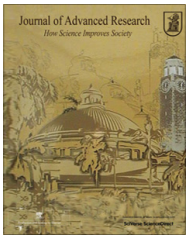
Journal of Advanced Research (2015) 6, 155–162

Cairo University

Journal of Advanced Research



ORIGINAL ARTICLE

A statistical experimental design approach to evaluate the influence of various penetration enhancers on transdermal drug delivery of buprenorphine

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ARTICLE INFO

Article history:
Received 27 September 2013
Received in revised form 25 December 2013
Accepted 12 January 2014
Available online 20 January 2014

Keywords:
Buprenorphine
Transdermal
Box–Behnken design
Skin penetration enhancer
Adhesion

ABSTRACT

A series of drug-in-adhesive transdermal drug delivery systems (patch) with different chemical penetration enhancers were designed to deliver drug through the skin as a site of application. The objective of our effort was to study the influence of various chemical penetration enhancers on skin permeation rate and adhesion properties of a transdermal drug delivery system using Box–Behnken experimental design. The response surface methodology based on a three-level, three-variable Box–Behnken design was used to evaluate the interactive effects on dependent variables including, the rate of skin permeation and adhesion properties, namely peel strength and tack value. Levulinic acid, lauryl alcohol, and Tween 80 were used as penetration enhancers (patch formulations, containing 0–8% of each chemical penetration enhancer). Buprenorphine was used as a model penetrant drug. The results showed that incorporation of 20% chemical penetration enhancer into the mixture led to maximum skin permeation flux of buprenorphine from abdominal rat skin while the adhesion properties decreased. Also that skin flux in presence of levulinic acid (1.594 μg/cm^2 h) was higher than Tween 80 (1.473 μg/cm^2 h) and lauryl alcohol (0.843 μg/cm^2 h), and in mixing these enhancers together, an additional effect was observed. Moreover, it was found that each enhancer increased the tack value, while levulinic acid and lauryl alcohol improved the peel strength but Tween 80 reduced it. These findings indicated that the best chemical skin penetration enhancer for buprenorphine patch was levulinic acid. Among the designed formulations, the one which contained 12% (wt/wt) enhancers exhibited the highest efficiency.

Introduction

A recent approach in drug delivery system is administering drugs with specific rates through skin as the site of application. In the past decade, much attention has been paid to a specific transdermal drug delivery system (TDD), also known as "patch" system [1]. This system has many advantages such as the elimination of the first pass effect and its side effects with

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Peer review under responsibility of Cairo University.

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http://dx.doi.org/10.1016/j.jare.2014.01.006

steady delivery of medicine over long period of time [2]. Nevertheless, this system has some limitations. It is known that some agents such as penetration enhancers and pressure sensitive adhesives can have influence on skin permeation flux and adhesive properties of TDDs [3–5]. Buprenorphine is a partially opiate drug with an analgesic potency of about 25–50 times higher than an equivalent dose of morphine. This drug has sufficiently low molecular weight with lipophilic properties so it can be a suitable candidate to be administered by TDDs. This drug has been used to relieve chronic and cancer pain via several routes such as sublingual and transdermal [6,7]. Transtec® is a transdermal formulation of buprenorphine which has become available in three dosage levels [8]. Although transdermal drug delivery has many advantages in relation to inherent barrier properties of the skin, but as yet it is not widely used. Many different approaches have been adopted to overcome the barrier properties of skin, such as mechanical and chemical penetration enhancers. Therefore, chemical penetration enhancers are used in TDDs to increase the diffusion rates of drugs to overcome the resistance of stratum corneum [9].

Although there are some literature sources that have evaluated the effects of chemical penetration enhancers on skin permeation flux and mode of behavior of different hydrophilic and hydrophobic drugs, but no report has been published yet on the role of buprenorphine with respect to skin permeation flux and adhesion properties of the final patches using an adhesive with carboxylic functionality incorporated with lauric alcohol, leuvinic acid, and a surfactant such as Tween 80, as skin penetration enhancers into the formulations. In the present work, the optimization of the final desirable formulations for skin permeation flux and adhesion properties was also accomplished by Box–Behnken method as a statistical tool and that such combination has not been tried before by other researchers.

The objective of the present work was to design new TDDs with an acrylic adhesive and different types and concentrations of chemical penetration enhancers (CPE) and to study their skin permeation flux and adhesion properties. For this purpose the best formulation was selected by employing response surface experimental design method. Therefore, levulinic acid, lauryl alcohol, and Tween 80 were used as penetration enhancers as variable parameters in order to evaluate their effects on skin permeation flux and adhesion properties of their corresponding systems.

Material and methods

Materials

Acrylic adhesive Duro-Tak 87-2196 was purchased from National Starch and Chemical Company, USA. Tween 80 and levulinic acid (LEA) were obtained from Merck, Germany. Lauryl alcohol (LA) was supplied by Fluka, USA. Buprenorphine, as an active ingredient, was obtained from Behansar Pharmaceutical Company, Iran. The backing layer with thickness of 85 μm and Scotchpak1022 as a release liner was provided from 3 M Company, USA. All solvents of high-performance liquid chromatography (HPLC) grades were purchased from Merck, Germany.

Determination of buprenorphine

The standard and real samples of buprenorphine were analyzed by HPLC (Younglin, SDV30) with UV detector at 285 nm. The HPLC separation system consisted of a PerfectSil Target C18 column (150×4.6 mm, 5 μm) equipped with a guard column (10×4.0 mm, 5 μm); the temperature of HPLC column was maintained at 40 °C. The mobile phase consisted of acetonitrile/KH_2PO_4 10 mM (45:55) with pH 3.0 ± 0.1 (adjusted by phosphoric acid) at 1 ml/min flow rate, and the volume of injection was set at 20 μl. A standard stock solution of buprenorphine (1000 μg mL^{-1}) was prepared in methanol. Calibration standard solutions of 0.5, 1, 5, 10, 15, 20, 30 μg/ml of buprenorphine were prepared by further dilution of a stock standard solution in phosphate buffer (pH 6). All of these solutions were stored in a refrigerator (4 °C) and brought to ambient temperature just prior to use. Each peak area was plotted against its corresponding concentration to obtain the calibration graph. The data of peak area versus concentration were treated by linear least square regression analysis. The method was validated according to the ICH guidelines [10]. The validation characteristics included accuracy, precision, linearity range, selectivity, limit of detection (LOD), and limit of quantitation (LOQ). The results showed a good correlation between analyte peak area and concentration with (r^2 = 0.9990). The limit of detection (LOD) and limit of quantitation (LOQ) in the release media were 0.15 and 0.5 μg mL^{-1}, respectively. Also, to evaluate the performance of the proposed method, it was used in the analysis of buprenorphine level in real samples.

Sample preparation

The preparation of buprenorphine patches was performed in two stages. At first, the pressure sensitive adhesive (Duro-Tak 87-2196) was thoroughly mixed with each chemical penetration enhancer and buprenorphine in a rotary mixer at room temperature to prepare formulations as given in Table 1. In the next step, the mixed solutions (total weight of each solution: 2 g) were coated on the $5 * 5$ cm^2 backing layer (outermost layer) of the patch by an Elcometer film applicator (3580 SPRL 75 mm) to obtain a layer with uniform thickness (80 μm). Next, the prepared film was kept at ambient temperature for 20 min and then placed in an oven of 50 °C for 40 min to remove the remaining solvent completely [11].

Skin preparation for permeation study

Male Sprague–Dawley rats, each weighing 250 ± 25 g, supplied by Razi Vaccine and Serum Research Institute were anesthetized with ether. The abdominal hair of each rat was shaved by hand razors, and a 5×5 cm^2 area of a full thickness abdominal skin was surgically removed. For removal of the residual fat, the dermis section of the skin was soaked in isopropyl alcohol. The skin was brought into contact with normal saline 1h before sampling from the diffusion cell [12–14]. *All Institutional and National Guidelines for the care and use of animals were followed.*

Permeation study

Permeation studies of buprenorphine from a drug-in-adhesive patch were performed in a well-characterized Chien diffusion

Table 1 Formulation components as independent variables (wt/wt%).

Run (randomly)	Run (formulation number)	Lauryl alcohol (wt/wt%)	Tween 80 (wt/wt%)	Levulinic acid (wt/wt%)	Adhesive (wt/wt%)	Buprenorphine content (wt/wt%)
4	1	0	4	8	80	8
13	2	8	8	4	72	8
1	3	4	0	8	80	8
2	4	0	0	4	88	8
10	5	0	8	4	80	8
3	6	8	0	4	80	8
15	7	4	8	8	72	8
7	8	4	4	4	80	8
5	9	4	0	0	88	8
6	10	0	4	0	88	8
8	11	4	8	0	80	8
11	12	4	4	4	80	8
12	13	4	4	4	80	8
9	14	8	4	0	80	8
14	15	8	4	8	72	8

cells with diffusion area of 1 cm^2 and kept at fixed temperature of 37 °C. The receptor compartment was filled with 3 ml phosphate buffer solution of pH 6 as a receptor medium. The prepared skin was cut by about $1.5 \times 1.5\ cm^2$ dimension and put on the receptor cell, and the transdermal patch was applied onto the stratum corneum (SC) of the skin. At each predetermined time interval (1, 2, 4, 8, 12, 24, 36, 48, 56, 72 and 96 h), a definite volume (3 ml) of solution was withdrawn from the receptor compartment which was immediately compensated by an equal volume of fresh phosphate buffer. Finally, the drug concentration of each sample was determined by a Younglin HPLC analyzer (SDV30) [13,15].

Data analysis

The skin flux of buprenorphine through the abdominal skin was calculated by plotting the cumulative amount of buprenorphine permeated through skin versus time. The steady state flux and lag time were estimated from the slope of the linear region of the obtained graph and its intercept on the *X*-axis, respectively [16].

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was performed on VEGA/TESCAN model operating at an accelerating voltage of 20 kV and magnification of 10,000×. The specimens were cryogenically fractured in liquid nitrogen and coated by a thin layer of gold to improve resolution.

Probe tack test

Tack tests were performed on all samples, each with 80 μm thickness, according to (ASTM D-2979), by using a Chemie Instrument Probe Tack-500 (Fair Field, Ohio, USA) for at least five samples [13].

Peel strength measurement at 180°

Peel tests on adhesive-coated tapes were carried out according to ASTM D-3330 [13]. The samples, each $2.5 \times 2.5\ cm^2$, were adhered to a stainless steel as a test panel and then rolled twice with a 4.5 kg roller to bond it to the test panel firmly. The tests were measured at a peel rate of 300 mm/min by using a Chemie Instrument adhesive/release tester AR-1000 (Fair Field, Ohio, USA). The test was repeated at least five times on 5 identical samples.

Thermal analysis

The glass transition temperature (T_g) of various formulations was measured by differential scanning calorimeter (DSC) on a PL-1500 with heating rate of 10 °C/min under N_2 atmosphere. It should be noted that exactly the same sample preparation steps, given in sample preparation method, were adopted for all samples except with different coating. Each test sample was coated on the release liner while the main sample was coated on the backing layer. The reason of such action was that at the time of testing, the coated layer needed to be separated from release liner for conducting such test.

Experimental design

The Design-Expert 6.0.0 software of response surface method was used to estimate the coefficient of model for statistical design of the experiments [17]. A response surface methodology (RSM) using Box–Behnken design, with three factors and three levels, was performed to investigate the effect of variable factors on system's response. Some factors in the analysis of variance table such as prediction of multiple correlation coefficients (prediction R^2), adjusted R^2, lack of fit, and *P*-value were important for selection of adequate models [18,19]. The modified quadratic was selected as a good fit for model. The concentration effects of levulinic acid (LEV), lauryl alcohol (LA), and Tween 80 (T), as independent variables, on skin permeation, tack value, and peel strength were investigated. In Box–Behnken design, the experimental points were placed on a hypersphere with some characteristics as follows:

- Number of experiments obtained from $N = 2\,k\,(k-1) + Cp$ where k would be the number of factors and Cp the number of central points.
- All factor levels adopted at three levels.

A number of 15 experiments were obtained with three factors and three levels, and they were augmented with three replications at the central point to estimate "pure error." A polynomial model, to include interactions and quadratic terms, was adopted as follows:

$$Y = \beta_0 + \sum_{i=1}^{k}\beta_i x_i + \sum_{i=1}^{k}\beta_{ii}x_{ii}^2 + \sum_{i=1}^{k}\sum_{i\leqslant jj}^{k}\beta_{ij}x_i x_j + \varepsilon \quad (1)$$

where Y denoting the response; k as the number of variables; x_i symbolizing the independent variables; ε the residual associated to the experiments; β_0 the constant of coefficient; and β_i, β_{ii}, and β_{ij} representing the coefficients of the linear, quadratic, and interaction parameters, in the order given.

For Box–Behnken model, with three variable factors and three levels ($k = 3$), the Eq. (1) was expanded as follows [17,19,20]

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{11}x_1^2 + \beta_{22}x_2^2 + \beta_{33}x_3^2 + \beta_{12}x_1 x_2 + \beta_{13}x_1 x_3 + \beta_{23}x_2 x_3) \quad (2)$$

In this study, the concentrations of independent variables were adjusted as 0%, 4%, 8% (wt/wt) and also all formulations contained 8% (wt/wt) buprenorphine as given in Table 1. The effects of independent variables on dependent variables, shown in three-dimensional plots, were obtained for responses based on the effects of three variable factors at three levels.

Results and discussion

Skin permeation studies

Skin permeation across rat skin for 15 formulations, each containing 8% (wt/wt) buprenorphine, was evaluated, and the results of permeation parameters were summarized and presented in Table 2. The skin permeation flux and the effects of levulinic acid (LEV), lauryl alcohol (LA), and Tween 80 (T) were determined by RSM to promote an empirical model. The quadratic equations for skin permeation were developed, and the ANOVA results for this model showed that the quadratic equation was no lack of fit, and the coefficient of prediction (R^2) and adjusted (R^2) were found to be 0.81 and 0.84, respectively. This meant that the model equation achieved from RSM was suitable to depict the skin permeation flux under

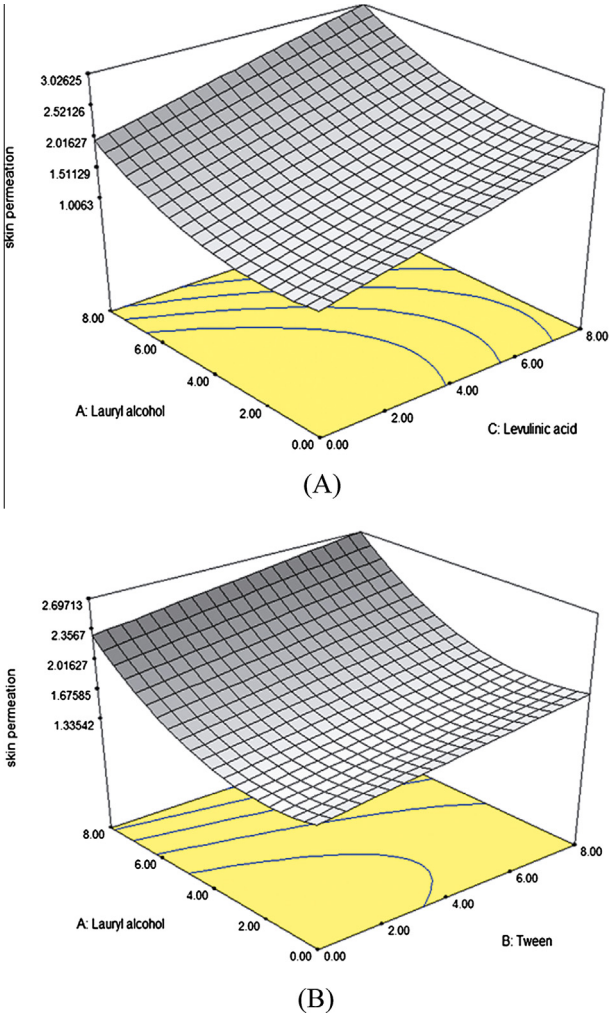

Fig. 1 Response surface for skin permeation flux versus (A) for LA and LEV at T = 4% and (B) for LA and T at LEV = 4%.

Table 2 Skin permeation parameters.

Run (formulation number)	Correlation coefficient	Skin permeation flux (μg/cm^2 h)	SD	Lag time (h)
1	0.994	2.026	0.5	0.81 ± 0.003
2	0.991	3.087	1.01	*n.d*[a]
3	0.972	2.544	1.001	4.27 ± 0.006
4	0.996	1.594	0.23	0.98 ± 0.007
5	0.991	1.341	0.02	2.57 ± 0.006
6	0.996	2.344	0.8	0.76 ± 0.001
7	0.988	2.669	0.8	*n.d*
8	0.996	1.445	0.12	1.36 ± 0.005
9	0.990	0.843	0.01	2.88 ± 0.001
10	0.995	1.473	0.1	1.38 ± 0.001
11	0.995	1.851	0.7	1.92 ± 0.006
12	0.991	1.282	0.3	1.26 ± 0.006
13	0.995	1.672	0.2	1.42 ± 0.004
14	0.984	1.681	0.86	3.36 ± 0.009
15	0.969	2.865	1.53	*n.d*
No enhancer	0.971	0.572	0.6	4.31 ± 0.003

[a] n.d = this value cannot be determined.

chemical skin penetration enhancer concentrations. The final model adopted for skin permeation flux was as follows:

$$\text{Skin permeation flux} = 1.66 + 0.44(\text{LA}) + 0.2(\text{T}) + 0.53(\text{LEV}) + 0.39(\text{LA})^2$$

To investigate the effects of LEV, LA and T on skin permeation of buprenorphine the response surface graphs were plotted and presented in Fig. 1. The Table 2 is given to confirm the claim made by Fig. 1. The plots in Fig. 1 show that the skin permeation flux is enhanced with increase in LEV, LA, and T percentages in each mixture. The simultaneous addition of LEV, LA, and adhesive (run 3) has had an additional effect, and hence, the skin permeation flux is increased. As it is listed in Table 2 and the coefficient of LEV(0.53) in equation of skin permeation flux, among all enhancers, the addition of LEV to the formulation (run 4) has resulted in higher skin permeation flux compared to formulations 9 (with lauryl alcohol only) and 10 (with Tween 80 only).

The effect of LA in enhancement of skin permeation flux could be due to the chemical structure of LA, because this fatty alcohol might disrupt the intercellular lipid bi-layers and increase the diffusion of the drug into the skin. Besides, LA might fluidize the lipids in stratum corneum (SC) and so increase the partitioning of the drug into skin [21,22]. Therefore, with increases in diffusion coefficient and partitioning of drug, the skin permeation flux might be enhanced.

Tween 80 as a non-ionic surfactant might enhance the skin permeation flux by two possible mechanisms. First, the surfactants increase the fluidity and solubility of lipid components of SC followed by their permeation into the intercellular of the SC. Then, the surfactants could come into interaction and bind with keratin fibrils and possibly disrupt the corneocyte. The chemical structure of Tween 80 may help the skin permeation of buprenorphine by lipophilic and hydrophilic mechanisms and therefore enhancing the partition process between the lipophilic content and hydrophilic protein [16,23,24]. As it is illustrated in Table 2, among some types of additives used in this study, the formulation containing LEV shows the highest skin permeation flux so it may have acted as a chemical skin penetration enhancer. The enhancement of skin permeation flux by LEV may be associated with disrupting the intercellular lipid domains [25], while Holas et al. [26] have reported the important role of hydrogen bonding taking place between the permeation enhancers and the drug. As our objective was to decrease the interaction between the drug and the adhesive, therefore the permeation of the drug through the skin was enhanced by LEV which might have increased skin permeation flux. The results given in Table 2 demonstrate that the simultaneous addition of LEV and LA into the mixture has boosted skin permeation flux compared to the mixture into which LEV and other enhancers have been added. This is clearly evident in SEM images, where the micrographs reveal higher solubility of buprenorphine in the patch matrix (Fig. 2) of LEV-LA (run

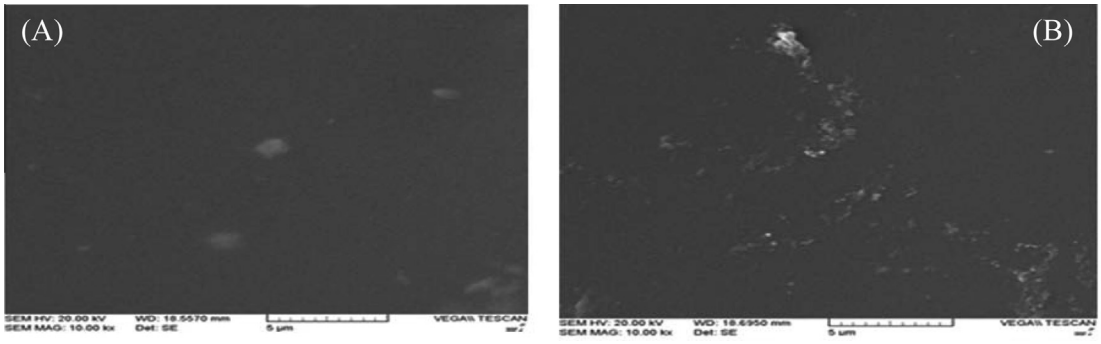

Fig. 2 SEM micrographs of (A) sample 3 (B) sample 4 at 10,000× magnification.

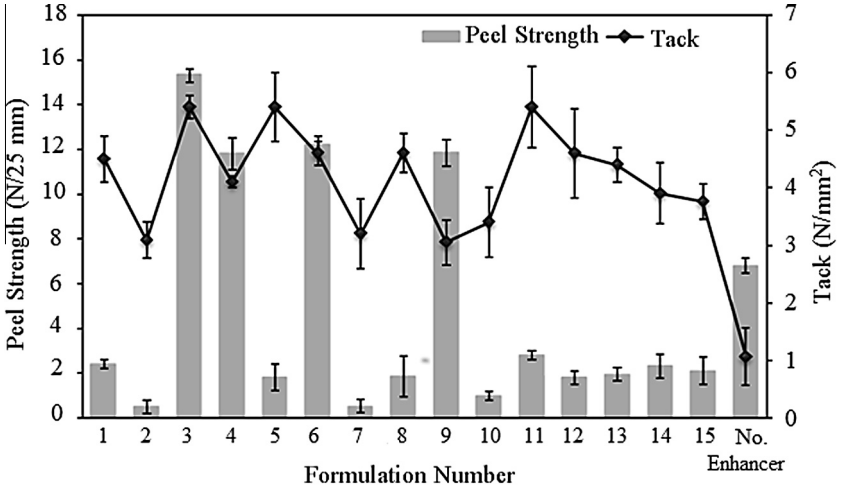

Fig. 3 Tack value for all samples.

3) and LEV samples. These images contain white spots which reveal the drug phase. The micrographs indicate that solubility of drug in formulation 3 (run 3) is higher than formulation 4 (run 4). The reason for this behavior can be explained by simultaneous addition of LEV and LA into the mixture and its effect on skin permeation flux.

Studies on adhesive properties (tack value and peel strength)

For prediction of tack value, a modified quadratic model was used. The quadratic equations for tack have been developed as:

$$\text{Tack} = 4.65 - 0.23(\text{LA}) + 0.19(\text{T}) + 0.39(\text{LEV}) - 0.51(\text{LA})^2 - 0.71(\text{LA})(\text{T}) - 0.63(\text{LEV})(\text{T})$$

ANOVA table illustrates that the quadratic model has no lack of fit, and adjusted R^2 and prediction R^2 are close to each other, and some factors such as LEV, LA * T and T * LEV are significant parameters, implies that P-value is less than 0.05. These results are observed, and the selected model seems adequate to show the actual relationship between the responses and significant variables.

Table 3 Glass transition temperature of samples.

Run (formulation number)	T_g (°C)
4	−37
9	−47.3
10	−55.7
No enhancer	−50.7

Tack is the property of adhesives that allows the immediate formation of a bond with another surface under light contact pressure. Tack is a complex response of adhesive surface and bulk properties, so viscoelastic properties and glass transition temperature of adhesive play important role in degree of tack value [27]. It is worth mentioning that another sample (with no enhancer) was prepared, besides other samples mentioned in Table 1, with the following specification:

LEV = 0%, LA = 0% and T = 0% (wt/wt) and designated as "no enhancer."

The reason for preparation of such sample was to estimate the effect of additives on adhesion properties. As shown in Fig. 3, by addition of each CPE to the mixture, the tack values were found to be higher than a sample having "no enhancer," and this aspect is included in tack value equation. It is evident that in Fig. 4, all skin permeation enhancers show increased tack value by up to 12% incorporated CPE adhesive.

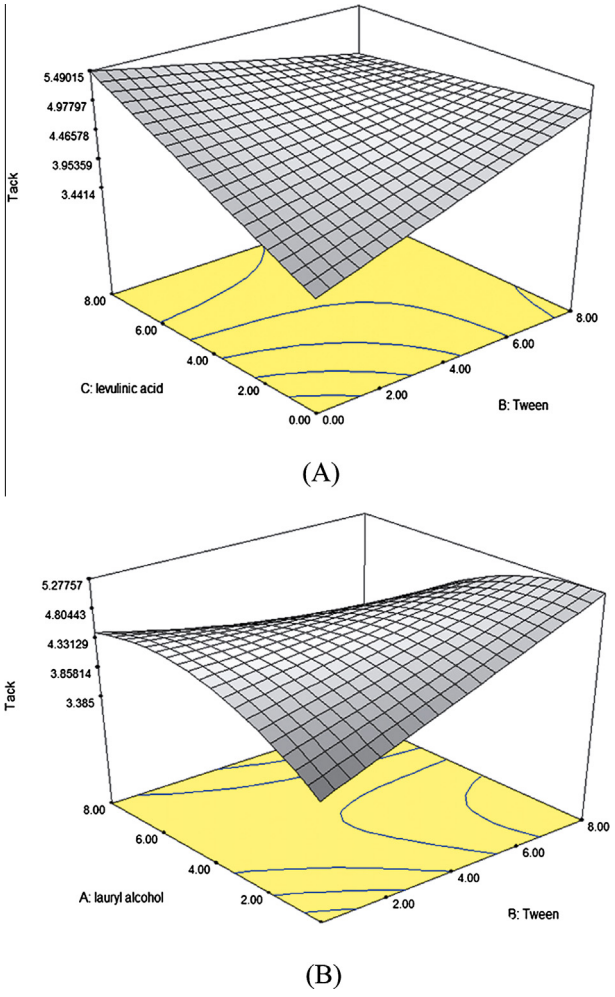

Fig. 4 Response surface for tack value versus (A) for T and LEV at LA = 4% and (B) for LA and T at LEV = 4%.

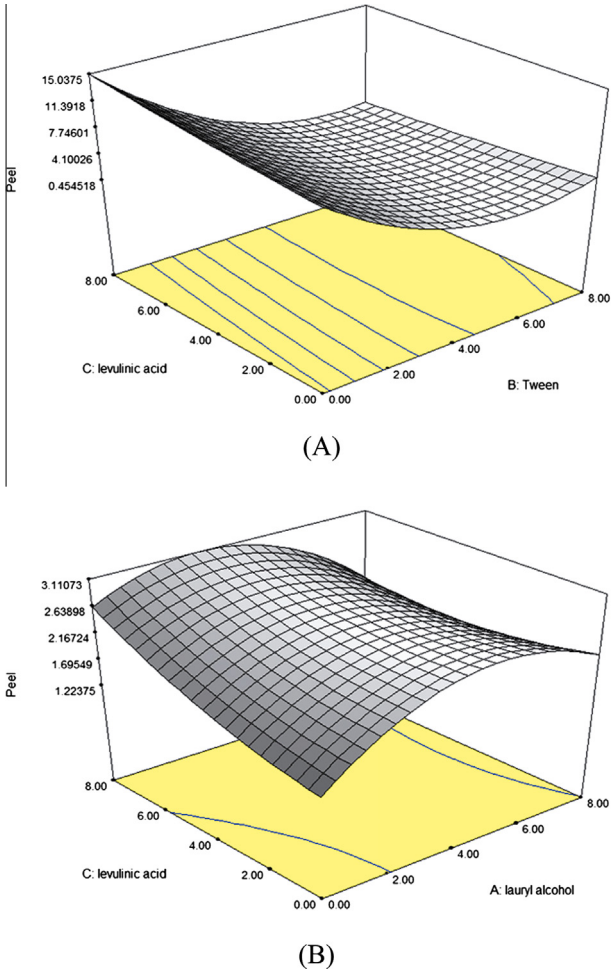

Fig. 5 Response surface for peel strength versus (A) for T and LEV at LA = 4% and (B) for LA and LEV at T = 4%.

Table 3 shows glass transition temperature (T_g) of the mixtures in presence of each skin penetration enhancer. As it is evident in samples containing LEV and LA of 4% (w/w) have higher T_g and Tween 80 (in 4% w/w) has lower T_g. As it is illustrated in Fig. 3, the tack values of all samples are higher than the sample with "no enhancer" and so CPE has acted as tackifier, though according to Table 3, Tween 80 has acted as a plasticizer, and LEV and LA have acted as tackifiers as well. The effect of plasticizer has been reported to lower the T_g and the modulus of the compound and thus increasing the fluidity of the adhesive and wetting of the adherent [28]. Therefore, the plasticizer has increased the tack value and has provided viscous flow of the adhesive for bonding with a low deformation rate. On the other hand, LEV and LA which have increased the T_g of the mixture might have also enhanced the tack value due to increased G'' at higher frequency [27,29].

The equation below describes the modeling of peel strength by using a quadratic model:

$$\begin{aligned}\text{Peel strength} = {} & 2.55 + 0.015(\text{LA}) - 5.69(\text{T}) + 0.3(\text{LEV}) \\ & - 0.82(\text{LA})^2 + 4.85(\text{T})^2 + 0.22(\text{LEV})^2 \\ & - 0.42(\text{LA})(\text{T}) + 0.4(\text{LA})(\text{LEV}) \\ & - 1.43(\text{T})(\text{LEV})\end{aligned}$$

There has been no lack of fit for this model. This model has significant terms such as T, LA^2, T^2, and T * LEV. Therefore, P-value is below 0.05 for these terms. Also, the adjusted R^2 and prediction R^2 were 0.98 and 0.94, respectively. Thus, this model has best prediction for response. It is shown in Fig. 5 that the incorporation of just LEV or LA into the mixture the peel strength would be higher than neat mixture (sample without enhancer) which may also be proved by peel strength equation as well. In Table 4, the coefficients in dependent variables equation with their P-values are presented. By addition of LEV and LA together into the mixture, the synergistic effect on peel strength was observed. The reason for that was due to increased T_g by addition of LEV and LA. Cantor et al. have shown that there is a relationship between T_g and peel strength of pressure sensitive adhesive [29]. In this respect, Kendall et al. have reported that the peel adhesion increases with higher T_g [29] and Schrijvers et al. have stated that peel and tack could be enhanced with increased T_g [29]. On the other hand, Taghizadeh et al. have found that the peel strength is decreased with lower T_g of the mixture [30]. Tween 80 reduces T_g of the mixture by increasing the space between the entanglement and free volume so it plays the role of a plasticizer. Therefore, the results have shown that peel strength is decreased by addition of Tween 80 into the mixture. It should be noted that the above effects are found to be valid up to 12% CPEs incorporated into the adhesive and after that the peel strength is dropped because of the relative reduction in adhesive content.

Table 4 Coefficients of dependent variables equation with their P-values.

CPE	Coefficient of equation	P-value
Skin permeation		
LA	+0.44	0.046
T	+0.2	0.044
LEV	+0.53	0.049
LA^2	+0.39	0.047
Tack		
LA	−0.23	0.051
T	+0.19	0.053
LEV	+0.39	0.049
LA^2	−0.51	0.051
(LA)(T)	−0.71	0.046
(LEV)(T)	−0.63	0.042
Peel strength		
LA	+0.015	0.052
T	−5.69	0.039
LEV	+0.3	0.051
LA^2	−0.82	0.041
T^2	+4.85	0.036
LEV^2	+0.22	0.052
(LA)(T)	−0.42	0.051
(LA)(LEV)	+0.4	0.053
(LEV)(T)	−1.43	0.046

Conclusions

The effects of different types of chemical penetration enhancers on skin permeation flux, tack value, and peel strength of buprenorphine transdermal patches were investigated. It was found that skin penetration flux of buprenorphine and adhesion properties of the patches were controlled by each permeation enhancer concentration. LEV, LA, and Tween 80 could enhance permeation flux of buprenorphine through the skin. Also, both LEV and LA together have had synergistic effect on skin permeation flux. According to adhesion properties, it was observed that by addition of LEV, LA, and Tween 80 into the matrix, the tack value was increased due to the two former roles as tackifiers and Tween 80 acting as a plasticizer. On the other hand by incorporation LEV and LA into the system, the peel strength was increased and by addition of Tween 80 the peel strength was reduced. All these effects were realized at maximum 12% (wt/wt) chemical penetration enhancers incorporated into the system, which beyond that concentration the adhesion properties (tack and peel) were reduced.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Acknowledgment

The authors express our gratitude to Ms. Mivehchi for the linguistic corrections and critical comments of the manuscript.

References

[1] Shingade G. Review on: recent trend on transdermal drug delivery system. J Drug Del Thera (JDDT) 2012;2:66–75.
[2] Mehdizadeh A, Ghahremani MH, Rouini MR, Toliyat T. Effects of pressure sensitive adhesives and chemical permeation enhancers on permeability of fentanyl through excised rat skin. Acta Pharm 2006;56:219–29.

[3] Dimas DA, Dallas PP, Rekkas DM, Choulis NH. Effect of several factors on the mechanical properties of pressure-sensitive adhesives used in transdermal therapeutic systems. AAPS PharmSciTech 2000;1:80–7.
[4] Gaur P, Mishra S, Purohit S, Dave K. Transdermal drug delivery system: a review. Asian J Pharm Clin Res 2009;2:14–20.
[5] Kim JH, Lee CH, Choi HK. Transdermal delivery of physostigmine: effects of enhancers and pressure-sensitive adhesives. Drug Dev Ind Pharm 2002;28:833–9.
[6] Davis MP. Buprenorphine in cancer pain. Supp Care Can 2005;13:878–87.
[7] Cowan A, Lewis J, Macfarlane I. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol 2012;60:537–45.
[8] Freye E, Anderson-Hillemacher A, Ritzdorf I, Levy JV. Opioid rotation from high-dose morphine to transdermal buprenorphine (Transtec®) in chronic pain patients. Pain Practice 2007;7:123–9.
[9] Subedi RK, Oh SY, Chun MK, Choi HK. Recent advances in transdermal drug delivery. Arch Pharm Res 2010;33:339–51.
[10] ICH harmonized tripartite guideline. Current Step 4 version, Parent Guideline dated 27 October 1994, (Complementary Guideline on Methodology dated 6 November 1996 incorporated in November 2005).
[11] Taghizadeh SM, Soroushnia A, Mirzadeh H, Barikani M. Preparation and *in vitro* evaluation of a new fentanyl patch based on acrylic/silicone pressure-sensitive adhesive blends. Drug Dev Ind Pharm 2009;35:487–98.
[12] Shokri J, Nokhodchi A, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar Jalali M. The effect of surfactants on the skin penetration of diazepam. Int J Pharm 2001;228:99–107.
[13] Taghizadeh S, Soroushnia A, Mohamadnia F. Functionality effect of pressure sensitive adhesives on *in vitro* drug release behavior of fentanyl drug in an adhesive patch. Iran J Sci Technol 2010;22:429–37.
[14] Amit Kumar J, Narisetty Sunil T, Ramesh P. Transdermal drug delivery of imipramine hydrochloride. I. Effect of terpenes. J Control Release 2002;79:93–101.
[15] Sharma K, Roy SD, Roos EJ. Inventors; US Patent 5069909, assignee. Transdermal administration of buprenorphine; 1991.
[16] Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. Int J Pharm 2003;250:359–69.
[17] Bezerra MA, Santelli RE, Oliveira EP, Villar LS, Escaleira LA. Response surface methodology (RSM) as a tool for optimization in analytical chemistry. Talanta 2008;76:965–77.
[18] Kim JS, Kim MS, Park HJ, Lee S, Park JS, Hwang SJ. Statistical optimization of tamsulosin hydrochloride controlled release pellets coated with the blend of HPMCP and HPMC. Chem Pharm Bull (Tokyo) 2007;55:936–9.
[19] Ferreira SLC, Bruns R, Ferreira H, Matos G, David J, Brandao G, et al. Box–Behnken design: an alternative for the optimization of analytical methods. Anal Chim Acta 2007;597:179–86.
[20] Hanrahan G, Lu K. Application of factorial and response surface methodology in modern experimental design and optimization. Crit Rev Anal Chem 2006;36:141–51.
[21] Benson HAE. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Del 2005;2:23–33.
[22] Kanikkannan N, Singh M. Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. Int J Pharm 2002;248:219–28.
[23] Lopez A, Llinares F, Cortell C, Herraez M. Comparative enhancer effects of Span® 20 with Tween® 20 and Azone® on the *in vitro* percutaneous penetration of compounds with different lipophilicities. Int J Pharm 2000;202:133–40.
[24] Ashton P, Walters KA, Brain KR, Hadgraft J. Surfactant effects in percutaneous absorption I. Effects on the transdermal flux of methyl nicotinate. Int J Pharm 1992;87:261–4.
[25] Sinha V, Kaur MP. Permeation enhancers for transdermal drug delivery. Drug Dev Ind Pharm 2000;26:1131–40.
[26] Holas T, Vávrová K, Klimentová J, Hrabálek A. Synthesis and transdermal permeation-enhancing activity of ketone, amide, and alkane analogs of Transkarbam 12. Bioorg Med Chem 2006;14:2896–903.
[27] Satas D. Handbook of pressure sensitive adhesive technology. USA: Van Nostrand Reinhold; 1989.
[28] Mahdavi H, Taghizadeh M. The effect of alpha hydroxy acids on the tack of pressure sensitive adhesive. Iran Polymer J 2005;14:379–85.
[29] Benedek I. Pressure-sensitive adhesives and applications. New York: Marcel Dekker, Inc.; 2004.
[30] Taghizadeh S, Lahootifard F. Effect of different skin permeation enhancers on peel strength of an acrylic PSA. J Appl Polym Sci 2003;90:2987–91.