled release of ethinylestradiol from ethylene-vinyl acetate membrane, Int. J. Pharm. 137 (1996) 95–102.
[16] S.C. Shin, C.W. Cho, I.J. Oh, Enhanced efficacy by percutaneous absorption of piroxicam from the poloxamer gel in rats, Int. J. Pharm. 193 (2000) 213–218.
[17] S.C. Shin, M.K. Yoon, Application of TPX polymer membranes for the controlled release of triprolidine, Int. J. Pharm. 232 (2002) 131–137.
[18] S.K. Chandrasekaran, S. Darda, A.S. Michaels, G.W. Cleary, Therapeutic system for administering clonidine transdermally, U.S. Patent 4,201,211 (1980).
[19] J. Urquhart, S.K. Chandrasekaran, J.E. Shaw, Bandage for transdermally administering scopolamine to prevent nausea, U.S. Patent 4,031,894 (1977).