MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 1, pp. 71–78, 2003

RESEARCH PAPER

Acrylate-Based Transdermal Therapeutic System of Nitrendipine

Dnyanesh N. Tipre and Pradeep R. Vavia*

University Department of Chemical Technology, Pharmaceutical Division, University of Mumbai, Matunga, Mumbai, India

ABSTRACT

The objective of the present research investigation was to fabricate an acrylate-based transdermal therapeutic system (TTS) of nitrendipine, which could deliver drug at maximum input rate so as to deliver drug in minimum patch size. Transdermal patches were fabricated using synthesized acrylate pressure-sensitive adhesives (PSAs): PSA1, PSA2, and commercially available PSA3 and PSA4 using *d*-limonene as permeation enhancer. Effect of concentration of *d*-limonene on permeation kinetics of nitrendipine in PSAs was studied. Fabricated TTS in mentioned PSAs were evaluated for in-vitro release and permeation kinetics through guinea-pig skin. Cumulative release of drug in PSA1, PSA2, PSA3, and PSA4 was observed to be 45%, 40%, 25%, and 25%, respectively, upto 24 hr. Flux of drug through guinea-pig skin calculated at 48 hr in PSA1, PSA2, PSA3, and PSA4, with and without *d*-limonene, was observed to be 0.346 ± 0.10, 0.435 ± 0.17, 0.410 ± 0.17, and 0.162 ± 0.06, and 0.625 ± 0.19, 1.161 ± 0.46, 0.506 ± 0.17, and 0.520 ± 0.18 ($\mu g/cm^2/hr$), respectively. The TTS in PSA2 showed comparatively high flux and could deliver drug at high input rate through transdermal route. PSA2 was found to have good rate-controlling property and could be successfully employed in transdermal delivery of nitrendipine.

Key Words: Nitrendipine; Transdermal patch; *d*-Limonene; Pressure-sensitive adhesives.

INTRODUCTION

Nitrendipine,[1] a calcium entry-blocker, effectively reduces blood pressure when given orally at doses of 5–20 mg/day. It is reported to be well absorbed following oral administration, but undergoes extensive first-pass metabolism; the absolute oral bioavailability is reported to range from 10% to 20%.[2] In view of the physicochemical and pharmacokinetic characteristics of nitrendipine, e.g., small oral dose, low molecular weight, good lipid solubility, and an extensive first-pass effect, it seems that there is potential for investigating the ability of nitrendipine to permeate human epidermis.

*Correspondence: Pradeep R. Vavia, University Department of Chemical Technology, Pharmaceutical Division, University of Mumbai, Matunga, Mumbai, 400 919, India; Fax: 91-22-414 56 14; E-mail: prv@pharma.udct.ernet.in.

DOI: 10.1081/DDC-120016685
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

A previous study that reported on nitrendipine transdermal therapeutic system (TTS) involved fabrication of nitrendipine patches in a polyisobutylene matrix using Azone® as permeation enhancer.[3] As acrylate pressure-sensitive adhesive (PSA) has gained wide commercial acceptance, attempts were made to fabricate TTS in acrylate PSA. It is well known that the flux and diffusion coefficient of drugs through the stratum corneum can be increased with transdermal penetration enhancers due to their ability to change the structure of lipophilic and/or keratinized domains in stratum corneum.[4] In the present study, *d*-limonene was incorporated as permeation enhancer, which is as effective as Azone® for improving flux of lipophilic drugs like nitrendipine.[5]

The objective of the present research investigations was to inspect suitability of synthesized and commercially available acrylate polymers in transdermal delivery of nitrendipine using *d*-limonene as permeation enhancer.

MATERIALS AND METHODS

Materials

Nitrendipine was supplied by Concept Pharmaceutical Ltd. (Aurangabad, India). *d*-Limonene, 2-Ethylhexyl acrylate (EHA), methyl mathacrylate (MMA), acrylic acid (AA), and vinyl acetate (VA) were purchased from Merck (Schuchardt, Germany). 2,2′-Azo-*bis*-isobutyronitrile (AIBN) was supplied by John Baker Inc. Scotchpak® No. 1006 and No. 1022 were gifted by 3M Corp. (MN). PRS-Permacel® (PSA3) gifted by Permacel (Mumbai, India). Polygrip adhesive® (PSA4) gifted by Ancher adhesives (Mumbai, India). Ethyl acetate (AR), methanol, acetonitrile, and tetrahydrofuran of HPLC grade were purchased from Ranbaxy Laboratory (New Delhi, India). All other chemicals used were of analytical grade.

Methods

Synthesis of PSA1 and PSA2

EHA, MMA, AA, and VA were purified from inhibitors by monomer purification method.[6] Free-radical solution polymerization[6,7] was employed for the synthesis of PSA1 (monomers—EHA:MMA:AA; 7.54:0.92:1.64 w/w/w) and PSA2 (monomers—EHA:MMA:AA:VA; 85:10:3:2 w/w/w/w) using 2,2′-azo-*bis*-isobutyronitrile (AIBN) as free-radical initiator. Monomers with predetermined composition were taken in a three-necked flask fitted with an overhead stirrer, a condenser, and an inlet for purging of nitrogen gas. The flask was sealed after charging with nitrogen and the reaction was carried out in a temperature-controlled bath with constant stirring. The conditions in polymer synthesis were maintained same and constant for both the polymers throughout reaction period. Quenching was done by the addition of sodium metabisulphite. The polymers were purified by extraction with methanol and subsequently air-dried. Reaction conditions of polymer synthesis are mentioned in Table 1.

Characterization of PSA1, PSA2, PSA3, and PSA4

Synthesized PSAs (PSA1 and PSA2) and commercially available PSAs (PSA3 and PSA4) were

Table 1. Reaction onditions in synthesis of PSA1 and PSA2.

Conditions	PSA1	PSA2
Monomers (% w/w):		
2-Ethylhexyl acrylate	7.54	85.0
Methyl methacrylate	0.92	10.0
Acrylic acid	1.64	3.0
Vinyl acetate	–	2.0
Initiator (AIBN)	1.0%	1.0%
Reaction solvent	Acetone	Acetone
Temperature (water bath)	80°C	80°C
Time of reaction (hr)	12 hr	12 hr
Quenching agent	Sodium metabisulphite	Sodium metabisulphite

characterized for film formation, glass-transition temperature (Tg), moisture uptake, refractive index, intrinsic viscosity, molecular weight, polydispersity, peel strength, moisture uptake, and skin irritation.

Adhesive films (100 mg spread on $2 \times 2\,cm^2$) of mentioned PSAs were cast on Scotchpak No. 1006 in ethyl acetate as casting solvent and dried. Films were observed for wrinkling, cracking, or deformation. The glass-transition temperature (Tg) of polymers was determined by differential scanning calorimetry (DSC) analysis on a Dupont 2000 Thermal Analyzer (Germany). The samples were cooled to liquid-nitrogen temperature and recording was carried out by programmed heating at the rate of 10°C/min. The films were kept at 75% relative humidity for 5 hr, equilibrated at room temperature for 10 min and moisture uptake of adhesive film (%w/w) was determined by Karl-Fischer titration. Refractive index was determined in ethyl acetate on Abbe's refractometer at room temperature. Intrinsic viscosity was determined in ethyl acetate using Ostwald viscometer at room temperature. Molecular weight was determined by gel-permeation chromatography on Jasco HPLC unit (Japan) attached to refractive index detector. Samples prepared in tetrahydrofuran were injected in column Lichrogel® (Merck; 250 mm × 4 mm; 5 μ) through a 20 μL loop. Mobile phase (tetrahydrofuran) was pumped through the column at flow rate of 0.8 mL/min. Standard polystyrene of known molecular weight was used to construct graph of molecular weight vs. retention time to determine molecular weight and polydispersity. The peel strength[8] of the adhesive films (100 mg cast on $2 \times 2\,cm^2$ on Scotchpak No. 1006) was determined on release liner (Scotchpak No. 1022) and human skin. An 180° peel-strength tester was operated at a fixed rate of 300 mm/min. A skin-irritation study of PSAs was carried out on 10 healthy male human volunteers in the age group of 22 to 28 years. PSAs films of about 100 μ thickness and $2 \times 2\,cm^2$ were applied on volar forearm of healthy male human volunteers for 24 hr. The portion in contact with adhesive was examined for the presence of irritation, redness, and edema.

Fabrication and Optimization of Monolithic TTS

The fabricated TTS was comprised of a backing membrane, an adhesive layer containing drug, and a release liner. Systems were fabricated by solvent evaporation technique.[6] An area of definite size ($2 \times 2\,cm^2$) was marked on the backing membrane Scotchpak No. 1006 by creating a depression using a hot metal rod. Crystallization of drug was found significantly reduced at drug:PSA1, 1:8 w/w; drug:PSA2, 1:18 w/w; drug:PSA3, 1:12 w/w; and drug:PSA4, 1:16 w/w on microscopic examination. Drug and PSAs at predetermined ratio were dissolved in ethyl acetate on weight basis. Films were cast by pipetting predetermined volume of drug-polymer solution to give films of polymer containing 8 mg of drug in $2 \times 2\,cm^2$. Transdermal patches in mentioned PSAs were kept at optimum chemical potential (saturation) and dose $2\,mg/cm^2$ of nitrendipine was kept constant in all TTS. After complete drying at room temperature, the crystal-free patches were covered with Scotchpak No. 1022 release liner, smoothed with a 4.5-lb roller, and kept in a desiccator until further use. Patches prepared in different PSAs were evaluated for in-vitro release study.

Permeation enhancer *d*-limonene was incorporated in drug-PSAs solution in ethyl acetate at different concentration (0.10% – 5.0% w/w of PSAs) before drying. Effect of concentration of *d*-limonene on permeation kinetics of nitrendipine through guinea-pig skin was studied. Optimum concentration of enhancer to achieve maximum flux of nitrendipine in PSAs was determined.

Drug Content Study

Drug content of the transdermal system was evaluated by dissolving an accurately weighed portion of the system (equivalent to 8 mg of drug) in about 25 mL of 5% v/v acetone in methanol. This solution was quantitatively transferred to volumetric flasks and appropriate dilutions were made with methanol. The resulting solution were filtered and analyzed by HPLC method.[9]

In-Vitro Release and Skin-Permeation Study

The nitrendipine patches in PSA1, PSA2, PSA3, and PSA4 were mounted separately on a Keshary-Chein cell[10] of 10 mL capacity. The transdermal system with $1\,cm^2$ of surface area was put in contact with receptor fluid for release study. The transdermal system with $1\,cm^2$ surface area of $2\,mg/cm^2$ dose was applied to the stratum corneum side of skin and then mounted in the diffusion cell with the dermal side in

contact with the receptor fluid for skin-permeation study. This receptor fluid consisted of 40% v/v PEG400 in double-distilled water and was maintained at $37 \pm 0.5^{\circ}C$ throughout the study. Uniform mixing of receiver phase was achieved with a small magnetic-stirrer driver by an external 500 rpm motor. At predetermined time intervals, the receptor fluid was removed and was replaced with fresh medium. The concentration of nitrendipine was determined by HPLC method.[9]

RESULTS AND DISCUSSION

Characterization of PSA1, PSA2, PSA3, and PSA4

The synthesized PSAs and commercially available PSAs were transparent and tacky. Characterization of polymers for different parameters viz. glass-transition temperature (Tg), moisture uptake, refractive index, intrinsic viscosity, molecular weight, polydispersity, peel strength, moisture content, and skin irritation are listed in Table 2.

Differential scanning calorimetry thermograms showed a blunt endothermic peak at $-16^{\circ}C$, $-40^{\circ}C$, $-20^{\circ}C$, and $-10^{\circ}C$ for PSA1, PSA2, PSA3, and PSA4, respectively, representing their glass-transition temperature (Tg). Moisture uptake was found to be high (0.63% w/w) in PSA1, which indicates high hydrophilicity compared to other PSAs. Refractive index value in the range 1.33–1.45 indicates transparency of PSAs. Intrinsic viscosity of PSA2 was found comparatively high due to high molecular weight. Low Tg of PSA2 imparts high peel-strength ($100\,g/4\,cm^2$) on human skin. It was observed that the peel strength and tack increases with increasing intrinsic viscosity and molecular weight of pressure-sensitive adhesives. The skin-irritation study on healthy human volunteers showed no redenning, irritation, itching, or edema at the site of application at the end of 24 hr, indicating no irritation or sensitization in the normal skin flora during its time in contact with skin. The PSAs were found to be suitable for fabrication of nitrendipine TTS.

Fabrication and Optimization of Monolithic TTS

Nitrendipine was released from PSA1 as half-order in the initial 12 hr. The release pattern was found to be consistent with the diffusion-controlled transport model.[11,12] After that, nitrendipine was released as zero-order and the release pattern was found to be consistent with the dissolution-controlled transport model.[13] Nitrendipine percent-cumulative-release amount was found to be 45% of the initial loading of nitrendipine upto 24 hr. Nitrendipine was released from PSA2, PSA3, and PSA4 as zero-order and found to be consistent with the dissolution-controlled transport model. The cumulative drug release from PSA2, PSA3, and PSA4 was found to be 40%, 25%, and 25%, respectively upto 24 hr.

Skin permeation followed zero-order kinetics. The rate of nitrendipine, which permeated through guinea pig skin, was lower than that of drug released from formulations. This indicated that the permeation of drug through skin was the procedure of rate limiting for in-vitro percutaneous permeation.

Optimum concentration of *d*-limonene was found to be 1.0%, 0.50%, 0.30%, and 1.0% in PSA1, PSA2, PSA3, and PSA5, respectively. Cumulative permeation (μg/48 hr) of nitrendipine without *d*-limonene

Table 2. Characterization of pressure-sensitive adhesives.

Parameters	PSA1	PSA2	PSA3	PSA4
Tg (°C)	−16°C	−41°C	−20°C	−10°C
Moisture uptake (% w/w)	0.63	0.43	0.32	0.22
Refractive index	1.33	1.45	1.40	1.40
Intrinsic viscosity	8.50	16.32	14.22	14.22
Molecular weight	82143	112052	89059	104834
Polydispersity	2.4380	1.9361	3.8389	3.2657
Peel strength ($g/2 \times 2\,cm^2$)				
Release liner	50 ± 5.0	60 ± 5.0	50 ± 5.0	55 ± 5.0
Human skin	60 ± 5.0	100 ± 5.0	65 ± 5.0	75 ± 5.0
Skin irritation	No irritation	No irritation	No irritation	No irritation

was found to be 16.60 ± 4.80, 20.88 ± 8.16, 19.68 ± 8.15, and 7.77 ± 2.88 (mean $\pm$ S.D., $n = 5$) in PSA1, PSA2, PSA3, and PSA4, respectively. Cumulative permeation (μg/48 hr) of nitrendipine at optimum concentration of *d*-limonene was found to be 30.00 ± 9.12, 55.72 ± 22.08, 24.32 ± 5.16, and 25.00 ± 5.64 (mean $\pm$ S.D., $n = 5$) in PSA1, PSA2, PSA3, and PSA4, respectively. The cumulative permeation was found to significantly ($p < 0.05$, "*t*" test) increase in all PSAs due to *d*-limonene.

Cumulative permeation of nitrendipine was found comparatively more in PSA2, with and without *d*-limonene. This might be because of low Tg (−41°C). High weight fraction of 2-Ethylhexyl acrylate and vinyl acetate decreases Tg of polymer, and makes it soft, flexible, tacky, and less stiff. High peel-strength (tack) of polymer caused a decrease in contact angle and an increase in wetability and intimate contact to the skin.

Effect of concentration of *d*-limonene on cumulative permeation through guinea-pig skin and enhancement ratio in PSA1 is shown in Figs. 1 and 2. The cumulative permeation, measured at 48 hr, was found to increase with increasing concentration to 1.0% and then found to decrease with further increasing concentration to 5.0%. This decrease in cumulative permeation at high concentration might be attributed to solubilization of nitrendipine by *d*-limonene, which favors partitioning of drug in adhesive. *d*-Limonene was found to enhance skin permeation of drug at the concentration of 1.0% in PSA1 (Fig. 1). Optimum time for maximum-enhancement ratio ($ER = 1.30 \pm 0.35$) was observed at 24 hr, which was found to decrease slowly upto 48 hr (Fig. 2). *d*-Limonene was found to enhance skin permeation of drug at the concentration of 0.50% in PSA2 (Fig. 3). Optimum time for maximum-enhancement ratio ($ER = 2.27 \pm 0.25$) was observed at 24 hr, which decreased slowly with time (Fig. 4). *d*-Limonene was found to enhance skin permeation of drug at the concentration of 0.30% in PSA3 (Fig. 5). Optimum time for enhancement ratio ($ER = 1.15 \pm 0.15$) was observed at 36 hr (Fig. 6). Permeation of drug was found to increase at 1.0% *d*-limonene in PSA4; however, no increment in cumulative permeation was observed after 36 hr, indicating partitioning favors in adhesive after 36 hr (Fig. 7). Although enhancement ratio was observed to be 1.75 ± 0.25 (Fig. 8), TTS was found inefficient to deliver nitrendipine for prolong periods. High enhancement ratio ($ER = 2.27 \pm 0.25$) of nitrendipine in PSA2 indicates high partitioning of *d*-limonene in stratum corneum.

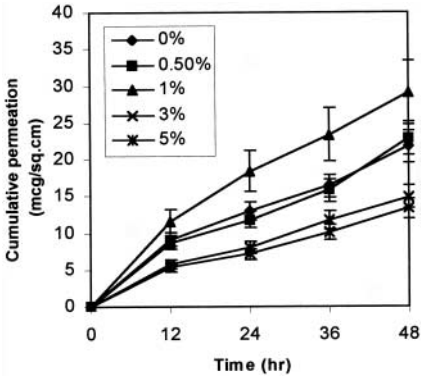

Figure 1. Effect of concentration of *d*-limonene on cumulative permeation of nitrendipine in PSA1. Each point represents mean ± S.D. of five determinations.

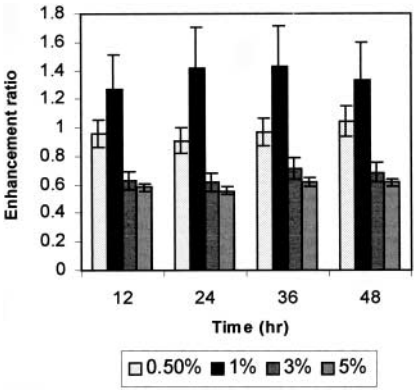

Figure 2. Effect of concentration of *d*-limonene on enhancement ratio of nitrendipine in PSA1. Each bar represents mean ± S.D. of five determinations.

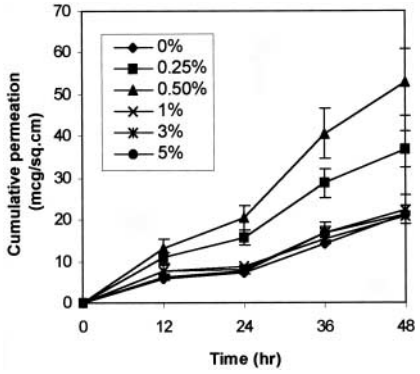

Figure 3. Effect of concentration of *d*-limonene on cumulative permeation of nitrendipine in PSA2. Each point represents mean ± S.D. of five determinations.

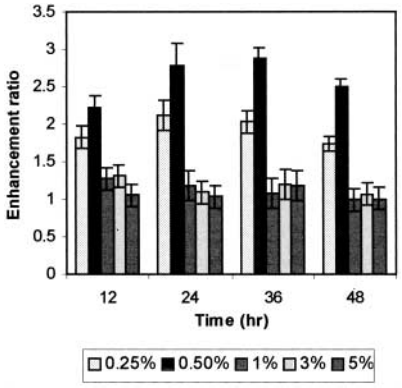

Figure 4. Effect of concentration of *d*-limonene on enhancement ratio of nitrendipine in PSA2. Each bar represents mean ± S.D. of five determinations.

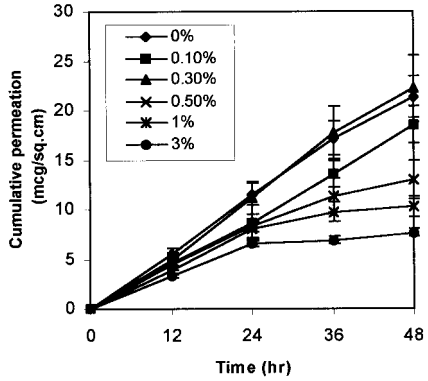

Figure 5. Effect of concentration of *d*-limonene on cumulative permeation of nitrendipine in PSA3. Each point represents mean ± S.D. of five determinations.

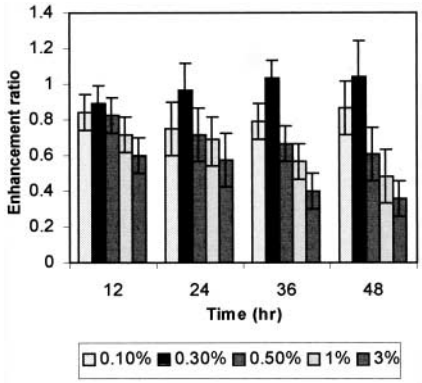

Figure 6. Effect of concentration of *d*-limonene on enhancement ratio of nitrendipine in PSA3. Each bar represents mean ± S.D. of five determinations.

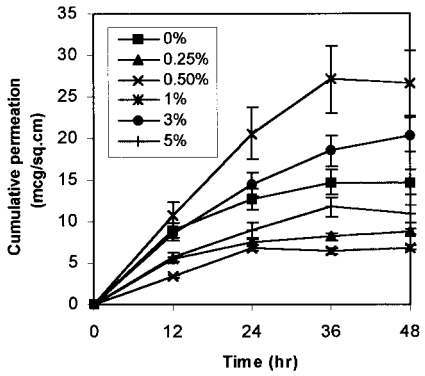

Figure 7. Effect of concentration of *d*-limonene on cumulative permeation of nitrendipine in PSA4. Each point represents mean ± S.D. of five determinations.

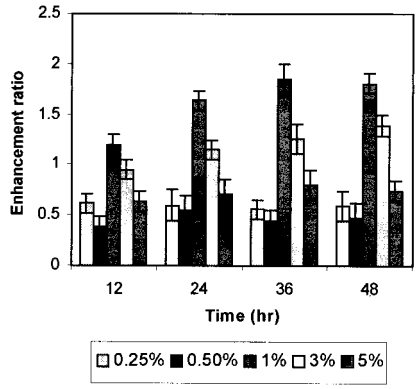

Figure 8. Effect of concentration of *d*-limonene on enhancement ratio of nitrendipine in PSA4. Each bar represents mean ± S.D. of five determinations.

It was observed that permeation enhancer at low concentrations do not affect partition coefficient (adhesive/skin) of drug in TTS. It disturbs the highly ordered lipid periodicity and increases diffusion coefficient of drug through stratum corneum. At high concentrations, the enhancer solubilizes drug in polymer matrix and decreases partitioning of drug in stratum corneum, which causes retardation. Thus, activity of enhancer was observed to be concentration-dependent. Hence, optimum concentration of permeation enhancers needed to be evaluated while designing transdermal therapeutic system.

Optimum concentration of *d*-limonene in PSAs, flux (with and without enhancer), enhancement ratio (ER, at optimum enhancer concentration), and enhancement time (ET) to reach ER in fabricated TTS are summarized in Table 3 with the evaluation

Table 3. Evaluation of TTS in pressure-sensitive adhesives.

PSAs	Drug: PSAs ratio (w/w)	*d*-Limonene (% w/w) polymer	Flux ($\mu g/cm^2/hr$)[a] at 48 hr		ER[b]	ET (hr)	Peel strength on skin[c] ($g/4\,cm^2$)	Weight of film[d] (mg)	Thickness of film[e] (μ)
			Without *d*-limonene	With *d*-limonene					
PSA1	1:8	1.0%	0.346 ± 0.10	0.625 ± 0.19	1.30 ± 0.35	24	60 ± 5.0	75.0 ± 4.0	125 ± 15.0
PSA2	1:18	0.50%	0.435 ± 0.17	1.161 ± 0.46	2.27 ± 0.25	24	100 ± 5.0	150.0 ± 5.0	325 ± 20.0
PSA3	1:12	0.30%	0.410 ± 0.17	0.506 ± 0.17	1.10 ± 0.10	36	65 ± 5.0	104.5 ± 8.0	225 ± 15.0
PSA4	1:16	1.0%	0.162 ± 0.06	0.520 ± 0.18	1.75 ± 0.25	36	75 ± 5.0	136.4 ± 5.5	250 ± 15.0

a,b,c,d,e represents the mean $\pm$ S.D. of five determinations.

ER: Enhancement ratio $= \dfrac{\text{Cumulative permeation with } d\text{-limonene}}{\text{Cumulative permeation without } d\text{-limonene}}$.

ET: Enhancement time (time to achieve maximum enhancement ratio).

parameters viz. peel strength, thickness and, weight of adhesive film.

CONCLUSION

The synthesized acrylate PSA2 copolymer was found to have good adhesion and rate-controlling properties. The synthesized PSA2 was found skin-compatible with desirable wear performance. Low Tg ($-41^\circ C$) and high peel strength ($100\,g/2 \times 2\,cm^2$ on human skin) of PSA2 delivered nitrendipine at maximum input rate and could be useful in fabrication of drug-in-adhesive transdermal system of nitrendipine. *d*-Limonene was found to be an effective permeation enhancer at 0.50% in PSA2. It would be feasible to deliver nitrendipine PSA2 through transdermal route in treatment of hypertension.

ACKNOWLEDGMENTS

We are thankful to the University Grant Commission, the Government of India, and AICTE for financial assistance towards research investigations. We are grateful to Concept Pharmaceuticals Ltd. for providing gift sample of nitrendipine, 3M Corporation for supplying components of TTS, and Permacel and Ancher Adhesives, India, for providing gift samples of adhesive.

REFERENCES

1. Karen, L.G.; Eugene, M.S. Nitrendipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. Drugs **1987**, *33*, 123–155.
2. Kann, J.; Krol, G.J.; Raemsch, K.D.; Burkholder, D.E.; Levitt, M.J. Bioequivalence and metabolism of nitrendipine administered orally to healthy volunteers. J. Cardovasc. Pharmacol. **1984**, *6*, 968–973.
3. Ruan, L.P.; Liang, B.W.; Tao, J.Z.; Yin, C.H. Transdermal absorption of nitrendipine from adhesive patches. J. Controlled Rel. **1992**, *20*, 231–236.
4. Santus, G.S.; Baker, R.W. Transdermal enhancer patent literature. J. Controlled Rel. **1991**, *25*, 1–20.
5. Levison, K.K.; Takayama, K.; Isowa, K.; Okabe, K.; Nagai, T. Formulation optimization of indomethacin gels containing a combination of three kinds of cyclic monoterpenes as percutaneous penetration enhancers. J. Pharm. Sci. **1994**, *83*, 1367–1372.
6. Mare, V.S.; Bharti, P.V.; Vavia, P.R. Acrylate terpolymer in fabrication of medicated skin patches. Polym. Adv. Technol. **2001**, *12*, 1–9.
7. Kokubo, T.; Sugibayashi, K.; Morimoto, Y. Diffusion of drug in acrylic-type pressure sensitive adhesive matrices. I. Influence of physical property of the matrices on the drug diffusion. J. Controlled Rel. **1991**, *17*, 69–78.
8. Minghetti, P.; Cilurzo, F.; Montanari, L. Evaluation of adhesive properties of patches based on acrylic matrices. Drug Dev. Ind. Pharm. **1999**, *25* (1), 1–6.
9. Tipre, D.N.; Vavia, P.R. Oxidative degradation study of nitrendipine using stability indicating,

HPLC, HPTLC and spectrophotometric method. J. Pharm. Biomed. Anal. **2001**, *24*, 705–714.

10. Tojo, K.; Keshary, P.R.; Chein, Y.W. Drug permeation through skin from matrix type drug delivery system. The Chemical Engineering Journal **1986**, *32*, B57–B64.
11. Ayres, J.W.; Lindstrom, F.T. Diffusion model for drug release from suspensions I: Theoretical considerations. J. Pharm. Sci. **1977**, *66*, 654–662.
12. Lindstrom, F.T.; Ayres, J.W. Diffusion model for drug release from suspensions II: release to a perfect sink. J. Pharm. Sci. **1977**, *66*, 662–668.
13. Chandrasekaran, S.K.; Paul, D.R. Dissolution-controlled transport from dispersed matrixes. J. Pharm. Sci. **1982**, *71*, 1399–1402.