Development of Transdermal Drug-Delivery Films With Castor-Oil-Based Polyurethanes

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ABSTRACT: Two different types of polyurethanes (PUs) were prepared with castor oil, ethylene glycol, isophorene diisocyanate and castor oil, and isophoren diisocyanate and poly(ethylene glycol) (400 or 600). PU films were prepared and characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, and gel permeation chromatography. We prepared transdermal patches by loading different amounts of drug, plasticizer, and penetration enhancer. *In vitro* drug permeability through the castor-oil-based aliphatic PU patches was examined with a Keshary–Chien diffusion cell. The effect of castor oil on the film-forming properties and the effect of penetration enhancers on diffusion characteristics of indomethacin (IDM) drug through the castor-oil-based PU were investigated. Prolonged release of IDM was observed from the prepared PU patches. *In vitro* drug diffusion revealed that slow and prolonged release of IDM was achieved in the absence of penetration enhancers. The use of penetration enhancers showed a significant effect on drug diffusion. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 103: 779–788, 2007

Key words: polyurethane; castor oil; drug delivery; transdermal

INTRODUCTION

Transdermal drug delivery (TDD) is one potential route for the systemic delivery[1] of drugs that offers many advantages over the traditional drug-delivery systems with a small concentration of drugs for slow release and without passage through gastrointestinal tract. In contrast to widely accepted ointment medicinal forms, TDD allows drugs to be administered in an individual-dose regimen and provides prolonged treatment. Being able to release the drug in a timely manner, TDD is useful for controlled release (CR) action over an extended period of time.[2] Polymeric membranes prepared from natural and synthetic origins are usually used for TDD, of which some are commercially exploited.[3] TDD has the advantage of no passage through the gastrointestinal tract, unlike the oral administration route, because the decomposition and hepatic first-pass biotransformation are easily circumvented, and drugs at lower dosages can be delivered for a longer time.[4]

Polyurethane (PU) has many biomedical applications due to its toughness, elasticity, good biocompatibility, and fabrication possibilities.[5,6] PUs are used as drug carriers, such as drug conjugates, implants, and colon-targeting polymers, in drug-delivery applications because of their nontoxic nature.[7–10] PUs prepared by the condensation polymerization of isocyanate and different kinds of polyols have many superior properties, including good chemical resistance, wear resistance, proper hardness, elasticity, good mechanical strength, blood compatibility, and extensibility. The properties, such as good elasticity, tensile strength, elongation, and blood compatibility, of PUs are extensively appreciated for their use as biomaterials.[11–13] The film-forming properties of castor-oil-based PUs have been studied recently;[14] they showed good compatibility with the human blood and calcification in static conditions. Material-induced hemolysis and changes in the platelet counts in blood samples after contact with PUs were very low.[15]

Antimicrobial substances can be incorporated into PU films by solvent casting to evaluate their drug-release rates, bacterial colonization, and morphological features to predict and understand their antimicrobial activity.[16] Varying the initial components and conditions of their synthesis, one can control their mechanical properties. Moreover, PUs can be synthesized from many renewable resources, such as castor oil and lignin.[17–20] The film-forming properties of castor-oil-based PUs have been studied recently;[21] these have shown compatibility with human blood and cal-

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cification in static conditions. Material-induced hemolysis and changes in platelet counts in blood samples after contact with PUs were very negligible.[22] Sustained delivery of different pharmaceutical agents, including caffeine, prostaglandin, and disulfiram, with PUs has also been investigated.[23–25] Numerous PU carriers have been developed from different diisocyanate monomers, which are widely used for the administration of drugs through implant drug-delivery, drug conjugates, and colon-specific drug-delivery routes.[7,8,10,26]

The clinical use of indomethacin (IDM), however, is often limited, particularly at high dose levels, because it causes some adverse reactions, such as irritation and ulceration of the gastrointestinal mucosa.[27] After the oral administration of IDM, the increase in initial plasma concentration appears to be responsible for its side effects.[28] To avoid the increase in the initial plasma concentration, an IDM-containing ointment was developed for percutaneous administration. A sustained plasma level was achieved without the high initial peak concentration[29] that is often observed with oral administration. IDM has the unusual property of attaining a higher concentration in the synovial fluid than in the general circulation at a steady state.[30] We, therefore, attempted to develop rate-controlled transdermal drug-delivery systems (TDDs) for the CR of IDM to be applied to joints in the treatment of rheumatoid arthritis.[31] In this study, castor-oil-based random copolyurethanes were prepared and tested for the transdermal delivery of IDM. Films prepared from these PUs have good transparency, flexibility, and mechanical stability. To understand the stability of the PU films, a moisture uptake study was carried out. The drug-diffusion characteristics of the two PU films prepared with castor oil, ethylene glycol (EG), and castor oil, poly(ethylene glycol) (PEG) were studied with IDM as a model drug; the release results are discussed to estimate the effectiveness of the developed systems.

EXPERIMENTAL

Materials

Analar-grade EG, *N,N′*-dimethylformamide (DMF), PEG, dichloromethane (DCM), and dibutylphthalate (DBP) were obtained from S. D. Fine Chemicals (Mumbai, India). Castor oil with 2.24 hydroxyl groups per molecule[32] was procured from S. D. Fine Chemicals and dried in an oven at 100°C before use. EG and DMF were dried over 4-Å molecular sieves before use. IDM, an anti-inflammatory drug; isophorone diisocyanate (IPDI); and dibutyl tin dilaurate were procured from Aldrich (Milwaukee, WI); these were used as received. Dialysis membrane 110 was procured from Himedia (Mumbai, India).

Preparation of castor-oil-based PU

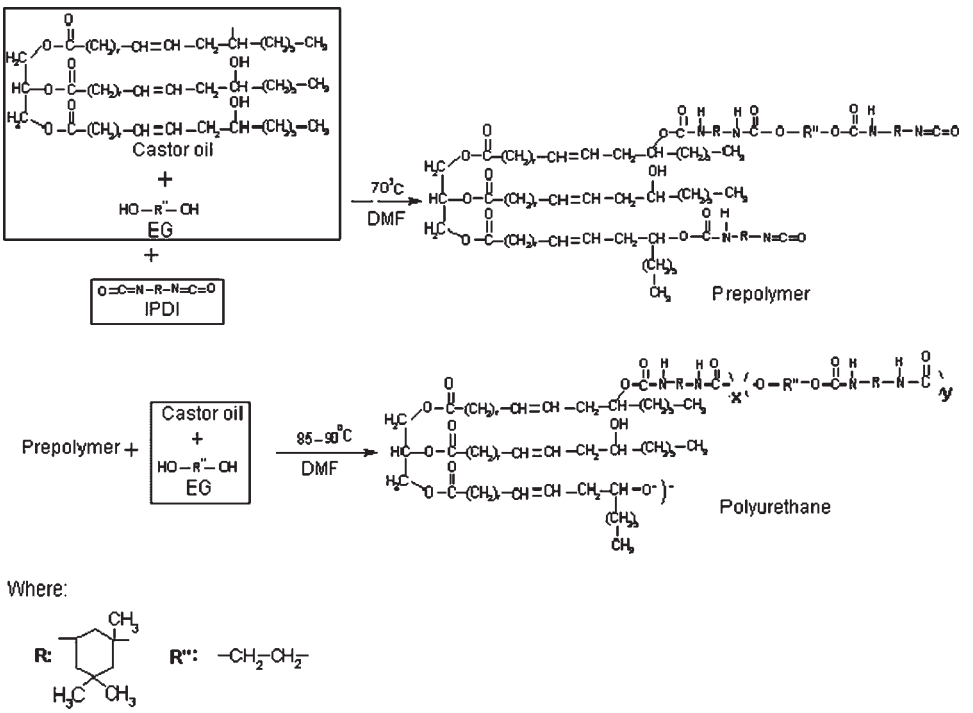
Moderate-molecular-weight-block PUs can be obtained by the mixing of two or more diols.[26] Castor oil (0.01 mol) and diol (0.1 mol) were dissolved in DMF in a 100-mL, round-bottom flask. Dibutyl tin dilaurate (0.02%) was added to the flask, and the mixture was stirred with a magnetic stirrer for 10 min under a nitrogen atmosphere. IPDI (0.22 mol) was added dropwise to this reaction mixture. The reaction mixture was stirred for 30 min and was subsequently heated at 70°C for 2 h to produce the isocyanate-terminated PU. The reaction mixture was cooled to ambient temperature; 0.1 mol of EG and 0.01 mol of castor oil were added to the isocyanate-terminated PU. The mixture was again heated at 85–90°C for 24 h. After the reaction was complete, the mixture was cooled to ambient temperature; the product was precipitated in distilled water, separated by filtration, and dried in a vacuum oven at 60°C. Different castor-oil-based PUs were prepared by variation of the ratio of EG with castor oil. The reactions leading to the formation of PUs are outlined in Scheme 1. The PUs prepared with different ratios of EG to castor oil and PEG to castor oil are given in Tables I and II, respectively.

Preparation of drug-loaded PU films

Transdermal films were prepared with PUs prepared from castor oil and EG with DBP and PEG as a plasticizer and penetration enhancer, respectively. PU (0.3 g) and IDM (30 and 40 wt % based on the PU-to-drug ratio) were dissolved in DCM. Drug-loaded PU films were cast on a plain mercury surface and the solvent was evaporated at ambient temperature. A yellow, transparent, flexible film was obtained in the presence of DBP. Another set of transdermal films were prepared with PU prepared from castor oil and different molecular weight PEGs by loading with 30 and 40% of IDM. Formulations prepared with PU films containing different amounts of IDM, DBP, and PEG are given in Table I, whereas the six formulations of PUs containing IDM along with different molecular weight PEGs are given in Table II.

Estimation of drug and moisture contents in the PU films

The drug-loaded PU film was dried in a vacuum oven at 40°C for 12 h, and a film with an area of 1 cm^2 was dissolved in DCM for the estimation of IDM. The total amount of IDM present in the PU film was determined from UV absorbance measured at a maximum wavelength of absorbance (λ_{max}) value of 320 nm. A PU film with the same dimensions was used for the drug-diffusion study. At the end of the diffusion study, the amount of drug remaining in the PU film was deter-



Scheme 1 Preparation of castor-oil-based PUs.

mined with a UV calibration curve by the dissolution of the film in DCM. The films prepared by the solvent-casting method were stored at ambient temperature. Before they were dried, they were weighed and kept in a desiccator over anhydrous calcium chloride at 35°C for about 24 h until a constant weight was obtained. The moisture content of the PU film was determined by the difference between the instant weight taken after drying and the initial weight reported as percentage moisture content.

In vitro diffusion study

Normal saline-containing phosphate buffer (pH = 7.4) was used as a bathing solution in the receptor compartment of the Keshary–Chien diffusion cell constructed indigenously,[33] as shown in Figure 1. A dialysis membrane, previously soaked in phosphate buffer solution, was mounted between the donor and receiver compartments of the diffusion cell with a capacity of 13.5 mL. A drug-loaded PU membrane 1 cm^2 in area was placed on the surface of the dialysis membrane in the cell. The receiver compartment was filled with 13.5 mL of phosphate buffer (pH = 7.4) solution and stirred at 200 rpm. Water was circulated around the diffusion cell to maintain the temperature at 37°C. Aliquot samples of about 10 mL were withdrawn from the receiver compartment at regular time intervals to study the diffusion of IDM through the PU film. The same amount of fresh buffer solution was then added to the cell each time, and the amount of IDM released was calculated from the previously established calibration curve obtained from the UV spectrophotometer.

TABLE I
Codes for Different PUs Developed and Formulations Prepared with EG and Castor Oil

Formulation code	EG	CO	DBP	PEG
PUEGCO1	90	10	—	—
PUEGCO2	80	20	—	—
PU-1	80	20	20	—
PU-2	80	20	20	10
PU-3	80	20	20	20
PUEGCO3	70	30	—	—
PU-4	70	30	20	—
PU-5	70	30	20	10
PU-6	70	30	20	20

Fourier transform infrared spectroscopy (FTIR)

Pure IDM and IDM-loaded PU films were mixed separately with KBr and pellets were prepared by the

TABLE II
PU Film Codes Prepared with Castor Oil and PEG

Formulation code	Molecular weight of PEG	PEG (%)	Castor oil (%)
PUPEG-1	600	80	20
PUPEG-2	600	60	40
PUPEG-3	600	50	50
PUPEG-4	400	80	20
PUPEG-5	400	60	40
PUPEG-6	400	50	50

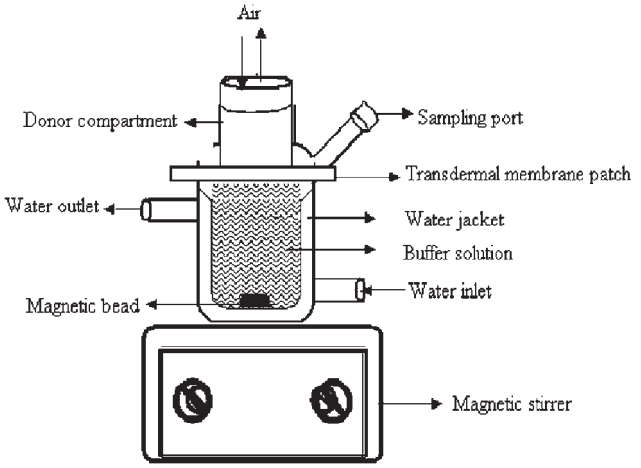


Figure 1 Schematics of the Keshary–Chien diffusion cell.

application of 5.5 metric tons of pressure in a hydraulic press. The pellets were scanned over the wave number range 4000–400 cm^{-1}.

Scanning electron microscopy (SEM) studies

SEM images of the plain and IDM-loaded PU films were recorded with a JSM 6400 scanning electron microscope (Jeol, Tokyo, Japan). SEM pictures for the blank PU indicated plain film, whereas IDM-loaded PU films indicated the presence of drug in the PU film.

Gel permeation chromatography (GPC)

The molecular weights of the prepared PUs were measured with GPC (Viscotek, Houston, TX) attached with a differential refractive-index detector (Viscotek VE 3580) with the use of two columns (Viscotek ge, $GMH_{H\ R}$-H). The flow rate of the mobile phase, that is, tetrahydrofuran, was set to 1 mL/min; polystyrene standards were used for calibration. Subsequently, the molecular weight of the PUs was reported as polystyrene-equivalent molecular weight.

Differential scanning calorimetry (DSC)

DSC thermograms of the PU films were recorded with a Rheometric Scientific (model-DSC SP, Surrey, United Kingdom). The DSC curves were recorded between 25 and 400°C.

RESULTS AND DISCUSSION

FTIR

The formation of PUs was confirmed by FTIR with films prepared with different ratios of castor oil and diol are shown in Figure 2. The absence of a peak due to isocyanate around 2260 cm^{-1} indicated a complete reaction between alcohol and isocyanate, resulting in the formation of a urethane linkage. A broad band located around 3345 cm^{-1} was due to N—H stretching of the urethane linkage. The characteristic peak of the carbonyl groups of the urethane linkage —NH—COO— appeared

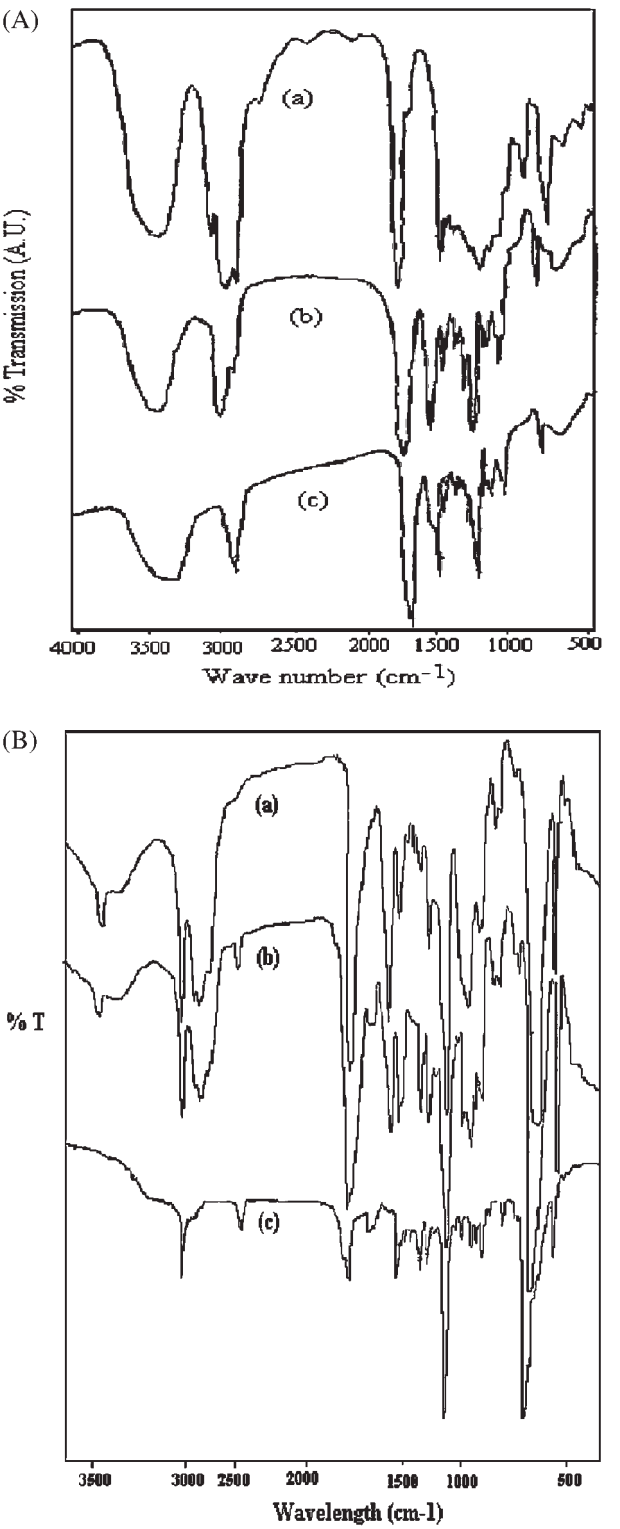


Figure 2 FTIR spectra of (A) (a) castor oil, (b) PU containing 10% castor oil, and (c) PU prepared with IPDI and EG and (B) (a) PUPEG-1, (b) PUPEG-1 loaded with 40% IDM, and (c) IDM.

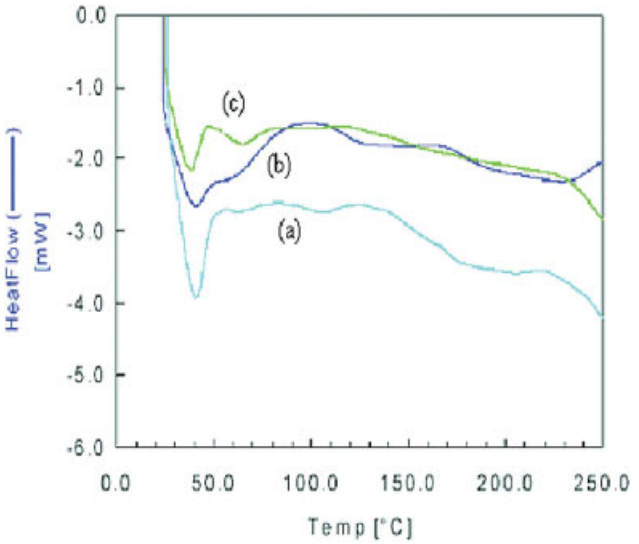


Figure 3 DSC spectra of (a) PUEGCO1, (b) PUEGCO2, and (c) PUEGCO3.

around 1708 cm^{-1}. The peak due to C—N stretching vibrations was located around 1530 cm^{-1}. The aliphatic C—H stretching vibrations were shown around 2850 cm^{-1}. These observations were in accordance with the FTIR spectral data for other PUs reported in the literature.[34] To study the polymer–drug interactions, FTIR spectra of the IDM-loaded films were recorded and are shown in Figure 2(a). The characteristic peaks of the drug around 2400 and 1600 cm^{-1} also appeared in the IDM-loaded polymer spectra. The peaks of the drug around 2400, 1215, 1600, 2400, and 1700 cm^{-1} were overlapped with the PU peaks, which indicated that drug–polymer interactions did not seem to occur.

DSC

DSC thermograms of the PUs are displayed in Figure 3. PU synthesized with 10, 20, and 30% castor oil, designated as PUEGCO-1, PUEGCO-2, and PUEGCO-3, had glass-transition temperatures (T_g's) at 40, 39, and

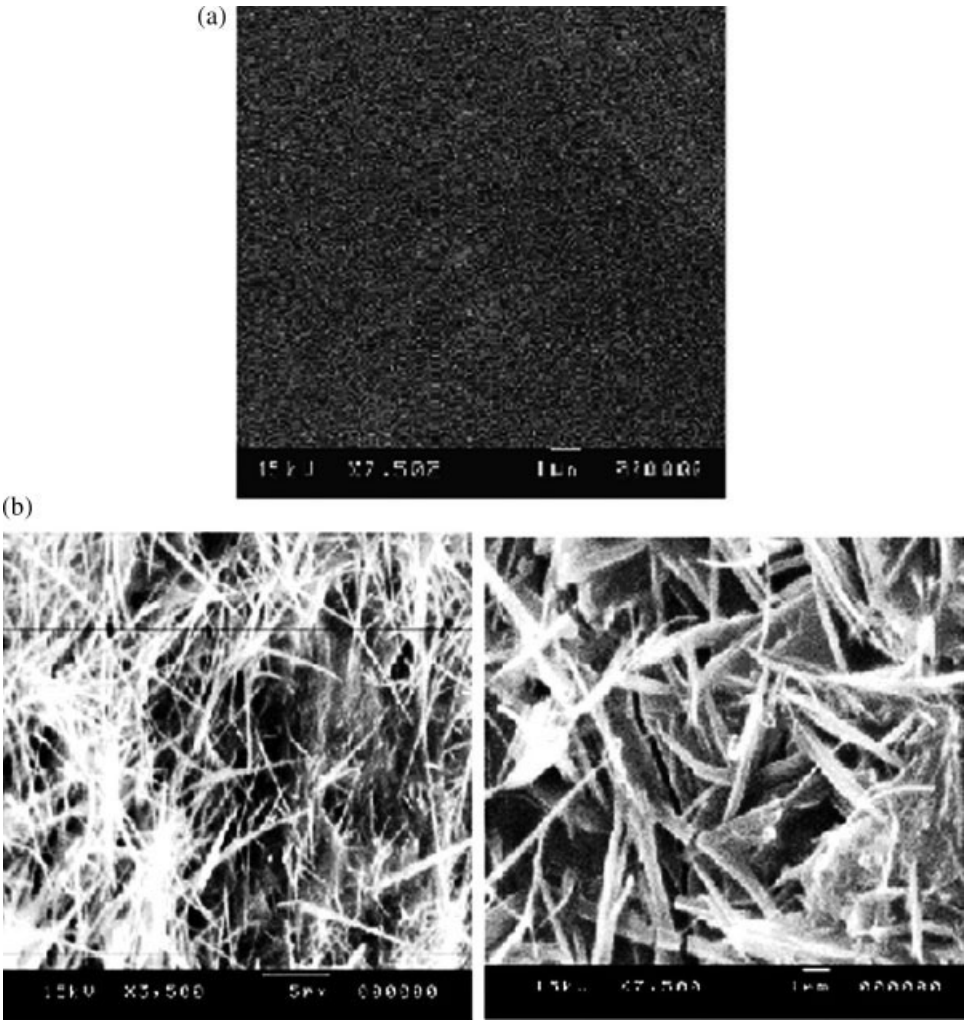


Figure 4 Scanning electron micrographs of the (a) plain PU film (without drug) and (b) drug-loaded PUEGCO film at different magnifications.

TABLE III
Average Molecular Weights and Polydispersity Indices of Different PUs

PU code	M_w	M_n	M_w/M_n
PUEGCO1	14,133	8,313	1.71
PUEGCO2	30,353	13,196	2.30
PUEGCO3	37,059	15,441	2.42
PUPEG-1	6,880	4,200	1.64
PUPEG-2	9,210	7,481	1.23
PUPEG-3	11,689	8,609	1.36
PUPEG-4	7,980	5,392	1.48
PUPEG-5	10,100	8,278	1.22
PUPEG-6	12,400	9,465	1.31

M_n = number-average molecular weight.

36°C, respectively. T_g shifted to the lower temperature with increasing content of castor oil of the PUs. The T_g values of the castor-oil-based PUs were in agreement with published reports.[35]

SEM

Scanning electron micrographs of the plain and IDM-loaded PU films are displayed in Figure 4(a,b). These micrographs showed the distribution of IDM in PU matrix as needlelike structures [Fig. 4(b)], whereas the plain PU film (without drug) did not show any needlelike structures [Fig. 4(a)].

GPC

The molecular weight and polydispersity of the PUs increased with increasing amount of castor oil in the PU polymer. The PU synthesized from ED and IPDI had a molecular weight of 2936, which increased with increasing amount of castor oil of the PUs. Moderate-molecular-weight PUs were obtained by the method adopted in this research (see Table III).

Drug and moisture contents in the PU membranes

An increase in IDM loading was observed with increasing amount of drug incorporated into the polymer solution. The thickness of the PU film was in the range 0.17–0.18 mm for the 30% IDM-loaded PU films, whereas for the 40% IDM-loaded PU films, the thickness was in the range 0.19–0.28 mm. The percentage moisture content was in the range 0.55–1.18 for the different PU films.

In vitro release studies

Transdermal release of the PU films and the effect of penetration enhancers on the release rates were evaluated by study of the *in vitro* release of IDM. The results for the different formulations are displayed in Figures 5 and 6. The amount of IDM remained after the diffusion studies through the PU films are given in Table IV. Drug diffusion was carried out with 30% IDM-loaded PU-1, PU-2, PU-3, and PU-4; the PU-5 and PU-6 matrix films are shown in Figure 5(a,b). A slow and prolonged drug release was observed for the PU films prepared with castor oil as one of the components. However, only 14.8% of the total IDM was released in 1 day from the PU-1 film. The percentage cumulative drug release in 1 day dropped to 11% with an increase in the castor oil content from 20 to 30% of the PUs. This type of decrease in percentage cumulative drug release with increasing castor oil content was due to an increase in the hydrophobicity of the PU films with increasing amounts castor oil. Faster release rates were observed when the penetration enhancers were used. For instance, the percentage cumulative release in 1 day increased from 14.8 to 18.8% and 33.6% when 10 and 20% of PEG were used as penetration enhancers in the PU-2 and PU-3 films, respectively. For the PU-4, PU-5, and PU-6 films, the percentage cumulative release of IDM increased from 11 to 16.7% when 10% PEG was used as the penetration enhancer; however, a further increase in IDM

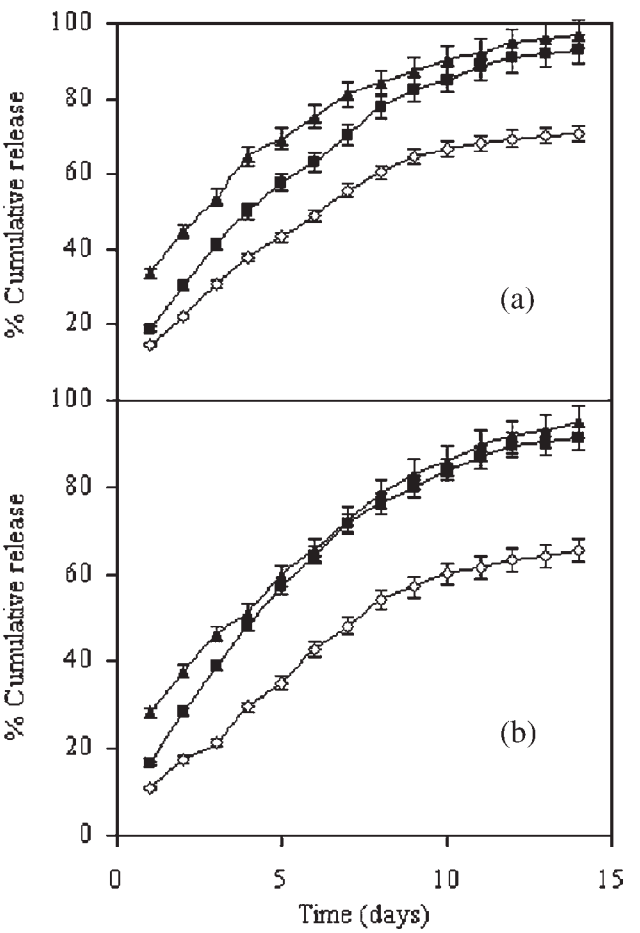


Figure 5 Percentage cumulative release of IDM from the 30% drug-loaded patch: (a) (□) PU-1, (■) PU-2, and (▲) PU-3 and (b) (□) PU-4, (■) PU-5, and (▲) PU-6.

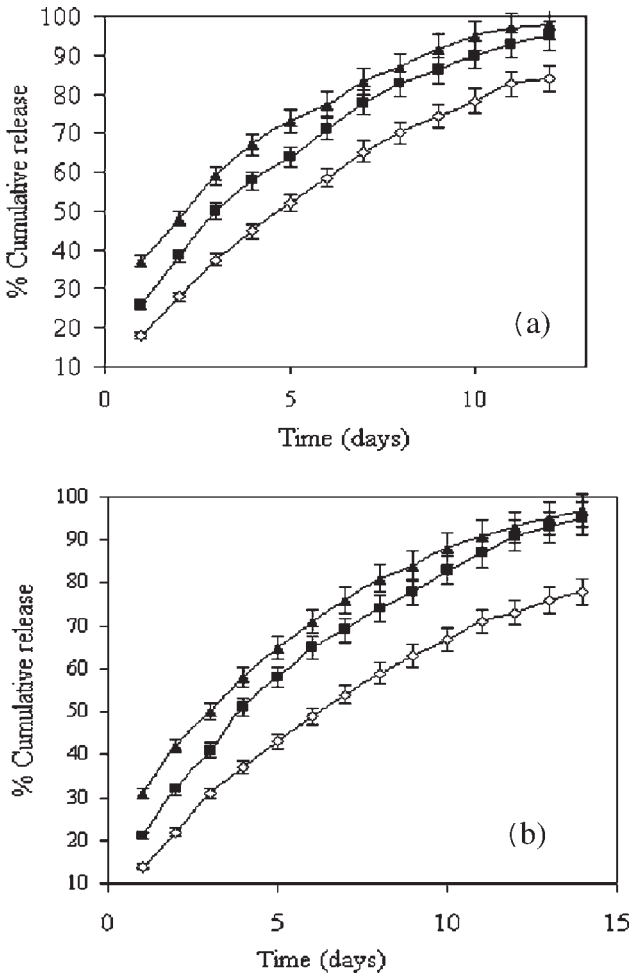


Figure 6 Percentage cumulative release of IDM from the 40% drug-loaded patch: (a) (□) PU-1, (■) PU-2, and (▲) PU-3 and (b) (□) PU-4, (■) PU-5, and (▲) PU-6.

release up to 28.3% was observed for the 20% PEG-containing PU matrix. The release patterns of IDM from the PU-4, PU-5, and PU-6 films are shown in Figure 5(b).

Penetration enhancers are substances that facilitate the absorption of a drug solution through the skin by temporarily diminishing the impermeability of the skin. Ideally, these materials should be pharmacologically inert, nontoxic, nonirritating, nonallergenic, compatible with the drug and excipients, odorless, tasteless, and colorless and have the good solvent properties. However, the enhancer should not lead to the loss of any body fluids, electrolytes as well as endogenous materials. Moreover, the skin should immediately regain its barrier properties on its removal. Table IV shows that 29 and 35% of IDM was remained in PU-1 and PU-4 films at the end of 14 days for films prepared without penetration enhancer. A significant increase in the release rate was observed when 10 and 20% of the penetration enhancer was used. The amounts of drug that remained after 14 days in the PU films were 6.8, 4.9, 8.8, and 5.6% for the PU-2, PU-3, PU-5, and PU-6 films, respectively.

For PU patches loaded with 40% IDM, higher release rates were observed when compared to 30% IDM-loaded films. The observed drug-release patterns for the 40% IDM-loaded PU-1 to PU-6 films are displayed in Figure 6(a,b). The amounts of drug remaining in the membranes after 14 days of the release study are given in Table IV. The increase in the release rate was due to the leaching of the hydrophilic fraction of the film, which resulted in the formation of pores. The release of IDM was diffusion-controlled at the low drug concentrations. A burst effect, observed initially, may have been due to the rapid dissolution of surface-adhered drug particles followed by the diffusion of IDM through the PU film. The *in vitro* permeation profiles showed an increase in the percentage of cumulative release with increasing amount of penetration enhancers. Sticky films were obtained when an excess amount of castor oil was used in the reaction. As shown in Figure 5, the total IDM loaded into the PU film would not have been released in the absence of penetration enhancers, and hence, more time was required for the release of very low amounts of IDM. From the release study, we concluded that PU films prepared with castor oil and EG could be used for the CR of IDM. On the basis of the release patterns given in the literature[2,36,37] for the therapeutic TDD of IDM, we concluded that a lesser IDM dose regimen is required for TDD.

Drug-release patterns of PU films prepared from castor oil and PEGs of different molecular weights and loaded with 30 and 40% of IDM are given in Figures 7 and 8, respectively. Faster release patterns were observed for PUPEG-1, PUPEG-2, and PUPEG-3 compared to PUPEG-4, PUPEG-5, and PUPEG-6 films. However, comparatively faster release rates were observed in those formulations containing higher amounts of PEG in the PU matrix. This was due to an increase in hydrophilic segments (PEG) of the PU matrix. The percentage cumulative release was also dependent on the amount of drug loaded into the PU film. For the PU films loaded with 40% IDM (i.e., PU-1, PU-2, and PU-3), 94, 83, and 73% of IDM were

TABLE IV
Percentage Drug Present in the PU Films After Diffusion for 14 Days

Formulation code	Drug remaining in the patch (wt %)	
	30% drug-loaded patch	40% drug-loaded patch
PU-1	29.2	12
PU-2	6.8	2
PU-3	4.9	—
PU-4	34.8	22
PU-5	8.8	5
PU-6	5.6	3

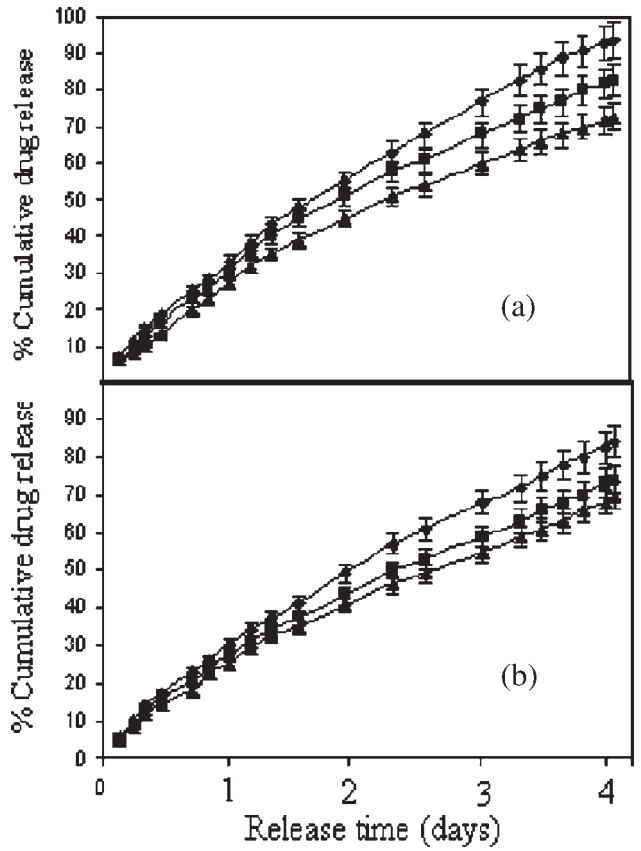


Figure 7 Percentage cumulative release of IDM from the (a) 40% IDM-loaded patch [(◆) PUPEG-1, (■) PUPEG-2, and (▲) PUPEG-3] and (b) 30% IDM-loaded patch [(◆) PUPEG-1, (■) PUPEG-2, and (▲) PUPEG-3].

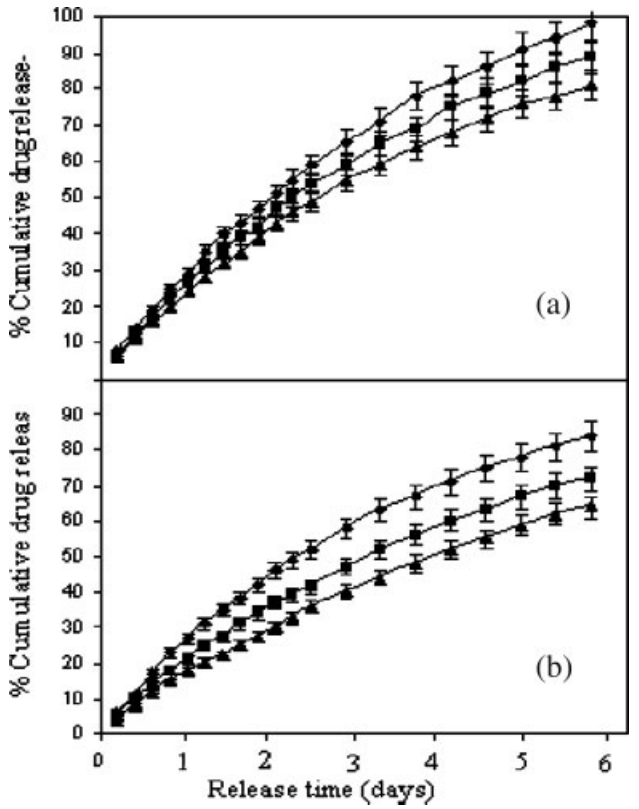


Figure 8 Cumulative release of IDM from the (a) 40% IDM-loaded patch [(◆) PUPEG-4, (■) PUPEG-5, and (▲) PUPEG-6] and (b) 30% IDM-loaded patch [(◆) PUPEG-4, (■) PUPEG-5, and (▲) PUPEG-6].

released in 4 days. However, the percentage cumulative release in 4 days dropped down to 84, 74, and 70% when PU films were loaded with 30% IDM. The 98, 89, and 81% of IDM was released in 6 days from the PU-4, PU-5, and PU-6 films, respectively, loaded with 40% IDM. However, the percentage cumulative release dropped to 84, 72, and 64% for 30% IDM-loaded films. When TDDs are developed with IDM or any other drug, it has been customary to use the support films such as poly(ethylene terephthalate) and ethylene vinyl acetate.[38,39] Kusam Devi et al.[40] used commercial semipermeable and transparent regenerated cellulose as a supporting film, which was permeable to low-molecular-weight substances. In all of these studies, interactions of drugs with the support layer were not discussed. In this study, the support layer (dialysis membrane 110) did not show any interactions with IDM.

Drug-release kinetics

From the diffusion study, we observed that IDM release from the developed PU transdermal patches depended on the amounts of castor oil and PEG incorporated in the PU matrix. The diffusion equation proposed by Higuchi and coworkers[41,42] ($M_t/M_\infty = kt^{0.5}$) was used to study the drug-release kinetics. Here, k is a kinetic rate constant, independent of the geometrical and structural properties of the membrane, which could be determined from the slope of the plot of M_t/M_∞ versus $t^{0.5}$; M_t is the amount of IDM released at time t; and M_∞ is the amount of IDM released after an infinite time. Ritger and Peppas[43] introduced the power law $M_t/M_\infty = kt^n$ to analyze drug release from PU matrices. The values of the exponent n were calculated from the slope of the plot of $\ln(M_t/M_\infty)$ versus $\ln t$. The values of k and n for different PU films loaded

TABLE V
Drug-Release Kinetics Data for the 30% Drug-Loaded PU Patch with the Higuchi and Power Law Equations

	Higuchi law		Power law	
Formulation code	k	r^2	n	r^2
PU-1	0.313	0.976	0.62	0.985
PU-2	0.306	0.985	0.61	0.988
PU-3	0.243	0.976	0.41	0.988
PU-4	0.337	0.978	0.72	0.984
PU-5	0.314	0.980	0.65	0.981
PU-6	0.272	0.991	0.50	0.994

r^2 = correlation coefficient.

TABLE VI
Drug-Release Kinetics Data for the 40% Drug-Loaded PU Patch with the Higuchi and Power Law Equations

Formulation code	Higuchi law		Power law	
	k	r^2	n	r^2
PU-1	0.31	0.995	0.612	0.994
PU-2	0.2753	0.986	0.51	0.999
PU-3	0.259	0.990	0.405	0.996
PU-4	0.311	0.998	0.658	0.996
PU-5	0.292	0.996	0.578	0.995
PU-6	0.251	0.992	0.427	0.996

TABLE VIII
Drug-Release Kinetics Data for the 30% Drug-Loaded PU Patch with the Higuchi and Power Law Equations

Formulation code	Higuchi law		Power law	
	k	r^2	n	r^2
PUPEG-1	0.118	0.993	0.754	0.999
PUPEG-2	0.117	0.995	0.755	0.995
PUPEG-3	0.115	0.994	0.697	0.992
PUPEG-4	0.103	0.998	0.772	0.988
PUPEG-5	0.102	0.997	0.771	0.996
PUPEG-6	0.101	0.992	0.813	0.995

T5-T8 with different amounts of IDM are given in Tables V–VIII. Generally, for thin PU films, if $n = 0.5$, this is indicative of the Fickian release, but if $0.5 < n < 1$, this indicates anomalous transport due to matrix swelling. In this work, the values of n were between 0.5 and 1, which indicated anomalous transport of IDM (see Table VI). Smaller values of k indicated the prolonged release of IDM from the PU films. The value of k decreased after the addition of penetration enhancers, which indicated higher release rates.

For the 40% drug-loaded PU patches, the release kinetics followed anomalous behavior. In some formulations, the value of n ranged between 0.51 and 0.57, which indicated that the transport was close to Fickian nature. However, a decrease in k showed that with higher amounts of penetration enhancers, higher release rates were observed. Also, a decrease in k indicated an increase in film thickness. However, in the majority of cases, the release of IDM through the different PU films fit the power law equation better than the Higuchi law equation (see Table VI).

For the PU films prepared with castor oil and PEG, the drug-release rate was dependent on the ratio of castor oil to PEG. The values of k and n were calculated according to the Higuchi and power law equations, and these are given in Tables VII and VIII for different drug loadings. Smaller values of k indicated the prolonged release of IDM for formulations containing a higher percentage of castor oil. The rate of drug release through the PU films with different IDM loadings was significantly different. All of the values of n were higher than 0.5, and therefore, the release mechanism was controlled by a combination of diffusion and swelling of the PU matrix; this was further indicative of a non-Fickian diffusion trend. Also, a linear relationship between the cumulative release of IDM and the square root of time was obtained after a steady state was reached (with correlation coefficient of 0.995), which indicated that the mechanism of drug release followed the diffusion-controlled process as described by the classical Higuchi relation.

TABLE VII
Drug-Release Kinetics Data for the 40% Drug-Loaded PU Patch with the Higuchi and Power Law Equations

Formulation code	Higuchi law		Power law	
	k	r^2	n	r^2
PUPEG-1	0.121	0.992	0.759	0.999
PUPEG-2	0.12	0.996	0.770	0.996
PUPEG-3	0.12	0.994	0.785	0.994
PUPEG-4	0.103	0.997	0.755	0.994
PUPEG-5	0.102	0.997	0.769	0.995
PUPEG-6	0.101	0.996	0.777	0.995

CONCLUSIONS

TDDSs were prepared with castor-oil-based PUs. FTIR spectral analysis confirmed the formation of PUs, whereas GPC indicated the formation of PUs with moderate weight-average molecular weights (M_w's) ranging from 14,133 to 37,059. The polydispersity of PUs prepared ranged between 1.71 and 2.42. A slow and sustained release of IDM was observed up to 14 days from the PU films. Faster drug-release rates were observed at higher IDM loadings and in the presence of penetration enhancers. Diffusion followed Fickian trends, except in a few cases, where it deviated slightly. The use of penetration enhancers showed a clear-cut dependence on drug-release rates.

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