Research Article

Lidocaine Transdermal Patch: Pharmacokinetic Modeling and *In Vitro–In Vivo* Correlation (IVIVC)

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Abstract. The present study aims to develop the correlation between *in vitro* and *in vivo* skin permeation of lidocaine in its transdermal patch. In order to minimize the run-to-run variability during *in vitro* skin permeation studies, release normalized cumulative percent ($\%C_{tn}$) was calculated. A suitable polynomial mathematical model was used to establish a correlation between time and $\%C_{tn}$. Percent *in vivo* absorbed was calculated by using numerical deconvolution (NDC) and non-compartmental analysis (NCA) methods. Pharmacokinetic (PK) parameters such as AUC_{last} and C_{max} were predicted with the established *in vitro–in vivo* correlation (IVIVC) models. The minimum prediction errors in NDC method for C_{max} were found to be -30.9 and -25.4% for studies I (*in vivo* study in human volunteers with one batch of Lidoderm patch; internal validation) and II (*in vivo* study in human volunteers with another batch of Lidoderm patch; external validation), respectively, whereas minimum prediction errors in NCA method were relatively low (3.9 and 0.03% for studies I and II, respectively) compared to those in NDC method. The prediction errors for AUC_{last} were found to be less than 2% for both methods and studies. The established method in this study could be a potential approach for predicting the bioavailability and/or bioequivalence for transdermal drug delivery systems.

KEY WORDS: bioequivalence; IVIVC; lidocaine; numerical deconvolution; transdermal.

INTRODUCTION

Transdermal drug delivery systems are generally used to achieve entry of drugs directly into systemic circulation, bypassing the first-pass metabolism, for the desired therapeutic effect. In support of this, very few transdermal

patches have been developed and marketed for local therapy (1). Most of the transdermal patches intended for local therapy exhibit plasma drug concentrations below the limit of quantification and hence pose low risk for systemic toxicities. Lidocaine topical patch (LTP) containing 5% w/w of lidocaine is approved by the USFDA under the brand name of Lidoderm® [reference listed drug (RLD)] for relief of pain associated with post-herpetic neuralgia (2). The systemic bioavailability (BA) of LTP is $3 \pm 2\%$ (3). The maximum plasma drug concentration achieved is ~ 45 ng/mL after application of three patches simultaneously for the period of 12 h, whereas the tolerable plasma drug concentration is 1500 to 5000 ng/mL for the treatment of cardiac arrhythmia (4). Hence, there is limited role of plasma drug concentration with respect to localized analgesic effect of LTP. Following administration of LTP, lidocaine produces local analgesic effect without complete sensory block (5). Even though evaluation of plasma drug concentration is not an accurate measure for drug availability at the site of action for topical products, in the absence of well-defined clinical methodology, bioequivalence (BE) with pharmacokinetic (PK) end point serves as a surrogate for establishing the equivalence between generic and branded LTP (6). The published draft guidance on Lidoderm® (RLD; non-binding) recommends the bioequivalence (BE) study along with adhesion test, skin irritation, and sensitization test to prove similarity of the generic LTP with the RLD (7). In response to Endo

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Pharma's Citizen Petition, FDA recommended (6) the following factors to be considered for the conduct of pharmacokinetic study:

- Lidocaine can be measured in plasma following its application onto the skin.
- Lidocaine is expected to pass through the stratum corneum to reach its site of action.
- Capillaries are present throughout dermal tissue beneath the stratum corneum, where lidocaine is expected to enter the bloodstream through these capillaries.
- Lidocaine is expected to be present in plasma at a concentration proportional to its presence at the site of action, when applied topically on to the skin.

The adverse drug reactions of LTP in severe cardiac impairment patients are due to the elevated plasma drug concentration. Moreover, lidocaine metabolites are known to be genotoxic, carcinogenic, and mutagenic (8). Generic development of transdermal patches is a challenging task because of various technical, intellectual property (IP), and regulatory issues. Establishing bioequivalence between RLD and test products is cumbersome due to low systemic bioavailability of LTP, when compared with other dosage forms. The reasons for bioinequivalence between test product and RLD might be the differences in qualitative and quantitative composition and the pharmaceutical processes adopted for the manufacture of these patches. Like other dosage forms, *in vitro* drug release testing (IVRT) methodologies are traditionally used for the optimization of formula and process for transdermal patches. Various IVRT methodologies are recommended by the Office of Generic Drugs (OGD), which include use of United States Pharmacopoeia (USP) apparatus 5 (paddle over disk method), USP apparatus 6 (rotating cylinder method), and USP apparatus 7 (reciprocating holder method) for topical and transdermal products (9). Vertical diffusion cell method has been adopted by USP to evaluate semisolid and transdermal dosage forms (10). Traditionally, these methods are used as quality control tools. To date, very few attempts have been made to develop biorelevant IVRT methods and to establish *in vitro*–*in vivo* correlation (IVIVC) for transdermal patches (11–15). The traditional IVIVC methods using PK model and numerical deconvolution (NDC) method have their own limitations such as requirement of intravenous (IV) data, unit impulse response (UIR) values, and errors associated with model building (16). Non-compartmental analysis (NCA) has been widely accepted by regulatory agencies to compare the pharmacokinetic data between test and RLD products to evaluate bioequivalence (17). In the present method, we have attempted to develop an NCA-based IVIVC model and then to compare the results with IVIVC model developed by NDC. The identified method(s) may be used as a biorelevant quality control (BRQC) *in vitro* tool for pharmaceutical quality assurance.

MATERIALS AND METHODS

Materials

Lidoderm® patch (Endo Pharmaceuticals, USA; Batch No. 13248 for study I and Batch No. Z0248 for study II) was obtained from the local pharmacy from the USA. Internal

Standard (Lidoacine-d10; Lot No. H154P19) was procured from C/D/N Isotopes Inc., Canada. All the reagents used for estimation of lidocaine were of analytical grade.

Ex Vivo Skin Permeation Studies

Franz diffusion cells were used to investigate the *ex vivo* skin permeation of lidocaine from transdermal patches. Human cadaver skin (HCS) was used as the barrier (18). A 0.64-cm² patch containing 3.2 mg of drug was placed on the surface of the HCS. Physiological parameters of the skin such as age and sex of the donor, skin cultivation site, transepidermal water loss, thickness of skin, and preparation method of the skin play an important role in *in vitro* skin permeation studies (19). Hence, these parameters were carefully monitored, controlled, and captured in the study protocol. The study protocol was approved by investigative review board. The temperature at which the study was performed is 37±2°C. Preparation of skin for *ex vivo* permeation study has been performed by thawing the skin in 0.9% NaCl for not more than 1 h at room temperature and cutting to appropriate Franz cell size (≈5 cm²). This was followed by transferring the piece of the skin to the Franz cell which was filled with pH 6.8 phosphate buffer to equilibration for around 30 min. Then, a 2.5-cm² portion of the transdermal patch was positioned on the diffusion cell, with the help of O-ring and glass disk assembly, and finally secured with the clamp. The reservoir compartment contained 5.0 mL of phosphate buffer, pH 6.8, from which 0.3 mL was withdrawn periodically using auto-sampler and analyzed by validated HPLC method. The cumulative medium correction was made to determine the total amount of lidocaine permeated at each time points. This experiment was repeated with three skin donors, and three diffusion cells were used at each time (n=3). %C_{t_n} was calculated using the following Eq. (1):

$$\%C_{t_n} = \frac{C_t \times V \times 100}{S \times C_T} \quad (1)$$

where %C_{t_n} = normalized value of cumulative percent drug permeated, C_t = concentration at time t, V = volume of dissolution medium, S = surface area of skin, and C_T = concentration at terminal time point.

In Vivo Studies

Human Volunteers. All the pharmacokinetic studies were approved by the Institutional Review Boards (IRBs) and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. In study I, 18 human volunteers were enrolled, and in study II, 36 human volunteers were enrolled. For both the studies, study population included healthy, non-smoking, non-drinking males and females (non-pregnant) between the ages of 18 to 45 years and with a body mass index of 18–30 kg/m². Subjects were screened by medical history, clinical laboratory tests, and physical and skin examination. Absence of pregnancy was evaluated by urine pregnancy test. Subjects not meeting the above said criteria were excluded from the study. Vital signs such as temperature, pulse rate, and blood pressure were assessed prior to each treatment

and also after 6 and 12 h of the patch application. Throughout the duration of both the studies, volunteers were continuously observed and questioned for the occurrence of any adverse events. Written consent was obtained from all participants prior to entry into the study.

Studies I and II

Studies I and II were performed in an open-label, single-center, and randomized environment. LTP is a 10 × 14 cm patch that contains 5% lidocaine within its adhesive layer, and each subject received three patches for application. All the transdermal patches were applied to clean, dry, non-oily, non-irritated, and non-recently shaved skin, on the lower/mid-back area. The application area selected was away from any significant fold/creases and at least 1 in away from the spine.

Blood samples of 7 mL were collected periodically at -1, 0, 1.5, 3, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 24, 30, and 36 h of post-patch-application, and plasma drug concentrations were determined by a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. General adhesion of the patches was analyzed at 2, 4, 6, 8, 10, and 12 h after application. The subjects with poor adhesion score were excluded from estimation of plasma drug concentration and PK analyses.

Bioanalytical Method for Estimation of Lidocaine

Blood samples were centrifuged and the plasma stored at -20°C until analysis by LC-MS/MS. The preparation of column and the quantification of lidocaine were similar to those mentioned in literature with slight modifications (20, 21). Lidocaine-d₁₀ was used as internal standard (IS). Lidocaine plasma concentrations were analyzed by fortifying a 50-μL sample aliquot with 20 μL of internal standard working solution. A 200-μL solution of 2.0% ammonium hydroxide was then added, vortexed, and centrifuged. Then, the organic layer was transferred to a clean tube and a 20-μL volume of this final extract was injected and analyzed via HPLC equipped with MS/MS detection. The intraday and interday precision and accuracy are found to be within 15% from both percent coefficient of variation (%CV) and percent difference from theoretical. The limit of quantification was found to be 0.2 ng/mL. The average recovery (%) of drug and IS was 95.4 and 99.6, respectively. Stability of QC samples in plasma during normal handling was determined to be acceptable after stressing with four freeze–thaw cycles and room temperature exposure for 24 h. Stability of the drug for 24 h in extracts was also acceptable. No interfering peaks were noted in blank plasma samples.

PK Analyses

From both studies, PK data of LTP was taken for further analysis. PK analysis for both studies was done by using Phoenix software version 6.3 (Pharsight™, Certara L.P.). The PK parameters such as peak plasma concentration ($C_{\max}$), time to reach $C_{\max}$ ($T_{\max}$), area under plasma concentration time curve from time zero to time of last measurable

concentration (AUC_{0-t}), area under plasma concentration time curve from time zero to time infinity (AUC_{0-inf}), and terminal elimination half-life ($t_{1/2}$) were calculated for both studies.

PK Modeling

PK modeling of lidocaine was performed by using plasma drug concentration–time profile of intravenous bolus (50 mg dose) data obtained from the literature (4). Compartmental analysis was performed by using Phoenix version 6.3 (Pharsight™, Certara L.P.). PK Solver was used for non-compartmental analysis (22). Selection of the model was based on best fit approach and other statistical parameters.

IVIVC

Level A correlation was estimated by a two-stage procedure: deconvolution followed by comparison of fraction drug absorbed *in vivo* (F_a) to the fraction of drug permeated *in vitro* (F_p). Percent *in vitro* permeated was calculated by Eq. (1). Percent *in vivo* absorbed profile was calculated by using NCA and NDC methods.

In NDC method, IV data which follows a two-compartment pharmacokinetic model was used to calculate the unit impulse response (UIR) values. The obtained UIR values were used to deconvolute the plasma drug concentration–time profiles of LTP. NDC method analysis was done by using Phoenix version 6.4 (Pharsight™, Certara L.P.). Equation (2) represents the percent *in vivo* permeation of the drug using numerical deconvolution method:

$$C(t) = \int_0^t C_\delta(t-u) r_{\text{abs}}(u) du \quad (2)$$

where r_{abs} is absorption rate time course, C_δ represents the concentration–time profile resulting from an instantaneous absorption of a unit amount of drug which is typically from bolus intravenous injection or reference oral solution data, $C(t)$ represents the plasma concentration *versus* time profiles of the tested formulations, and u is the variable of integration.

In NCA method, the percent *in vivo* permeated was estimated by using the following Eq. (3):

$$\% \text{ in vivo absorbed} = \frac{AUC_{(0-t)} \times K_{\text{el}} \times V_d}{F \times D} \times 100 \quad (3)$$

where $AUC_{(0-t)}$ = area under time curve from time point (0–t), K_{el} = elimination constant, V_d = volume of distribution, F = percent bioavailable from the formulation, and D = dose administered.

The internal validation for the developed IVIVC by NCA method has been carried out by comparing the observed values *versus* predicted values from the same study, whereas external validation was performed by using predicted values of study I *versus* observed values of study II and *vice versa*.

The percent prediction error (%PE) was calculated by using the Eq. (4):

$$\%PE = \frac{\text{Observed Value} - \text{Predicted value}}{\text{Observed value}} \times 100 \quad (4)$$

RESULTS AND DISCUSSION

Ex Vivo Skin Permeation Studies

The results of *ex vivo* skin permeation of lidocaine from LTP are shown in Fig. 1a. The average cumulative amount (μg) and percent (%) of drug permeated from the LTP in 24 h were 205.89 ± 52.31 and 6.43 ± 1.6 , respectively. However, the percent *in vivo* absorption of lidocaine from patches was reported as $3 \pm 2\%$ (8). The differences between *ex vivo* and *in vivo* skin permeation could be due to various reasons such as skin preparation methods, viability of the skin, age of the skin, area of harvesting, and analytical method parameters such as surface area, drug loading, and volume of the media. The run-to-run variation in average cumulative permeation due to the above mentioned factors is rate limiting for establishing IVIVC, and hence $\%C_{tn}$ was calculated to overcome the variation. The comparative statistical analysis of $\%C_{tn}$ in three different studies ($n=3$ for each study) at all the time points, except first time point, shows less variability when compared to percent cumulative release. The calculated RSD (%) was found to be 16 and 58 for $\%C_{tn}$ and percent

cumulative release, respectively. Figure 1b represents the $\%C_{tn}$ of LTP. The release kinetics of the drug from drug delivery system was computed with respect to main mathematical models such as Higuchi's kinetics, zero-order kinetics, first-order kinetics, and polynomial method. The goodness of fit for various models investigated for Lidoderm topical patches ranked in the following order:

polynomial > first-order > zero-order > Higuchi's kinetics.

All the kinetic models, other than the polynomial, did not fit at the initial time points. Table I summarizes the statistical analysis of various mathematical models. Polynomial model was chosen for establishing IVIVC and to calculate the average flux.

In Vivo Study

The PK parameters of studies I and II are summarized in Table II. Figure 2 depicts the plasma concentration profiles for both the studies. Out of 18 volunteers, 17 volunteers completed the study I. Mean C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were found to be 39.7 ng/mL (CV=54.6%), 568.1 ng·h/mL (CV=49.7%), and 590.8 ng·h/mL (CV=48.7%), respectively. A total of 35 volunteers (out of 36) completed the study II. Mean values for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were found to be 38.5 ng/mL (CV=23%), 564.3 ng·h/mL (CV=11.1%), and 582.6 ng·h/mL (CV=9.6%), respectively.

Pharmacokinetic Modeling

Pharmacokinetic modeling plays an integral part in the establishment of IVIVC (23). Pharmacokinetic parameters

Fig. 1. **a** *In vitro* skin permeation profiles for study I and study II. Percent lidocaine permeated. Data are presented as mean $\pm$ SEM ($n=3$). **b** *In vitro* skin permeation profiles for study I and study II. Amount lidocaine permeated. Data are presented as mean $\pm$ SEM ($n=3$)

Table I. *In Vitro* Release Kinetics of Both Study I and Study II

Parameter	Amount permeated		Percent permeated	
	Study I	Study II	Study I	Study II
Higuchi				
Observed r^2	0.9590	0.959	0.959	0.9559
Adjusted r^2	0.8758	0.8612	0.8758	0.8612
AIC	71.96	71.50	60.11	60.84
First-order				
Observed r^2	0.8869	0.8947	0.9847	0.9811
Adjusted r^2	0.4344	0.5312	0.9370	0.9268
AIC	84.09	81.23	54.68	55.71
Second-order				
Observed r^2	0.9452	0.9559	0.9452	0.9556
Adjusted r^2	0.8834	0.9093	0.8834	0.9093
AIC	71.45	68.09	59.60	57.00
Zero-order				
Observed r^2	0.9452	0.9556	0.9469	0.9556
Adjusted r^2	0.8834	0.9093	0.8872	0.9093
AIC	59.60	57.4	59.71	57.44
Polynomial				
Observed r^2	0.995	0.998	0.9971	0.998
Adjusted r^2	0.992	0.996	0.995	0.996
AIC	–	–	–	–

AIC Akaike information criterion

Table II. Comparative Analysis of PK Modeling

Parameter	IV			Study I		Study II	
	NCA	One-compartment	Two-compartment	NCA	One-compartment	NCA	One-compartment
C_0 (ng/mL)	5944.20	5312.05	6002.22	–	–	–	–
C_{max} (ng/mL)	5415.21	–	–	39.71 ± 23.38	28.53	38.56 ± 16.24	25.59
AUC_{0-t} (ng·h/mL)	2680.53	1165.19	2617.41	568.01 ± 280.67	702.07	564.31 ± 204.34	712.84
$t_{1/2}$ (h)	1.4	0.152	Slow: 0.072 Fast: 1.27	6.0	$t_{1/2a}$: 7.07 $t_{1/2e}$: 7.66	5.7	$t_{1/2a}$: 6.61 $t_{1/2e}$: 7.58
A (ng/mL)	–	–	4698.51	–	989.08	–	585.63
Alpha (1/h)	–	–	9.60	–	0.098	–	0.091
B (ng/mL)	–	–	1303.71	–	–	–	–
Beta (1/h)	–	–	0.54	–	–	–	–
AIC	–	163.50	116.50	–	125.38	–	128.30
Adjusted r^2	–	0.96	0.99	–	0.93	–	0.92

$t_{1/2a}$ absorption half-life, $t_{1/2e}$ elimination half-life, *Slow* from central compartment to peripheral compartment, *Fast* peripheral compartment to central compartment, *AIC* Akaike information criterion, *NCA* non-compartmental analysis

were obtained by using non-compartmental analyses (NCA). The obtained parameters such as AUC_{0-t} , C_{max} , T_{max} , and $t_{1/2}$ cannot be used directly in a compartment model, and their transformation to compartment model PK parameters is essential. Compartmental (one-compartment and two-compartment) PK parameters, such as absorption rate constant (K_a), elimination rate constant (K_{el}), and volume of distribution (V_d), were obtained using non-compartmental parameters such as AUC_{0-t} , T_{max} , and $t_{1/2}$ (24). One-compartment and two-compartment open models are frequently used for deconvolution of the plasma drug concentration time profile to obtain percent *in vivo* drug absorption. However, the prediction error associated with one-compartment and two-compartment models affects the quality of obtained deconvoluted data. Intravenous PK data obtained from the literature (4) was used for estimation of percent *in vivo* absorbed from NDC method. Based on the AIC values and r^2 provided in Table II, the two-compartmental open model was selected as the best fitting PK model for lidocaine. Two-compartmental and non-compartmental PK parameters were used for establishing IVIVC by NDC and NCA methods, respectively. Table II summarizes the comparative statistical

analysis of lidocaine administered through IV and extravascular (transdermal) route of administration.

IVIVC

Level A correlation between normalized percent cumulative *in vitro* permeation and *in vivo* permeation was established using non-compartmental analysis (NCA) and numerical deconvolution (NDC) method. The presence of test

Fig. 2. PK profiles of study I and study II. Data are presented as mean $\pm$ SEM ($n=17$ for study I; $n=35$ for study II)

Fig. 3. a Fraction of drug permeated *in vitro* and *in vivo* for study I. b Fraction of drug permeated *in vitro* and *in vivo* for study II

Fig. 4. **a** Levy's plot of NCA for study I. **b** Levy's plot of NCA for study II. **c** Levy's plot of NCA of study I (external validation). **d** Levy's plot of NCA of study II (external validation)

Fig. 5. **a** Levy's plot of NDC for study I. **b** Levy's plot of NDC for study II. **c** Levy's plot of NDC for study I (external validation). **d** Levy's plot of NDC for study II (external validation)

Fig. 6. **a** Comparison for percent *in vivo* drug release of study I from both NCA and NDC methods. **b** Comparison for percent *in vivo* drug release of study II from both NCA and NDC methods

formulation is usually required for the development of IVIVC, in order to understand and validate the above method; *in vitro* permeation and *in vivo* absorption data of RLD product only has been utilized in the current study. The percent (%) *in vivo* permeated was predicted by non-compartmental analysis of PK data obtained from study I and study II using Eq. (3). The main objective of using NCA was to reduce the residuals/errors during the modeling. Moreover, the dose normalization was done using the cumulative amount drug in the body at 36 h. Figure 3a, b shows the relationship between F_p and F_a . Various mathematical models were evaluated and the best fitting model was selected based on statistical parameters. The best fitting mathematical model for studies I and II were

$y = -0.0061x^2 + 1.7885x - 16.267$ and $y = -0.0089x^2 + 2.0357x - 14.084$, respectively. The PK parameters such as C_{max} and AUC_{last} were predicted with the above established equations. Figure 4a, b shows Levy's plots for study I and study II obtained between *in vitro* time and *in vivo* time with a correlation coefficient (r^2) of 0.9977 and 0.9976, respectively. The sensitivity of the established IVIVC methods was evaluated by constructing the Levy's plots between *in vitro* study I versus *in vivo* study II and *in vitro* study II versus *in vivo* study I and is depicted from Fig. 4c, d, respectively. The slope and regression values obtained from Levy's plots indicated the robustness of the developed mathematical models for both studies (I and II). The advantages of this IVIVC method over conventional methods are (a) minimal compartmental modeling error, (b) easy to calculate *in vivo* permeation, and (c) simple mathematical expressions. Unlike Loo–Riegelman method, IV data is not required to calculate the unit impulse response (UIR) for deconvolution process.

Using Phoenix® (version 6.4), IVIVC was established with numerical deconvolution method. Figure 5a, b shows Levy's plots of study I and study II with r^2 values of 0.9976 and 0.995, respectively. The internal validation for established IVIVCs was carried out by using the established mathematical expression, whereas external validation was done using flipping of the mathematical expressions between studies I and II. Figure 5c, d shows the externally validated Levy's plot for both study I and study II.

The comparison of percent *in vivo* release for both NCA and NDC methods is illustrated in Fig. 6a, b, respectively. Table III summarizes the predicted PK values and associated errors of NCA and NDC methods for both the studies (I and II). The percent prediction error of C_{max} in study I, using internal validation method, was found to be -30.9 and 3.9% for NDC and NCA methods, respectively. The high prediction error of C_{max} in NDC might be due to two-compartment PK modeling error for both studies I and II. The direct deconvolution of plasma drug concentration with time profile using NCA analysis resulted in low prediction error, especially for internal validation. Moreover, the external validation results obtained from the NCA and NDC methods for studies I and II confirm the comparability of NCA method over NDC method. A prediction error of less than 2% in both studies of NCA and NDC methods imparts the robustness of NCA method in line with NDC method.

Table III. Validation and Prediction of PK Parameters

Study	PK model	Type of validation	Observed		Predicted		% Prediction error	
			C_{max}	AUC_{last}	C_{max}	AUC_{last}	C_{max}	AUC_{last}
Study I	NDC	Internal	39.71 ± 23.38	568.01 ± 280.67	27.40	569.06	-30.9	0.1
		External			30.60	578.07	22.9	1.7
	NCA	Internal			41.30	579.69	3.9	2.0
		External			50.68	579.19	27.6	1.9
Study II	NDC	Internal	38.56 ± 16.24	564.31 ± 204.34	29.38	562.05	-23.8	0.4
		External			28.76	564.60	-25.4	0.1
	NCA	Internal			45.9	563.35	16.1	-0.2
		External			38.57	553.0	0.03	2.0

NDC numerical deconvolution, NCA non-compartmental analysis

The objective of the present study was to correlate *in vitro* and *in vivo* skin permeation profiles of lidocaine in its transdermal patches. Additionally establishing the bioequivalence between RLD and test products is a tedious process. The objectives of the present study can be better achieved if the bioequivalence is achieved between an in-house developed transdermal patch of lidocaine and an RLD. However, as a preliminary study, we used two separate batches of RLD product to study the correlation of *in vitro* and *in vivo* skin permeation profiles and then to establish bioequivalence between two different batches. We wanted to establish pharmacokinetic modeling and *in vitro*–*in vivo* correlation (IVIVC) for different batches of RLD and then to adopt the same principles for the developed (test) product.

Moreover, there are no reports available on the establishment of IVIVC for commercialized transdermal patch (15). The transdermal patch like Lidoderm® has poor bioavailability (3, 8) which is considered as a bottleneck for developing IVIVC. In the present study, we attempted to establish a preliminary IVIVC method by NCA method to demonstrate the correlation between *in vitro* and *in vivo* skin permeation of lidocaine. IVIVC was also established using NDC method, but the mathematical expression obtained from NDC method was used to evaluate the IVIVC obtained from NCA method. Both NDC and NCA methods provided a good correlation between *in vitro* and *in vivo* drug permeation across the skin; however, the NCA method was found to be superior to the NDC method. Since, $C_{\max}$ is one of the critical PK parameters for establishing bioequivalence, and hence, both methods were used to predict the $C_{\max}$ values. The predicted $C_{\max}$ values for NCA method were found to be closer to the observed value, when compared with $C_{\max}$ values obtained from NDC method. This further confirms the superiority of NCA method in establishing IVIVC over NDC method in this study.

CONCLUSION

The present study successfully develops the correlation between *in vitro* and *in vivo* skin permeation of lidocaine in its transdermal patch. Based on the results of the present study, the NCA method is a superior approach over NDC method in predicting the $C_{\max}$ and AUC_{last} after administration of LTP. The NCA method would be most useful if the drug has longer absorption half-life and shorter elimination half-life. The study successfully shows that NCA method may be used as a biorelevant quality control (BRQC) *in vitro* tool for quality assurance of transdermal products. However, detailed studies are required to validate the results obtained from this study.

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Conflict of interest None

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