Formulation and *In Vitro* Evaluation of Transdermal Delivery of Zidovudine—An Anti-HIV Drug

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ABSTRACT: This study was designed to develop matrix type of transdermal-controlled delivery system for zidovudine using Eudragit L100 by varying the amounts of drug in addition to polyethylene glycol as a plasticizer and Tween 80® as a penetration enhancer. Transparent smooth and flexible films were characterized for weight, thickness uniformity, and drug content. Drug interactions with the polymer films were studied by differential scanning calorimetry, whereas X-ray diffraction was used to understand the drug polymorphism in the films. The *in vitro* drug release experiments were performed in phosphate buffer using the Keshary-Chien diffusion cell. Variations of drug release profiles were analyzed using the Ritger and Peppas empirical equation to describe the type of release mechanism. The exponent n values of the equation varied over the wide range of 0.75–2.23, suggesting non-Fickian to super Case-II type of diffusion transport. Statistical analyses of release data performed by the analysis of variance (ANOVA) method indicated significant differences within experimental measurements. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 1268–1274, 2011

Key words: anti-HIV drugs; zidovudine; transdermal delivery system; Eudragit; *in vitro* release

INTRODUCTION

Human immuno deficiency virus (HIV), a retrovirus, is known to cause acquired immuno deficiency syndrome (AIDS) as the HIV infection develops. Even-though morbidity and mortality of AIDS patients are now reduced and the patient survival time has been prolonged, the present treatments do not eradicate HIV and cure AIDS completely. Efforts to search for new anti-HIV agents to provide an effective treatment are still continuing ever since the discovery of HIV in 1981. Zidovudine (AZT) (3′-azido-3′-deoxythymidine), the first anti-HIV compound approved for clinical use, is being widely used for antiretroviral (ARV) therapy, either alone or in combination with other ARV agents. During ARV therapy, it is crucial to maintain systemic drug concentration within the therapeutic level throughout the treatment course.[1–3] Oral AZT has a short elimination half-life with a low bioavailability and hence, frequent high doses are required to maintain its therapeutic level to avoid the dose-dependent toxic side effects.[4,5] Another limitation to therapeutic effectiveness of AZT is its dose-dependent hematological toxicity. After oral administration, it is rapidly absorbed from the gastrointestinal tract with a peak plasma concentration of 1.2 mg/mL at 0.8 h. It is also rapidly metabolized to the inactive glucuronide with a mean elimination half-life of 1 h, thus necessitating frequent administration of large doses (200 mg/every 4 h) to maintain therapeutic drug levels. The steady-state plasma pre-dose (4 h after the last dose) and 1.5 h post-dose concentrations of AZT in adult patients after chronic oral administration are 0.16 μg/mL, which is far below the minimum target concentration and 0.62 mg/mL that is above the mean ID_{50} for hematopoietic progenitor cells. Hence, for maintaining an effective plasma concentration and for avoiding sub-therapeutic and toxic concentrations, continuous delivery of AZT is necessary. Because of the high first pass metabolism, oral sustained delivery may not be a good option and hence, transdermal route is a better alternative, to achieve constant plasma levels, reducing the frequency of dosing regimen.

To avoid the serious toxic effects resulting from its oral administration, transdermal delivery of AZT has been attempted by many researchers,[2,3,6–8] since it offers many advantages over other routes to treat systemic illnesses. Hydrophilic AZT would adversely affect its permeability through the stratum corneum and hence, polymeric vehicles to improve transdermal permeation of AZT have been investigated.[9–12] Researchers also have demonstrated the enhanced AZT permeation using a mixture of

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hydrophilic vehicles (i.e., isopropyl alcohol/water, polyethylene glycol-400 [PEG- 400]/water, and ethanol/water).[13–15] Eudragit RL (ERL) and Eudragit RS (ERS) have been used before to develop transdermal films for controlled release (CR) of drugs[16]; of these, ERL is more permeable to water than ERS.[17] To achieve control over their drug release characteristics, the transdermal devices were developed by varying the ratio of polymers.[18–20] Eudragits are known to produce the crystallization-free polymeric films leading to higher drug release and skin permeation.[20] The rapid drug release (burst effect) from these polymers due to rapid dissolution of the surface drug can be useful in dermal penetration of drugs.[21]

This study is an extension of our previous efforts[22–24] on the development of matrix type of transdermal delivery systems using Eudragit L100 along with PEG for the CR of AZT. Placebo and drug-loaded films have been characterized by thermal and X-RD analyses. *In vitro* release was performed in phosphate buffer (PBS, pH 7.4) at 37°C using Keshary-Chien diffusion cell. These results have been fitted to an empirical equation of Ritger and Peppas[25] to understand the release mechanism, since such data are useful in further developing similar type of devices using the appropriate drug-polymeric ratio.

MATERIALS AND METHODS

Materials

Zidovudine was procured from Cipla Ltd., Bangalore, India. Acetone, polyethylene glycol (PEG-600) and Tween® 80 were all purchased from s.d. Fine Chemicals, Mumbai, India. Dialysis Membrane-110 was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India. PEG-1450 was purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI). Eudragit L100 was obtained from Rohm GmbH Chemische Fabrik (Darmstadt, Germany). Throughout the study, double distilled Milli Q water was used.

Preparation of zidovudine-loaded transdermal films

Films developed from Eudragit L100 containing PEG-600 and PEG-1450 as a plasticizer contained different amounts of drug (5%, 10%, and 20% by weight) with Tween® 80 as the penetration enhancer. The formulation details along with assigned codes are given in Table I. Films were prepared by solution casting followed by solvent evaporation. Eudragit polymer, plasticizer (5% w/w of dry weight of polymer), penetration enhancer (5% w/w of dry weight of polymer), and drug were all dissolved in acetone and stirred to produce homogeneous solution. Bubble-free solution was casted onto petri dish plates, films were dried in an oven at 35°C for 8 h and stored in a desiccator until further evaluation. There was no change in physical appearance or texture of the films even after storage. Drug-loaded films were characterized for film thickness, weight variations, and drug content. Thickness of the films was measured by digital vernier calipers at five different areas of the film and the average thickness.

Determination of zidovudine in the films

Films having specific size (area, 1.32 cm^2) were cut into small pieces and put into a 50 mL beaker. Phosphate buffer (pH 7.4) (12.5 mL) was added and the solution was kept for 4 h with occasional sonication. Solutions were filtered and drug concentration was determined[26] using HPLC (Shimadzu, Duisburg) using Spherisorb ODS column (5 μm, 250 × 4.6 mm inner diameter, Waters Corporation, Milford, MA) equilibrated with methanol : water (80 : 20, vol/vol) mixture at 25°C under a flow rate of 1.0 mL/min at the wavelength of 265 nm.

TABLE I
Formulation Compositions of Transdermal Films

Formulation code	Eudragit L100 (mg)	Plasticizer (5 %)	Drug loading (%)	Penetration enhancer
F1	600	PEG-600	5	(b)
F2	600	PEG-1450	5	(b)
F3	600	PEG-600	10	(b)
F4	600	PEG-1450	10	(b)
F5	600	PEG-600	20	(b)
F6	600	PEG-1450	20	(b)
F7 (Control)	600	(a)	10	(b)
F8	600	PEG-600	10	5 % Tween 80
F9	600	PEG-1450	10	5 % Tween 80

(a) and (b) not added.

Differential scanning calorimetry

Differential scanning calorimetric (DSC) experiments were performed on pure drug, placebo (Eudragit with PEG 600) and drug-loaded films using DSC (DSC7, Perkin Elmer) thermal analyzer. Samples were heated at the rate of 10°C/min from 25 to 400°C under an inert nitrogen atmosphere at a flow rate of 10 mL/min.

X-ray diffractometry

X-ray diffraction experiments were carried out on pure drug, placebo, and drug- containing films using powder X-RD technique with Philips model PW-1710 diffractometer attached to digital graphical assembly and computer with Cu-NF-25 KV/20-mA tube as the Cuα-radiation source in the angle range of 0°–50° of 2θ.

In vitro drug release

In vitro drug release was performed in 7.4 pH PBS using Keshary-Chien diffusion cell.[22,23] Appropriate size of the polymer films (area exposed to donor compartment was 1.32 cm^2) mounted between donor and receptor compartments of the diffusion cell (using dialysis membrane as the permeating barrier) that were held tightly by the springs. Donor compartment was empty and open to air, whereas the receptor compartment was filled with PBS and stirred at 100 rpm rotation speed. The entire assembly was maintained at 37°C using thermostatic water bath (Julabo LABORTECHNIK GMβH, Seelbach, Germany). The amount of drug released was determined by withdrawing each time 1 mL aliquot at the selected time intervals. The volume withdrawn was replaced with an equal volume of fresh and pre-warmed PBS. Analysis was done by HPLC.

Statistical analyses

Statistical analyses were done using SPSS statistical package. Analysis of the variance followed by least significant difference (LSD) procedure was used for comparison of drug release rates through different formulations and $p \leq 0.05$ was considered significant in data analysis.

RESULTS AND DISCUSSION

Preparation and physicochemical characterization of drug-loaded transdermal films

Monolithic matrix type films loaded with AZT were prepared by solution casting. In all, nine formulations were prepared by varying the amount of drug, plasticizer, and penetration enhancer as outlined in Table I. PEG-600 and PEG-1450 were used in concentrations of 5% (w/w) as the plasticizer, and Tween® 80 was used as the penetration enhancer. Various trials were taken to optimize the formulation to achieve the desired film thickness, flexibility, weight, drug loading, and release profiles. Physicochemical properties of the films are summarized in Table II. Films were transparent having uniform thicknesses in the range of 0.24–0.28 mm. Drug content of the films were varied from 1.62 to 7.55 mg per weight of the film. Films with uniform drug content and minimum batch variability were produced that weighed ~40 to 54 mg.

Differential scanning calorimetry

Thermal studies for pure drug, placebo, and drug-loaded films performed in the temperature range of 25–400°C at the heating rate of 10°C/min under inert nitrogen atmosphere at a flow rate of 10 mL/min are displayed in Figure 1. The change in baseline for all the samples around 50°C is attributed to slight moisture present in all the samples.

TABLE II
Physicochemical Properties of Transdermal Films

Formulation code	Thickness (mm)	Weight (mg)	Drug content (mg)	*n*	*r*[a]
F1	0.28	53.33	1.62	0.95	0.98
F2	0.26	48.66	1.67	0.97	0.92
F3	0.27	50.33	6.94	2.09	0.86
F4	0.27	49.00	3.82	0.83	0.96
F5	0.26	51.33	6.87	1.36	0.93
F6	0.27	51.00	7.55	2.23	0.90
F7 (control)	0.26	54.30	3.19	0.75	0.66
F8	0.26	51.30	2.00	0.79	0.98
F9	0.27	45.66	4.64	0.82	0.88
Placebo	0.24	40.00	–	–	–

[a] Statistical estimations were done at 95% confidence level.

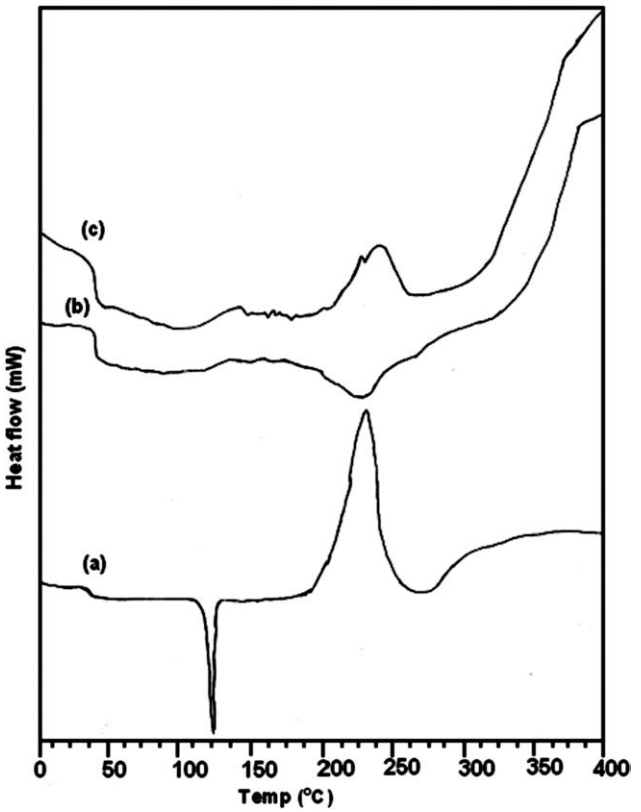

Figure 1 DSC thermograms of (a) pure drug, (b) placebo film and (c) drug-loaded film, F4.

Endothermic peak of AZT has appeared at its melting temperature as follows: 125°C (curve a). Placebo film (curve b) has shown an endothermic transition at 230°C, but no peak was observed near the endothermic peak exhibited by pure AZT. No melting endotherm is observed due to drug in the formulated films (curve c). Overall, the DSC results suggest the absence of any physical interactions between the polymer matrix and AZT.

X-ray diffraction

X-ray diffraction patterns of pure drug (curve a), placebo film (curve b), and drug-loaded film (curve c) are presented in Figure 2. Placebo film shows an envelope, at 16°. Diffractogram of AZT has several characteristic sharp peaks. The highest crystalline AZT peaks occurred at 2θ of 8.22°, 14.3°, 15.4°, 16.4°, 20.2°, 22°, 24.2°, and 26.4°, but series of smaller peaks are observed at 2θ of 9.8°, 19.2°, 30.2°, 32°, 34.6°, and 36.4°. In case of drug-loaded film, a peak at 16.7° is observed corresponding to placebo, but no peaks were observed in drug-loaded films corresponding to the crystalline AZT at 2θ of 8° to 26°, indicating that drug in the matrix film is not present completely in the crystalline state, but is in the amorphous solid dispersion state.

In vitro release studies

In vitro drug release was carried out in PBS using Keshary-Chien diffusion cell with dialysis membrane acting as the membrane barrier. The cell design is the same as discussed before.[22,27] The effect of AZT loading (5 %, 10% and 20% (w/w) in the polymer matrix) on its release from Eudragit films was studied at 37°C for up to 24 h. According to *in vitro* release profiles of films at different drug loadings with PEG-600 depicted in Figure 3(A), we see that AZT release decreased with increasing drug loading. However, the differences in the release rates of 10 and 20 wt % AZT-loaded films are not significant, but with 5 wt % AZT-loaded film, the release is quite large, probably due to facile solubility of AZT at its lower concentrations in PBS media.

The release results of the formulations containing different AZT concentrations with PEG-1450 as the plasticizer depicted in Figure 3(B) indicate that the release is reduced in 10% AZT-containing film, whereas an overshoot effect is observed for 5 wt % AZT-loaded films followed by drug release up to 24 h. Thus, this release data do not follow any systematic trend on effect of drug loading as was observed before for formulations containing PEG-600 as a plasticizer. Thus, one can see that with higher molecular weight plasticizer such as PEG-1450, the release rates are also higher, probably due to more hydrophilic nature of the polymer.

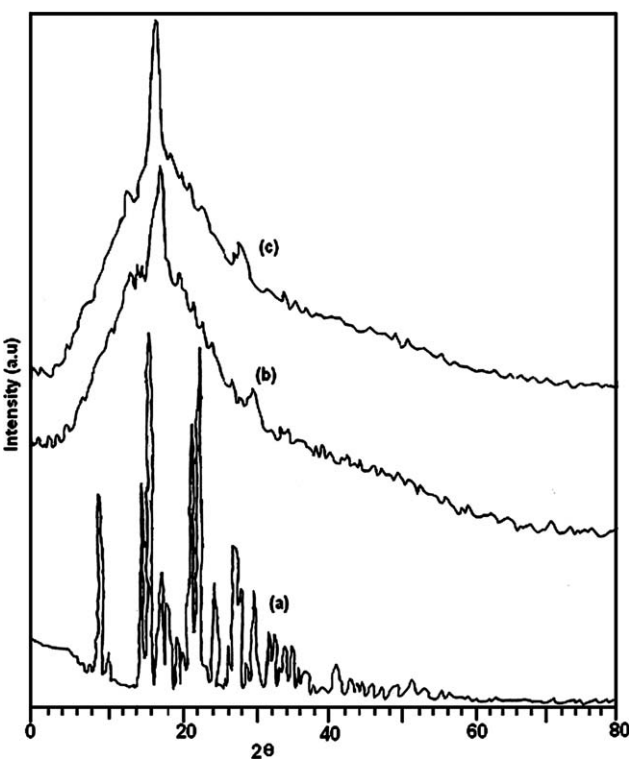

Figure 2 X-RD diffractograms of (a) pure drug, (b) placebo film and (c) drug-loaded film F4.

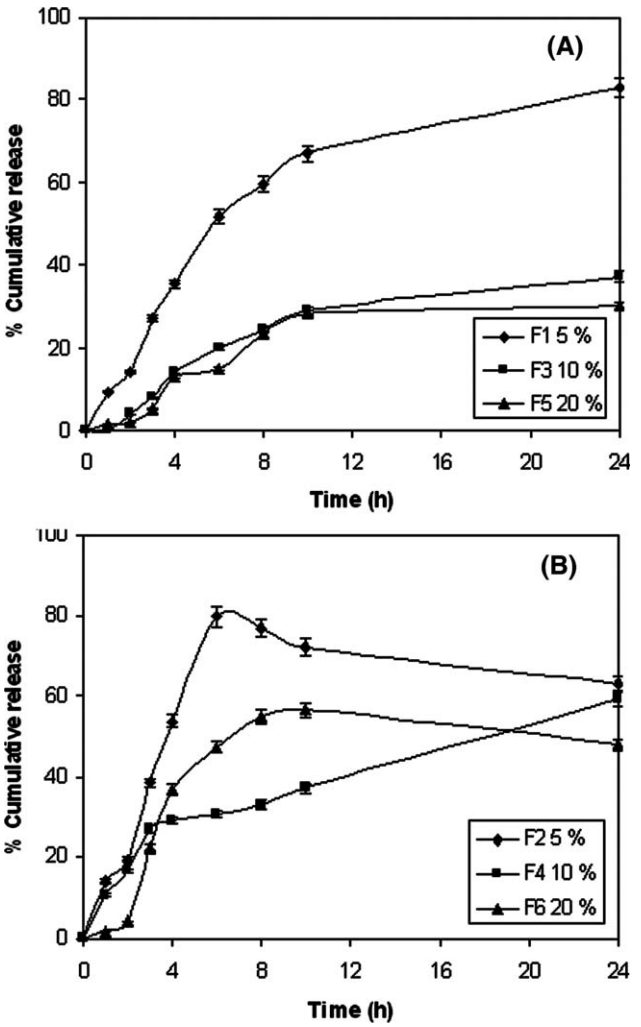

Figure 3 Effect of drug loading on *in vitro* release profiles: (A) 5% PEG-600 containing formulations and (B) 5% PEG-1450 containing formulations.

To perform a comparative study of drug release characteristics from formulations containing different drug loadings, a statistical analysis was made using the ANOVA method. The results of this analysis suggests that for formulations containing PEG-600, the F value was 4.63 ($df = 23$, $p = 0.021$), indicating significant difference in the release rates of AZT, whereas for PEG-1450, the F value was 0.49 ($df = 23$, $p = 0.619$), indicating insignificant difference in the release rates. This can also be confirmed form the release data displayed in Figure 3(A,B).

Drug release from a matrix type of release device is generally governed by diffusion.[28] During the process of dissolution of drug from the film matrices, its diffusion in the dissolution media is governed by the thermodynamic compatibility of PEG polymers along with Tween 80 and the drug itself.[29,30] In transdermal systems of the type studied here, one can consider two steps.[31,32] The first step accounts for changes in the intermixing of individual drug molecules at the matrix surface that depends on the rate of hydration, whereas the second step controls the rate of transport of drug from the surface across the skin, adjacent to the matrix film that is, towards the bulk of the *in vitro* media. Molecular diffusion is thus the driving force to induce the CR of drug,[33] which depends on the structural and morphological characteristics[34] in the amorphous regions and free volume spaces of the polymer matrix.[35] If pores are larger than the size of drug molecules, diffusion occurs by localized activated jumps from one pre-existing cavity to another, but smaller pre-existing cavities are unable to accommodate larger diffusing drug molecules. Eudragit is chemically polymethylmethacrylate, which has a larger cavity size in its network[36] compared with drug molecule. The matrices prepared from Eudragit (Eudragit, Eudragit: PEG-600/PEG-1450) seem to exert an influence on the diffusion of AZT, since the transport of drug is restricted by variations in three-dimensional segmental movements of the polymer chains.[37]

Plasticizers generally tend to reduce brittleness, improve flow, impart flexibility, increase toughness, strength, tear resistance, and impact resistance of the polymer. Thus, the effect of plasticizers on drug release from the Eudragit-matrix was studied at 37°C. The effectiveness of plasticizer was determined by comparing the drug release rates in the presence as well as absence of the plasticizer. In this study, two plasticizers with different molecular weights namely, PEG-600 and PEG-1450 were employed. From the release profiles of these formulations displayed in Figure 4, it is seen that enhanced release was observed for formulation F4 than formulation F3 as well as the control, indicating the effect of plasticizer on *in vitro* release of AZT. A comparison of drug release from AZT-containing Eudragit was

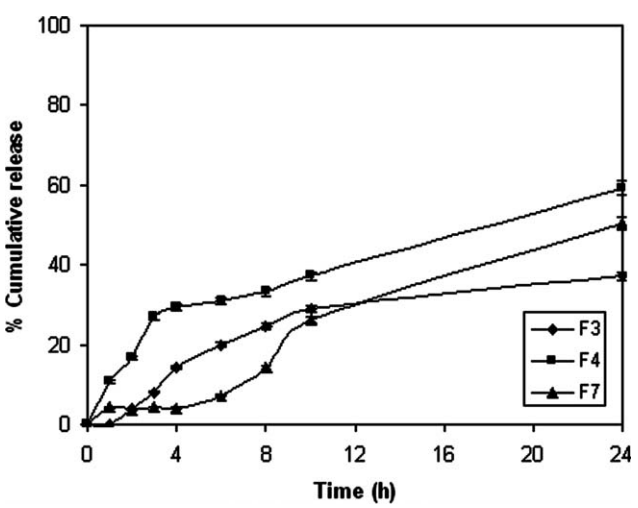

Figure 4 Effect of plasticizer concentration on *in vitro* release profiles.

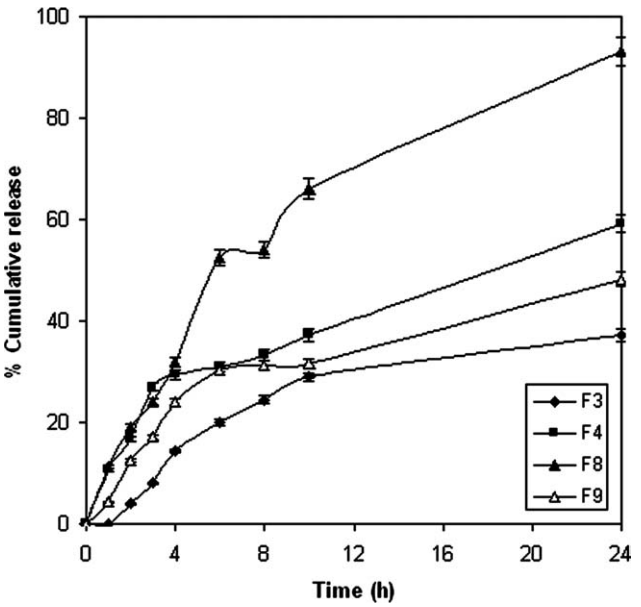

Figure 5 Effect of penetration concentration on *in vitro* release profiles.

also statistically evaluated by the ANOVA method. The F value was found to be 4.54 ($df = 23$, $p = 0.023$), indicating significant differences in the release of AZT.

In our study, Tween® 80 was used as a penetration enhancer. The release profiles of formulations F8 and F9 containing PEG-600 and PEG-1450 respectively along with 5 wt % of enhancer (Tween 80) and the data for F3 and F4 (without addition of enhancer) are shown in Figure 5. As observed before in Figure 4, the release data of F4 are higher than F3, but widely varying release profiles can be seen with F8 and F9. For instance, the release of F8 is much higher than F9, indicating the effect of the type of PEG used especially in the presence of Tween 80. Nonionic surfactants such as Tween 80 in the presence of two different molecular weight PEGs has produced a significant difference in the release profiles. By comparing formulations F3 and F4 with F8 and F9, we find that the rate of drug release was higher for Eudragit containing PEG-600 in the presence of Tween 80. Such a considerable increase in cumulative release of AZT through the matrix containing PEG-600 is due to the fact that low molecular weight PEG-600 seems to exert a synergic effect compared with high molecular weight PEG1450 in releasing the drug. To understand the differences in drug release rates of formulations F3, F4, F8, and F9, statistical evaluation by the ANOVA method was used. The calculated F value was found to be 2.93 ($df = 31$, $p = 0.05$), indicating significant differences in the release of AZT from the formulation containing Tween 80® as the enhancer with PEG 600; but in the case of PEG 1450, Tween 80 did not seem to enhance the release of AZT as reported before.[38] The increase in the rate of AZT release in the presence of enhancer could be due to pore e formation, resulting from the leaching out of drug from the film, thus creating free channels for liquid media to penetrate, thereby facilitating increased dissolution and transport of AZT.

The results of fractional release (M_t/M_∞) have been fitted to the empirical equation.[25]

$$\frac{M_t}{M_\infty} = Kt^n \tag{1}$$

where the values of the exponent, n represent the diffusion anomalies, whereas k is an empirical parameter that represents the interaction between drug and the polymer. In case of drug release from the swellable matrices, if $n = 0.5$, then transport is Fickian; if $0.5 < n < 0.1$, then transport follows anomalous (non-Fickian) trend. For $n = 1$, the zero-order release is operative, whereas for $n > 1$, transport is super Case-II. To investigate the type of drug transport trend, we have fitted the release data to eq. (1) and calculated the n values at 95% confidence limit, and these data for all formulations given in Table II suggest its variation from 0.75 to 2.23, meaning that transport changes from non-Fickian to super Case-II.

CONCLUSIONS

This study deals with the development of transdermal films prepared from Eudragit L100 and loaded with AZT, an anti-HIV drug. The films were prepared by solution casting using two different PEGs as the plasticizers along with Tween 80 as the enhancer to obtain transparent, smooth, and flexible patches. DSC performed on the drug-loaded films when compared with the placebo films along with pure drug, indicated no physical interactions between AZT and the matrix polymer. Drug crystalinity in the polymer matrix was confirmed by X-RD; AZT inside the matrix film was not in its crystalline form. *In vitro* drug release results were influenced by the extent of drug loading as well as the type of plasticizer along with the penetration enhancer. Empirical analysis of the release data gave n values ranging between 0.75 and 2.23, suggesting the change of transport from non-Fickian to super Case-II.

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