Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 322 (2006) 1–5
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Rapid communication

# A new copolymer membrane controlling clonidine linear release in a transdermal drug delivery system

Xiaoping Zhan, Guochun Tang, Sijing Chen, Zhenmin Mao *

*School of Pharmacy, Shanghai Jiaotong University, Shanghai 200240, China*

Received 5 January 2006; received in revised form 16 May 2006; accepted 17 May 2006
Available online 22 May 2006

**Abstract**

A new type of copolymer membranes was prepared through photosynthesis of mixtures of three different monomers. The membranes present a linear permeation property in clonidine transdermal drug delivery system. Monomers used in the photosynthesis were 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and *sec*-butyl tiglate. Permeation property of the membranes with different monomer ratios and thickness were investigated. When clonidine concentrations were in 3.0–5.0 mg/ml range, membranes showed near zero order permeation rates. An optimized membrane was characterized by FTIR, DSC and SEM.


*Keywords:* Transdermal drug delivery system (TDDs); Photosynthesis; Clonidine; Controlled release membrane; Polyacrylates

## 1. Introduction

Transdermal drug delivery systems, in comparison to conventional pharmaceutical dosage forms, offer many advantages, including improved systemic bioavailability of active pharmaceutical ingredients, fewer administration frequency, longer duration of therapeutic action, reduction of side effects and steady drug delivery profile, etc. In recent years, there has been an increased interest in controlled transdermal drug delivery systems, as a new approach for drug administration (Langer, 2004; Thomas and Finnin, 2004; Naik et al., 2000).

Clonidine is a widely used antihypertensive drug. Its relatively small molecule and high potency make it an ideal candidate for study of transdermal drug delivery systems. Oral administration of clonidine may cause some side effects, such as dry mouth, drowsiness, dizziness, constipation and sedation. By using transdermal drug delivery systems, it is found to be able to reduce some of its side effects, minimizing concentration fluctuation and maintaining a steady blood drug concentration over a prolonged period of time (Schenk and Fischer, 2004; Huber and Fischer, 2004; Huber and Bostedt, 2001; Gong and Lei, 1999).

Several technologies have been developed and used in transdermal drug delivery systems. The use of controlled release membranes is one of the methods to regulate drug release. In such transdermal drug delivery systems, the controlling factor of drug permeation is an inert polymer membrane. However, only few types of polymers, such as microporous polypropylene membrane and ethylene vinyl acetate copolymer membrane have been successfully used in membrane controlled transdermal drug delivery systems (Claudia and Barbara, 2004; Krishnaiah et al., 2002; Mare et al., 2003; Valenta and Auner, 2004; Sanli and Asman, 2004; Shin et al., 2002; Tipre and Vavia, 2003). In our lab, a new type of polyacrylates polymer was synthesized by UV curing method and studied in membrane controlled drug release systems. In this method, membranes were photosynthesized by UV radiation of mixtures of three acrylate monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and *sec*-butyl tiglate in different ratios with photo initiator, benzoyl peroxide. The effects of monomers' ratios, membranes thicknesses and clonidine concentration on the membrane permeation rates were investigated. The membranes were characterized by FTIR, DSC, SEM. It was found that the new type of membranes could control clonidine linear release in the transdermal drug delivery systems.

* Corresponding author. Tel.: +86 2134204796; fax: +86 2134204050.
*E-mail addresses:* zmmao@sjtu.edu.cn, sjtupharmacy@yahoo.com (Z. Mao).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.05.031

## 2. Materials and methods

### 2.1. Materials

2-Hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and *sec*-butyl tiglate were purchased from Aldrich (USA). Benzoyl peroxide and clonidine hydrochloride were purchased from National Medicine Corporation (CHN). Acetonitrile and methanol were HPLC grade. All other chemicals were reagent grade and used as received.

### 2.2. Synthesis of copolymer membranes

Three monomers, 2-hydroxy-3-phenoxypropylacrylate (**A**), 4-hydroxybutyl acrylate (**B**) and *sec*-butyl tiglate (**C**) were mixed in the ratios of **A**:**B** = 5:5; **A**:**B**:**C** = 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, then photo initiator, benzoyl peroxide (5%, w/w) was added to the mixtures and stirred to dissolve completely. In this process, no other solvents were needed to dissolve monomers and photo initiator since liquid monomers usually could dissolve solid initiator completely.

The mixed solution was poured onto stainless steel plates and treated under UV radiation for 4 min (UV spectrum: 200–400 nm, 3000 W). The distance between plates and UV lamp was 12 cm. The membranes formed were then carefully removed from the stainless plates with scalpel and stored in distilled water. The thicknesses of the membranes were measured at several points by digital micrometer, and the mean values were calculated.

### 2.3. Study of clonidine permeation through copolymer membranes

The permeation properties of the copolymer membranes with clonidine hydrochloride aqueous solution were studied using the modified Keshary–Chien cell (Chien, 1987). The copolymer membranes were clamped between the donor cell and receptor cell. The cell has an effective area of 0.785 $cm^2$. Phosphate buffer (pH 7.4) was used as receptor solution. The receptor cell filled with the buffer solution 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. The cumulative amounts of clonidine released from the donor cell were analyzed by HPLC (Shin and Byun, 1996; Shin et al., 2000; Shin and Yoon, 2002).

### 2.4. HPLC analysis of clonidine

The HPLC system (Waters, USA) was consisted of a 1525 binary HPLC pump, a 717 plus 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 a buffer solution (1.16 g of D-10-camphorsulfonic acid dissolved in 1000 ml of 0.1 M sodium acetate):acetonitrile:methanol (6:1:1), and was adjusted to pH 3.0 with phosphate acid. The liquid chromatography was equipped with a 5 μm, 4.6 mm × 150 mm C8 column (Angilent XDB) with flow rate at 1 ml/min. Sample injection volume was 20 μl. The wavelength of UV detector was set at 220 nm.

### 2.5. Data analysis

The cumulative amount ($Q_t$, μg/$cm^2$) of clonidine permeated through the copolymer membrane was plotted as a function of time ($T$, h). The slope of the linear portion of the plot was represented as the permeation rate ($J$, μg/$cm^2$/h). All the membrane 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 between various groups. The data were considered to be significant differences at $p < 0.05$.

### 2.6. 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 were dried in vacuum before analysis.

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

The glass transition temperature ($T_g$) of the copolymer membranes was measured on a Pyris 1 differential scanning calorimeter (Perkin-Elmer, USA) at a heating rate of 10.00 °C/min from −60.00 to 120.00 °C under nitrogen environment. The membranes must be dried in vacuum before analysis.

### 2.8. Scanning electron microscopy (SEM) analysis of the copolymer membranes

The external morphology of the copolymer membranes was analyzed before and after the drug permeation experiment using a Sirion 200 scanning electron microscopy (Philips, Netherlands). For SEM analysis, the surfaces of corresponding membranes 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 different monomer ratios on the permeation rates

Membranes were synthesized by UV radiation with different monomers and with different monomer ratios. Permeation properties of those membranes were summarized in Table 1. Monomers **A** and **B** have hydroxyl groups and long linear chains. When polymerized, these monomers would result in compact mesh in polymer. Hydroxyl groups and linear chains in the monomers would also give good plasticity to the membranes. Monomer **C** has short, but branched chain that would increase

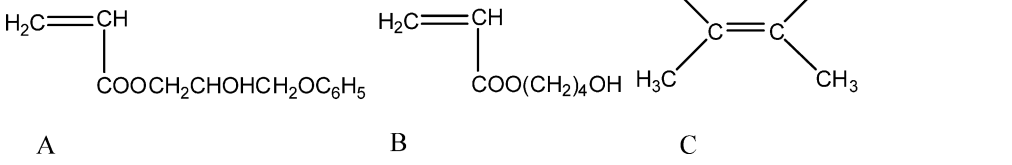
Table 1
Effects of monomers ratios on the clonidine permeation rates

| Monomers ratios | Permeation rate ($\mu g/cm^2/h$) ($n=3$)[a] | Correlation coefficient ($r^2$) ($n=3$)[a] |
|---|---|---|
| **A**:**B** = 5:5 | 14.701 (0.3418) | 0.9922 (0.0016) |
| **A**:**B**:**C** = 4.5:4.5:1 | 30.242 (0.5129) | 0.9953 (0.0033) |
| **A**:**B**:**C** = 4:4:2 | 38.738 (0.0182) | 0.9985 (0.0011) |
| **A**:**B**:**C** = 3.5:3.5:3 | 38.984 (0.2290) | 0.9907 (0.0062) |
| **A**:**B**:**C** = 3:3:4 | 42.659 (0.4834) | 0.9947 (0.0040) |
| **A**:**B**:**C** = 2.5:2.5:5 | 55.468 (0.1521) | 0.9925 (0.0096) |
| **A**:**B**:**C** = 2:2:6 | 58.039 (0.8527) | 0.9965 (0.0045) |
| **A**:**B**:**C** = 1:1:8[b] | None | None |

*Note*: The clonidine concentration in the donor cell was 3.0 mg/ml. The thickness of copolymer membranes was 14 μm.
[a] The values are represented as mean (S.D.).
[b] The membrane formed was too fragile to perform permeation experiment.

the mesh size in polymers. Increasing content of monomer **C** would increase pore size in copolymer membrane, in general. This would increase the permeation rate of membrane as observed in the experiments. However, it would also decrease plasticity of the membranes. Taking into consideration of permeation property and plasticity, membrane with monomer ratios of **A**, **B** and **C** (4:4:2) was chosen as optimized copolymer membrane for further experiments.

Moreover, HPLC analysis showed that only clonidine peak was detected and no monomers' peaks were detected in the permeation experiment over 24 h, which indicated that there was no monomers remained in the copolymer membranes. This might suggest that copolymer membranes would be safe in use regarding to the possible toxicity and irritation related to the monomers.




A B C

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

Membranes (**A**:**B**:**C** = 4:4:2) with different thickness (14, 20 and 26 μm) were synthesized and used to determine the thickness effect on drug permeation rates. The results were listed in Table 2. It was clear that as the thickness of the membranes increased, the permeation rate of the membranes decreased, as excepted from Fick's law. To study the boundary layer effects in

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

| Membrane thickness (μm) | Permeation rate ($J$, $\mu g/cm^2/h$) ($n=3$)[a] | Correlation coefficient ($r^2$) ($n=3$)[a] |
|---|---|---|
| 14 | 38.738 (0.0182) | 0.9985 (0.0011) |
| 20 | 11.202 (0.3980) | 0.9816 (0.0114) |
| 26 | 6.5522 (0.3604) | 0.9850 (0.0071) |

*Note*: The ratio of monomers **A**, **B** and **C** was 4:4:2. The clonidine concentration in the donor cell was 3.0 mg/ml.
[a] The values are represented as mean (S.D.).

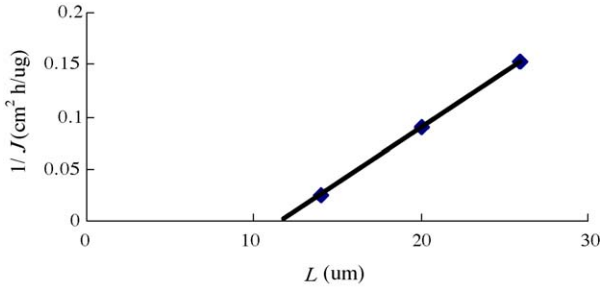



Fig. 1. Variation of $1/J$ with thickness ($L$) of the membrane, the intercept on the $X$-axis was taken as $PR_b = 11.54$ (correlation coefficient $r^2 = 1$), this indicated that the effect of a boundary layer was occurred.

permeability measurements, permeation rate ($J$) of the copolymer membranes at different thickness was determined according to the equation derived from Fick's law of diffusion, which can be expressed as

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

where $dM_t/dt$ is the amount of solute that permeates through the membrane in unit time, $A$ the permeation area, $\Delta C$ the concentration difference between the donor layer and receptor side, $P$ the permeability coefficient, and $L$ is the membrane thickness. In systems where a boundary layer develops on either side of the membrane, effective thickness of the membrane increases and the flux will be decreased. 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 Fig. 1. $1/J$ was linearly dependent on $L$, the intercept on the $X$-axis was taken as $PR_b$. This indicated that the effect of a boundary layer was occurred.

### 3.3. Effects of the drug concentration on the permeation rates

Clonidine solutions in different concentrations (0.5, 1.0, 3.0, 5.0 and 7.0 mg/ml) were used to determine the effects of drug concentration on the permeation rates. Membranes made from three different monomers of **A**, **B** and **C** in a ratio of 4:4:2 were employed. The thickness of the membranes was 14 μm. Permeation data (Table 3) showed that the permeation rates increased with the increasing of the clonidine concentration up to 3.0 mg/ml. But in the clonidine concentration range from 3.0 to 5.0 mg/ml, there was no significant increasing of the permeation rates ($p > 0.05$). The permeation

Table 3
Effects of the drug concentration on the permeation rates

| Clonidine concentration (mg/ml) | Permeation rate ($J$, $\mu g/cm^2/h$) ($n=3$)[a] | Correlation coefficient ($r^2$) ($n=3$)[a] |
|---|---|---|
| 0.5 | 16.258 (0.5249) | 0.9958 (0.0016) |
| 1.0 | 28.499 (0.5182) | 0.9905 (0.0063) |
| 3.0 | 38.738 (0.0182) | 0.9985 (0.0011) |
| 5.0 | 39.149 (0.2496) | 0.9966 (0.0026) |
| 7.0 | 48.239 (0.6184) | 0.9968 ($9.07 \times 10^{-4}$) |

*Note*: The ratio of monomers **A**, **B** and **C** was 4:4:2. The thickness of the copolymer membranes was 14 μm.
[a] The values are represented as mean (S.D.).

rates increased again when clonidine concentration was over 5.0 mg/ml. The increase of permeation rates when clonidine concentration below 3.0 mg/ml may be the results of that most of drug molecules passed the membranes through small portion of large pores existed in the membranes. In this case, drug molecules have little or no interactions with the functional groups of the membranes when passed through the membranes. When the drug concentrations were between 3.0 and 5.0 mg/ml, the clonidine molecules passed through the majority pores of the membranes and had interaction with the functional groups of the copolymers. Hydrophilic function groups of the membranes, such as hydroxyl and ether groups, might retain the drug passage and led to the zero order permeation rates in this drug concentration range. When the clonidine concentration was above 5.0 mg/ml, high osmotic pressure might prevail over the interactions between the membranes' functional groups and the clonidine molecules. This might explain the increasing of the permeation rates again above 5.0 mg/ml. No time lag and burst effect were observed in all clonidine concentrations. The absence of the time lag might indicate that equilibrium between the drug solution and the membrane was established instantaneously.

### 3.4. Characterization of optimized copolymer membrane

Membrane made from three different monomers of **A**, **B** and **C** in a ratio of 4:4:2 was characterized. 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, peaks at 1598, 1494, 1454, 758, and 694 $cm^{-1}$ were originated from the aromatic ring, the very strong peak at 1730 $cm^{-1}$ was due to the C=O stretching in acrylate, the less intense peaks at 1170, 1245 $cm^{-1}$ were designated to the C–O–C stretching in acrylate, 1045 $cm^{-1}$ was due to the C–O(H) stretching (Fig. 2).

In DSC thermogram, the glass transition temperature ($T_g$) value of membrane was 26.515 °C (Fig. 3), this low $T_g$ value indicated that the membrane had a good plasticizing effect, and in accordance with the membrane's soft appearance.

The SEM photograph of the membrane before drug permeation experiment showed that the membrane structure was homogeneously dense and had no visual pores (Fig. 4). The SEM photograph of the membrane after drug permeation experiment showed the formation of sponge and cellular surface. This result indicated that the hydrophilic clonidine hydrochloride dif-

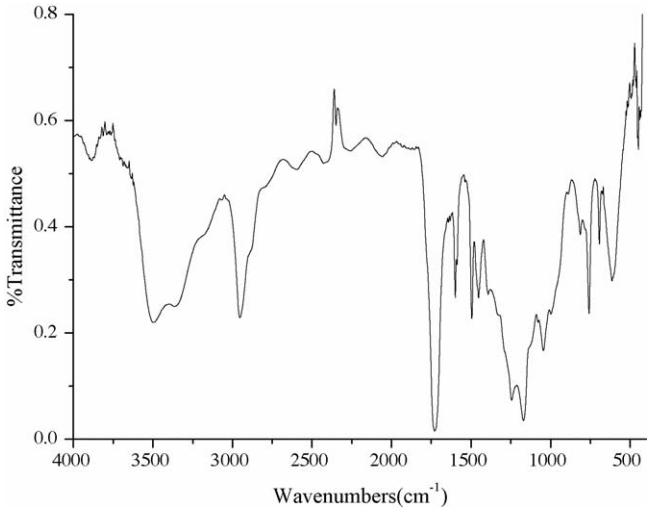



Fig. 2. FTIR of the optimized copolymer membrane, 3600–3100 $cm^{-1}$ (νOH), 2952 $cm^{-1}$ (νCH), 1598, 1494, 1454, 758 and 694 $cm^{-1}$ (νCH, aromatic ring). 1730 $cm^{-1}$ (νC=O), 1170 and 1245 $cm^{-1}$ (νC–O–C), 1045 $cm^{-1}$(νC–OH).

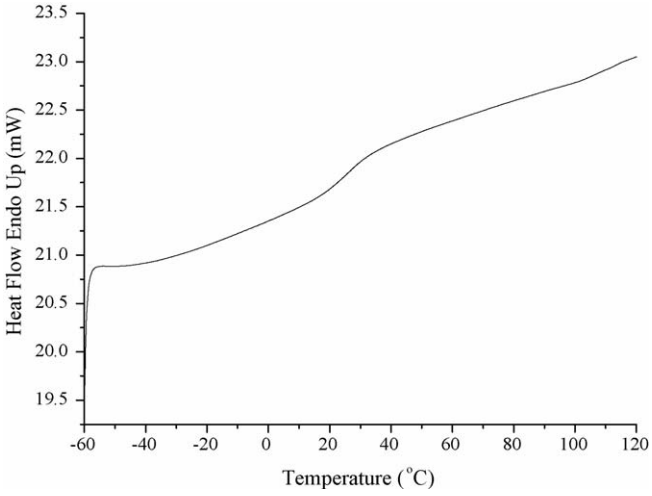



Fig. 3. DSC characterization on the optimized copolymer membrane, $T_g = 26.515$ °C.

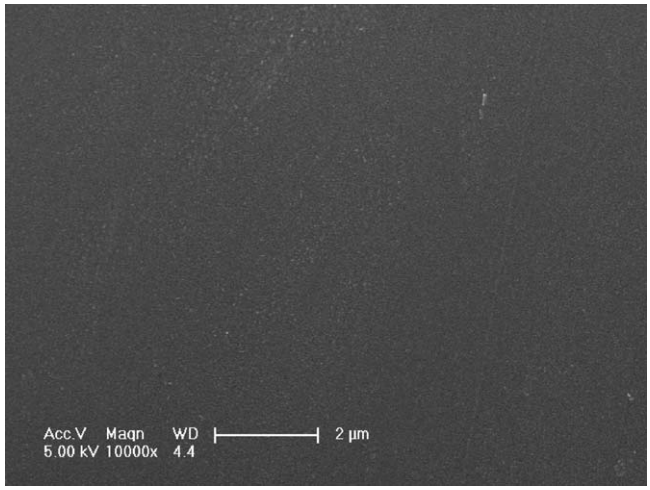



Fig. 4. SEM photograph of the optimized copolymer membrane before drug permeation experiment, the membrane surface structure was homogeneous and there were no visual pores (original magnification 10,000×).

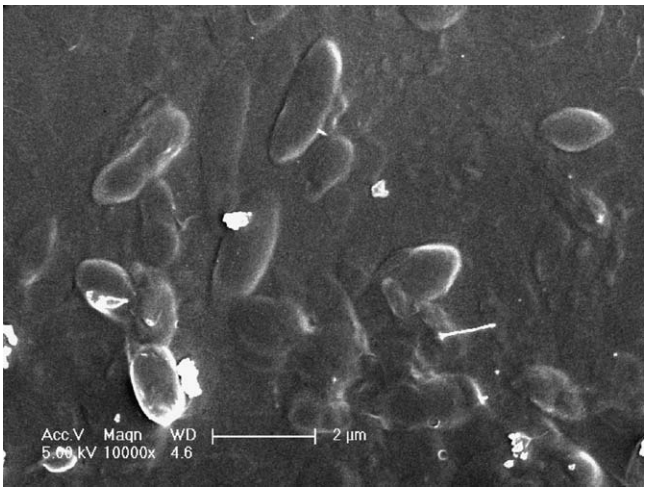



Fig. 5. SEM photograph of the optimized copolymer membrane after drug permeation experiment. The membrane surface was spongy and cellular (original magnification 10,000×).

fused in the swollen membrane during permeation experiment (Fig. 5).

## 4. Conclusion

Membrane plays an important role in membrane controlled transdermal drug delivery systems. Permeation property of the membrane directly affects TDDs' efficiency. Membrane preparation using photosynthesis could offer a new approach in searching new types of membranes with permeation property optimized to each individual drug. With this method, polymers synthesized with different monomers in different ratios could be easily prepared and used in membrane preparation. Therefore, a large number of membranes with different monomers in different ratios could be prepared and tested using targeted drug in short period. In this study, membranes made from three different monomers of **A**, **B** and **C** in a ratio of 4:4:2 were found to have interesting permeation property. When using clonidine as testing drug, the permeation rate increased as thickness of membranes decreased. The permeation rate increased in general, when clonidine concentration increased. But when clonidine concentration was in 3–5 mg/ml range, the permeation rates kept constant. The SEM study proved that the membrane could have spongy formation and clonidine could pass through the membrane. The membrane also showed good physical property. More copolymer membranes are currently under investigation, it is possible that this new type of membranes could be employed as controlled release membranes in transdermal drug delivery systems.

## Acknowledgments

Authors would like to express our appreciation for the support from School of Pharmacy, and the Analysis and Testing Centre at Shanghai Jiao Tong University.

## References

Chien, Y.W., 1987. Transdermal Controlled Systemic Medications. Marcel Dekker, New York, pp. 132–137.
Claudia, V., Barbara, G.A., 2004. The use of polymers for dermal and transdermal delivery. Eur. J. Pharm. Biopharm. 58, 279–289.
Gong, X.L., Lei, X.H., 1999. Compound transdermal nicotine–clonidine paster for giving up smoking. CN Patent 1239656.
Huber, P., Bostedt, K.T., 2001. Transdermal system for the administration of clonidine. EP Patent 1103260.
Huber, P., Fischer, W., 2004. Transdermal systems for the delivery of clonidine. US Patent 2004028726.
Krishnaiah, Y.S.R., Satyanarayana, V., Bhaskar, P., 2002. Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers. Int. J. Pharm. 247, 91–102.
Langer, R., 2004. Transdermal drug delivery: past progress, current status, and future prospects. Adv. Drug Deliv. Rev. 56, 557–558.
Mare, V.S., Bharti, P.V., Vavia, P.R., 2003. Acrylate terpolymer in fabrication of medicated skin patches. Polym. Adv. Technol. 14, 466–474.
Naik, A., Kalia, Y.N., Guy, R.H., 2000. Transdermal drug delivery: overcoming the skin's barrier function. Pharm. Sci. Technol. Today 3, 318–326.
Sanli, O., Asman, G., 2004. Release of diclofenac through gluteraldehyde crosslinked poly(vinyl alcohol)/poly(acrylic acid) alloy membrane. J. Appl. Polym. Sci. 91, 72–77.
Schenk, D., Fischer, W., 2004. Transdermal systems for the release of clonidine. US Patent 2004208917.
Shin, S.C., Byun, S.Y., 1996. Controlled release of ethinylestradiol from ethylene-vinyl acetate membrane. Int. J. Pharm. 137, 95–102.
Shin, S.C., Cho, C.W., Oh, I.J., 2000. Enhanced efficacy by percutaneous absorption of piroxicam from the poloxamer gel in rats. Int. J. Pharm. 193, 213–218.
Shin, S.C., Kim, J., Yoon, M.K., Oh, I.J., Choi, J.S., 2002. Transdermal delivery of triprolidine using TPX polymer membrane. Int. J. Pharm. 235, 141–147.
Shin, S.C., Yoon, M.K., 2002. Application of TPX polymer membranes for the controlled release of triprolidine. Int. J. Pharm. 232, 131–137.
Thomas, B.J., Finnin, B.C., 2004. The transdermal revolution. Drug Discov. Today 9, 697–703.
Tipre, D.N., Vavia, P.R., 2003. Acrylate-based pressure sensitive adhesive in fabrication of transdermal therapeutic system. Polym. Adv. Technol. 14, 502–507.
Valenta, C., Auner, B.G., 2004. The use of polymers for dermal and transdermal delivery. Eur. J. Pharm. Biopharm. 58, 279–289.