Formulation and evaluation of transdermal drug delivery of topiramate

Suneetha Cherukuri, Uma Rajeswari Batchu¹, Kiranmai Mandava¹, Vidhyullatha Cherukuri², Koteswara Rao Ganapuram³

Department of Pharmaceutics, Bomma Institute of Pharmacy, Khammam, ¹Department of Pharmaceutical Chemistry, Bharat Institute of Technology, JNTUH, Hyderabad, ²Department of Pharmaceutics, MITS College of Pharmacy, ³Department of Pharmaceutical Analysis, Nalanda College of Pharmacy, Nalgonda, Telangana, India

Abstract

Background: Transdermal drug delivery system (TDDS) was designed to sustain the release and improve the bioavailability of drug and patient compliance. Among the various types of transdermal patches, matrix dispersion type systems disperse the drug in the solvent along with the polymers and solvent is allowed to evaporate forming a homogeneous drug-polymer matrix. The objective of the present study was to design and formulate TDDS of topiramate (TPM) and to evaluate their extended release in vitro and ex vivo.

Materials and Methods: In the present study, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising TPM with different ratios of hydrophilic and hydrophobic polymeric combinations using solvent casting technique.

Results: The physicochemical compatibility of the drug and the polymers was studied by Fourier transform infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The patches were further subjected to various physical evaluations along with the ex vivo permeation studies using pig ear skin.

Conclusions: On the basis of results obtained from the physical evaluation and ex vivo studies the patches containing the polymers, that is, Eudragit L 100 and polyvinylpyrrolidone, with oleic acid as the penetration enhancer were considered as the best formulations for the transdermal delivery of TPM.

Keywords: Eudragit L 100, matrix dispersion system, oleic acid, penetration enhancers, permeation studies, polyvinylpyrrolidone

INTRODUCTION

Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery, and transdermal patches are devised to treat various diseases.¹ TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption.² These therapeutic advantages reflect the higher marketing potential of TDDS.³

Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital.
as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Chemical penetration enhancers act as accelerators or sorption promoters and can enhance drug flux. Sulfoxides - dimethyl sulfoxide, azone, pyrrolidines-N-methyl-2-pyrrolidone, fatty acids lauric acid, capric acid, myristic acid, oleic acid, terpenes and essential oils - menthol, eugenol, oxazolidinones-4-decyloxazolidin-2-one, surfactants - tween 80, span 20 are the various classes of penetration enhancers used in TDDS.

Nicotine patches were the first transdermal success raising the market value of TDDS in medicine to newer heights. Estradiol, fentanyl, testosterone, lidocaine, and some other drug combinations are the TDDS available in the present pharma market. Methotrexate, repaglinide, diclofenac and aceclofenac are the few drugs for which TDDS have been reported. Combination drugs such as theophylline-salbutamol sulfate and ketoprofen fumarate-salbutamol sulfate TDDS were also formulated and evaluated in vitro.

Topiramate (TPM) is a novel antiepileptic drug derived from the naturally occurring monosaccharide D-fructose. It is not structurally related to other antiepileptic drugs and was originally synthesized as the part of a search for fructose-related compounds with hypoglycemic activity. It has multiple mechanisms of action such as sodium and calcium channel blockade; potassium channel activation; glutamate receptor antagonism; gamma-aminobutyric acid potentiation; and carbonic anhydrase inhibition. The objective of this study was to design and formulate TDDS of TPM and to evaluate their extended release in vitro and ex vivo.

MATERIALS AND METHODS

TPM was procured from MSN Organics Pvt. Ltd., Hyderabad as a gift sample. Polyvinyl alcohol was purchased from SD - Fine chemicals, Mumbai. Ethyl cellulose, oleic acid, propylene glycol (PG) were purchased from SD – Fine chemicals, Mumbai. Eudragit-L 100 and hydroxypropyl methyl cellulose (HPMC) were purchased from Yarrow -Chem products, Mumbai. Polyvinylpyrrolidone, cellulose acetate phthalate (CAP), carboxol 940, tween 80, chloroform, dichloromethane were purchased from Accord labs, Secunderabad. All chemicals and reagents used in the present study were of analytical reagent grade (AR grade).

Preformulation studies

Before formulating the drug substance into a transdermal patch (dosage form), preformulation studies were carried out to establish the physicochemical characteristics of a drug (TPM) and its compatibility with different excipients.

Compatibility study of drug with the excipients was determined by Fourier transform infrared (FTIR) spectroscopy (Shimadzu 1800).

Calibration curve of topiramate

Wavelength maximum of TPM was found to be 263.5 nm using ultraviolet (UV)-visible spectroscopy (Elico SL159, Hyderabad). Standard solution (10 µg/ml) was prepared from stock solution (1 mg/ml) with phosphate buffer (pH 7.4). Aliquot of standard drug solution ranging from 1 to 8 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with phosphate buffer pH 7.4. Thus, the final concentration ranges from 1-8 µg/ml. The absorbance of each solution was measured at 263.5 nm against phosphate buffer (pH 7.4). A plot of concentrations of the drug versus absorbance was plotted. The linear regression analysis was applied.

Formulation of transdermal patch

In the present study, drug loaded matrix type transdermal patches of TPM were prepared by solvent casting method using different ratios of hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, polyvinylpyrrolidone (PVP), eudragit L100, Cellulose acetate phthalate (CAP), carbopol and polyvinyl alcohol (PVA). A weighed amount of PVA (2.5% w/v) was added to a requisite volume of warm distilled water and a homogeneous solution was made by constant stirring and intermittent heating at 60°C for a few seconds and poured into glass molds already wrapped with aluminium foil around open ends and were kept for drying at 60°C for 6 h, forming a smooth, uniform, and transparent backing membrane. Backing membrane was used as a support for drug-polymer matrix. The polymers in different ratios as given in Table 1 were dissolved in the respective solvents. Then, the drug was added slowly in the polymeric solution and stirred with the help of magnetic stirrer to obtain a uniform solution. Propylene glycol (PG) was used as a plasticizer. Oleic acid and tween 80 were used as the penetration enhancer. Then the solution was poured on the glass molds of 5 cm × 5 cm and dried at the room temperature. Then the patches were cut into 1 cm × 1 cm patches and preserved in the polyethylene bag at 40°C and 75% relative humidity for further evaluation.

Preliminary screening

Evaluation of transdermal patches

All the prepared formulations were subjected for preliminary screening to check the effect of various polymer combinations.
Microscopic pictures of transdermal patches

Microscopic pictures of all the formulations were observed using an electronic microscope with digital camera to determine the surface of the films formed and uniform dispersion of drug and polymer.

In addition to microscopic study, transdermal patches were evaluated for their physicochemical characteristics.

Thickness

The thickness of the prepared transdermal films was measured by screw gauge with least count at five different sites, and the average was calculated with an SD.[23]

Folding endurance

The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tends to break. It is determined as the number of times the film is folded at the same place either to break the film or to develop visible cracks.[24]

Weight variation

The patches were subjected to weight variation by individually weighing ten selected patches randomly and the average was calculated.[25]

Drug content uniformity

Each patch from different formulations (patch size of 1 cm², equivalent to 25 mg of drug) was dissolved in phosphate buffer (pH 7.4) and shaken continuously for the 24 h using a magnetic stirrer to extract the drug from the patch. After filtration and dilution with phosphate buffer, % drug content was measured spectrophotometrically at a wavelength of 264 nm.[26]

In vitro drug release studies

In vitro drug release studies were carried out using the paddle over disc method.[27] Dry films of known thickness were cut into circular shape, weighed, and fixed over a glass plate with an adhesive. The plate was then placed in a 500 mL phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32°C ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm, and samples (5 mL aliquots) were withdrawn at appropriate time intervals up to 12 h and analyzed for drug content at 264 nm using double beam UV-visible spectrophotometer (Elico SL159, Hyderabad). The experiment was performed in triplicate, and the mean value was calculated.

Based on physicochemical characterization and drug release patterns, F17, F9, and F5 formulations were selected to which permeation enhancers like oleic acid and tween 80 were incorporated, and resultant new formulations with permeation enhancers were labeled from F26 to F31 and details were given in Table 2. For all six formulations, ex vivo diffusion studies were performed using pig ear skin.

Table 1: Composition of different formulations of transdermal patches of topiramate

| Polymer       | Matrix forming polymer | Formulation and ratio | Drug (TPM), mg | Solvent system                      |
|---------------|------------------------|-----------------------|----------------|-------------------------------------|
| HPMC          | Eudragit L 100         | F1 (2:0.1)            | 625            | Methanol:dichloromethane (1:1)      |
|               |                        | F2 (2:0.25)           |                |                                     |
|               |                        | F3 (2:0.50)           |                |                                     |
|               |                        | F4 (2:0.75)           |                |                                     |
|               |                        | F5 (2:1)              |                |                                     |
| HPMC          | PVP                    | F6 (2:0.1)            | 625            | Alcohol:water (1:1)                 |
|               |                        | F7 (2:0.25)           |                |                                     |
|               |                        | F8 (2:0.50)           |                |                                     |
|               |                        | F9 (2:0.75)           |                |                                     |
|               |                        | F10 (2:1)             |                |                                     |
| HPMC          | Ethyl cellulose        | F11 (2:0.1)           | 625            | Chloroform:methanol (1:1)           |
|               |                        | F12 (2:0.25)          |                |                                     |
|               |                        | F13 (2:0.50)          |                |                                     |
|               |                        | F14 (2:0.75)          |                |                                     |
| HPMC          | CAP                    | F15 (2:1)             | 625            | Chloroform:methanol (1:1)           |
|               |                        | F16 (2:0.25)          |                |                                     |
|               |                        | F17 (2:0.50)          |                |                                     |
|               |                        | F18 (2:0.75)          |                |                                     |
|               |                        | F19 (2:1)             |                |                                     |
| HPMC          | Carbopol               | F21 (2:0.75)          | 625            | Methanol:dichloromethane (1:1)      |
|               |                        | F22 (2:1)             |                |                                     |
|               |                        | F23 (2:2)             |                |                                     |
|               |                        | F24 (2:3)             |                |                                     |
|               |                        | F25 (2:4)             |                |                                     |

TPM: Topiramate, HPMC: Hydroxyl propyl methyl cellulose, PVP: Poly vinyl pyrrolidone, CAP: Cellulose acetate phthalate


## Ex vivo skin permeation study

An *in vitro* permeation study was carried out by using Franz diffusion cell. The skin samples were obtained from the back of pig ear and using a depilatory preparation hair was removed. The skin samples were washed with phosphate buffer (pH 7.4). The prepared skin was mounted between donor and recipient compartments of diffusion cell. Then the formulated patches were positioned over the skin by placing the patch on the stratum corneum side of the skin toward the donor compartment, and dermis side was facing toward receptor compartment. The receptor compartment of the diffusion cell was filled with phosphate buffer (pH 7.4) and every 1 h, 5 ml of sample was taken and replaced the same with receptor fluid, and the sample was analyzed for drug content at 264 nm using double beam UV-visible spectrophotometer (Elico SL159, Hyderabad).

## Kinetic modeling of dissolution data

Drug release kinetics were analyzed by various mathematical models such as a zero-order and first-order kinetic models; Higuchi and Korsmeyer–Peppas models to ascertain the kinetics of drug release.

**Zero order kinetics**

\[ Q_1 = Q_0 + K_0 t \]

Where \( Q \) is the amount of the drug dissolved in time \( t \), \( Q_0 \) is the initial amount of drug in the solution (most times, \( Q_{50} \)) and \( K \) is the zero order release constant.

**First order kinetics**

\[ \ln Q_t = \ln Q_0 - K_1 t \]

Where \( Q_t \) is the amount of drug released in time \( t \), \( Q_0 \) is the initial amount of drug in the solution and \( K \) is the first order release constant.

**Higuchi model**

\[ Q_t = K_H t^{1/2} \]

Where \( Q_t \) is the amount of drug released in time \( t \), \( K_H \) is release rate constants.

**Korsmeyer–Peppas model**

\[ Q_t / Q_\infty = at^n \]

Where \( n \) is the release exponent and the function of \( t \) is \( Q_t / Q_\infty \) (fractional release of the drug).

## Statistical comparison of dissolution profiles

The model independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor \( f_2 \) was used as a basis for comparison between dissolution profiles of different samples. The release profiles are considered to be similar when \( f_2 \) is between 50 and 100. The release profile of products was compared using an \( f_2 \) which is calculated from following formula:

\[
 f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum_{i=1}^{n} W_i (R_i - T_i)^2 \right)^{0.5} \times 100
\]

Where \( n \) is the release time and \( R_i \) and \( T_i \) are the reference and test value at time \( t \).

## RESULTS

Transdermal patches of TPM were prepared by matrix type solvent casting method to achieve a controlled release, improved bioavailability of the therapeutic drug and to reduce the toxicity. This is the first report on transdermal drug delivery of TPM and found to be effective compared to previously reported dosage forms of TPM.

## Preformulation studies

Preformulation studies, that is, FTIR studies revealed the compatibility of excipients and polymers with TPM. Calibration curve of TPM was constructed and found to be linear and microscopic pictures of formulations with different polymers were compared.

## Evaluation of transdermal patches

The prepared formulations were evaluated for different physicochemical characteristics such as thickness, folding endurance, weight variation and % drug content and the results were shown in Table 3. However, above-mentioned parameters were also studied for optimized formulations with permeation enhancers, but no significant change was found in these parameters with permeation enhancers.
Drug release studies

The release characteristics of all prepared formulations were studied in vitro and compared. The results were given in Figures 1-4. Based on these results, F17, F9, and F5 were taken as optimized formulations. The in vitro release data of F17, F9, and F5 formulations was fitted well into the zero order and first order equations. Korsmeyer–Peppas and highuchi models were also applied to test the release mechanism, and results are shown in Table 4. $T_{50}$ and $T_{90}$ of transdermal formulations of TPM without permeation enhancers were calculated from respective graphs.

Ex vivo permeation studies through pig car skin

After carrying out the in vitro dissolution studies, optimized formulations (F17, F9, F5) with controlled drug release were subjected to the ex vivo drug permeation studies (Approval no 318/PO/ERC/S/01/CPCSEA). The results of drug permeation studies from optimized formulations with and without permeation enhancers using pig ear skin are depicted in Figures 5-7. $T_{50}$ and $T_{90}$ of transdermal formulations of TPM with permeation enhancers were calculated from respective graphs.

DISCUSSION

The microscopic pictures of TPM were revealed that the formulations prepared from ethylcellulose and carbopol were observed to be nonuniform in drug distribution. In microscopic pictures of formulations prepared from CAP, surface morphology was good in lower concentrations. Transdermal patches prepared from Eudragit L 100 and PVP were found to have the uniform surface morphology from lower to higher ratios of the polymer, indicating that the drug was uniformly distributed all over the patch.

Evaluation of transdermal patches

The prepared formulations with different polymer concentrations were smooth, opaque, flexible and uniform. The thickness of the films varied from 0.230 to 0.834 mm and highest thickness was of found to be 0.834 mm for F15, and lowest was of F1. From these values, it was observed that the thickness of the polymer depends on the solubility and concentration of the polymer. As the solubility decreases and concentration increases would increase the thickness of the patch. It infers that usage of the competent polymer is the prerequisite step to prepare a patch of optimum thickness, which can retard the release of drug from the patch. Weight variation of all the formulations varied from 0.054 ± 0.0114 – 0.146 ± 0.020. Low SD values in the film ensure uniformity of the patches prepared by solvent casting technique. The folding endurance was

Table 3: Evaluation of physicochemical characteristics of topiramate transdermal patches

| Formulation | Polymer          | Thickness | Percentage of weight variation | Folding endurance | Percentage of drug content |
|-------------|------------------|-----------|--------------------------------|-------------------|----------------------------|
| F1          | Eudragit L 100   | 0.230±0.1303 | 0.054±0.0114 | 298±1.23          | 82.45±0.003              |
| F2          | Ethylcellulose   | 0.098±0.0101 | 0.078±0.01 | 304±2.45          | 95.21±0.0034             |
| F3          | Carbopol         | 0.326±0.0230 | 0.120±0.02 | 315±2.11          | 76.04±0.0064             |
| F4          | PVP              | 0.548±0.0016 | 0.138±0.0014 | 322±0.14         | 89.71±0.0076             |
| F5          | 0.648±0.0083     | 0.146±0.020  | 312±3.23          | 87.32±0.0032 |                     |
| F6          | 0.388±0.0286     | 0.052±0.023  | 224±5.67          | 87.16±0.0042 |                     |
| F7          | PVP              | 0.414±0.0324 | 0.167±0.034 | 264±2.45          | 84.25±0.0053             |
| F8          | 0.454±0.0610     | 0.068±0.078  | 236±5.34          | 89.70±0.0023 |                     |
| F9          | 0.506±0.0403     | 0.099±0.0678 | 244±2.78          | 82.82±0.0043 |                     |
| F10         | 0.614±0.0054     | 0.123±0.0786 | 246±3.54          | 85.91±0.0076 |                     |
| F11         | Ethylcellulose   | 0.584±0.0409 | 0.075±0.0102 | 209±6.27          | 87.71±0.0063             |
| F12         | 0.632±0.0249     | 0.097±0.0234 | 213±6.39          | 89.96±0.0086 |                     |
| F13         | 0.742±0.0496     | 0.123±0.0308 | 210±6.43          | 77.87±0.0054 |                     |
| F14         | 0.744±0.0114     | 0.137±0.0143 | 234±7.02          | 92.62±0.0078 |                     |
| F15         | 0.834±0.0403     | 0.144±0.0102 | 245±2.37          | 92.53±0.0045 |                     |
| F16         | CAP              | 0.276±0.0207 | 0.054±0.034 | 154±4.67          | 85.34±0.0032             |
| F17         | 0.32±0.0371      | 0.064±0.0234 | 176±5.67          | 88.67±0.0027 |                     |
| F18         | 0.448±0.0238     | 0.098±0.0103 | 165±3.8           | 81.68±0.0028 |                     |
| F19         | 0.696±0.0013     | 0.134±0.0342 | 157±5.98          | 84.84±0.0054 |                     |
| F20         | 0.820±0.0111     | 0.146±0.0123 | 174±2.76          | 84.52±0.0054 |                     |
| F21         | Carbopol         | 0.213±0.0456 | 0.064±0.023 | 158±8.52          | 83.64±0.0075             |
| F22         | 0.225±0.01201    | 0.075±0.0101 | 172±10.58         | 90.12±0.0083 |                     |
| F23         | 0.231±0.0342     | 0.098±0.0100 | 170±10.25         | 85.84±0.0032 |                     |
| F24         | 0.239±0.2045     | 0.112±0.023  | 168±9.56          | 82.63±0.0808 |                     |
| F25         | 0.254±0.431      | 0.122±0.034  | 152±13.23         | 92.01±0.0432 |                     |

PVP: Polyvinylpyrrolidone, CAP: Cellulose acetate phthalate

Table 4: Kinetic model fitting data for optimized formulations

| Formulations | Zero order | First order | Higuchi | Peppas | n |
|--------------|------------|-------------|---------|--------|---|
| F17          | 0.93155    | 0.67937     | 0.85233 | 0.897091 | 0.88795 |
| F9           | 0.93157    | 0.59613     | 0.77001 | 0.83638 | 1.06916 |
| F5           | 0.9395     | 0.6091      | 0.78709 | 0.948879 | 1.36023 |
found to be >150 revealed that the prepared patches were having the capability to withstand the mechanical pressure along with good flexibility. The formulations prepared with Eudragit L100 was found to have the highest value of folding endurance and formulations made of CAP, PVP and carbopol respectively were found to have the lowest value of folding endurance. The drug content of all the formulations was in the range of 76.04% ±0.0564−95.21% ±0.0134 indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. All the results showed that the patches were uniform, as it was evidenced by SD value, which were <0.01 for all the factorial design batches.

**Drug release studies**

Drug release studies are required for predicting the reproducibility of the rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance.[35] Drug release of F1–F25 formulations were varied between 40.19% and 97.03%. The order of *in vitro* drug release data was found to be highest for HPMC K15: Eudragit L 100 polymer and lowest for HPMC K15: Carbopol polymer.
The results indicated that the release of drug from patches increases with increasing concentration of HPMC K15 M. The cumulative percent of drug release in 12 h was noted. The drug release was found to increase with the increasing concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelataneous pores. The formulation of such pores leads to decreasing mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate.

The in vitro release data of the formulations F5, F12, F14, F15, F18, F19, F21, F23 were best fitted into peppas model having the maximum $r^2$ values of (0.952386), (0.854381), (0.874045), (0.758754), (0.90489), (0.892499), (0.966253), (0.992909), respectively than the other models. All the remaining formulations were following the zero order model as the best fit model. This indicates that as the concentration of the hydrophilic polymer in which 2% HPMC was used, was not sufficient for the formation of a matrix transdermal patch. Hence, zero order was found to be the best fit model for TPM release from formulations. From this, we can infer that concentration of the HPMC polymer plays a key role in drug release kinetics with a permeation enhancer.

**Ex vivo permeation studies through pig ear skin**

The results of ex vivo drug permeation studies were compared for optimized formulations with and without permeation enhancers. When compared with formulations without permeation enhancers the drug diffused from formulations with tween 80 was increased. The results indicated that drug penetration was increased with permeation enhancers and the percent drug permeated from F26 was found to be up to 32.57% and from F27 it was found to be 43.27%. In F28 the maximum drug permeated up to 55.7%. However, the formulations F30, F31 (HPMC: PVP; 2:0.75), (HPMC: Eudragit; 2:1) with oleic acid as permeation enhancer shows optimum permeation. Drug permeation from CAP was less when compared with that of PVP and eudragit because CAP is a cellulose derivative. $T_{50}$ and $T_{90}$ were calculated from the graph in which $T_{50}$ was >12 h in all the formulations, but $T_{50}$ was >12 h in F26, F27, F29.

**CONCLUSIONS**

The transdermal patches of TPM prepared by solvent casting method using a combination of ethylcellulose, PVP, eudragit L 100, CAP, carbopol in various ratios using PG as plasticizers and oleic acid, Tween 80 as a permeation enhancers were studied. All the formulations showed good physicochemical properties such as thickness, weight variation, drug content, and folding endurance. The in vitro release data showed that drug release from the patch has been affected by the type and concentration of the polymer. From this data, optimized formulations were screened. Effect of penetration enhancers such as oleic acid and Tween 80 have been checked for optimized formulations using ex vivo permeation studies. These studies indicated that when compared with formulations without permeation enhancers the drug diffused from formulations with permeation enhancers was increased. Moreover, the formulations F30 (HPMC: PVP; 2:0.75), F31 (HPMC: Eudragit; 2:1) with oleic acid as permeation enhancer shows optimum permeation. The above formulations gave a maximum drug permeation of 88%, 85%, respectively over 12 h. These two formulations were considered as best formulations among the prepared patches. The findings of this study revealed that the problems of TPM with reported oral formulations for pediatrics with epilepsy can be overcome by applying TPM topically in the form of a transdermal patch.

**Acknowledgments**

Authors are thankful to Dr. Bindu Madhavi, Associate professor, Nalanda College of Pharmacy for her constant encouragement and guidance.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Ashill CS, Michniak BB. Percutaneous penetration enhancers: Local versus transdermal activity. Pharm Sci Technolo Today 2000;3:36-41.
2. Balaji P, Thirumal M, Gowri R, Divya V, Ramassamy V. Design and evaluation of matrix type of transdermal patches of methotrexate. Int J Pharm Chem Biol Sci 2012;2:464-71.
3. Funke AP, Schiller R, Motzkus HW, Günther C, Müller RH, Lipp R.
Transdermal delivery of highly lipophilic drugs. In vitro fluxes of antiepileptics, permeation enhancers, and solvents from liquid formulations. Pharm Res 2002;19:661-8.

4. Guy RH. Current status and future prospects of transdermal drug delivery. Pharm Res 1996;13:765-9.

5. Kligman AM. Topical pharmacology and toxicology of dimethyl sulfoxide I. JAMA 1965;193:796-804.

6. Kunal M, Hetalk KP, Vishnu AP. Formulation and characterization of drug in adhesive transdermal patches of Diclofenac acid. Int J Pharm Pharm Sci 2012;4:296-9.

7. López A, Linares F, Cortell G, Herréz M. Comparative enhancer effects of Span20 with Tween20 and Azone on the in vitro percutaneous penetration of compounds with different lipophilicities. Int J Pharm 2000;202:133-40.

8. Etropolski MS, Okamoto A, Shapiro DY, Rauschkolb C. Dose conversion between tapentadol immediate and extended release for low back pain. Pain Physician 2010;13:61-70.

9. Martella G, Costa C, Pisani A, Cupini LM, Bernardi G, Calabresi P. Antiepileptic drugs on calcium currents recorded from cortical and PAC neurons: Therapeutic implications for migraine. Cephalalgia 2008;28:1315-26.

10. Murphy SN, Rani S, Hiremath R. Formulation and evaluation of controlled-release transdermal patch of theophylline-salbutamol sulfate. Drug Dev Ind Pharm 2001;27:1057-62.

11. Nira SS, Rajan BM. Formulation and evaluation of transdermal patches and to study penetration enhancement effect of eugenol. J Appl Pharm Sci 2011;1:96-101.

12. Rakesh PP, Grishma P, Ashok B. Formulation and evaluation of transdermal patch of Accelofenae. International Journal of Drug Delivery 2009;41-51.

13. Sarpongad PP, Zatz JL. Evaluation of penetration enhancement of lidocaine by nonionic surfactants through hairless mouse skin in vitro. J Pharm Sci 1986;75:176-81.

14. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. ISRN Pharm 2011;2011:651909.

15. Shaker DS, Ghanem AH, Li SK, Warner KS, Hashem FM, Higuchi WI. Mechanistic studies of the effect of hydroxypropyl-beta-cyclodextrin on in vitro transdermal permeation of corticosterone through hairless mouse skin. Int J Pharm 2003;253:11-11.

16. Shin SC, Lee HI. Controlled release of triprolidine using ethylene-vinyl acetate membrane and matrix systems. Eur J Pharm Biopharm 2002;54:201-6.

17. Tanner T, Marks R. Delivering drugs by the transdermal route: Review and comment. Skin Res Technol 2008;14:249-60.

18. White HS, Smith MD, Wilcox KS. Mechanisms of action of antiepileptic drugs. Int Rev Neurobiol 2007;81:85-110.

19. White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia 1999;40 Suppl 5:S2-10.

20. Yousuf M, Ahmad M, Ali I. Ketotifen fumarate and salbutamol sulfate combined transdermal patch formulations: In vitro release and ex vivo permeation studies. Int J Pharm Sci 2013;75:569-77.

21. Chauhan I, Bajpai M. Formulation and evaluation of transdermal drug delivery of saloxifene hydrochloride. Int J Pharm Sci Res 2010;1:72-9.

22. Vijayan V, Sumanth MH, Suman L, Vinay T, Srinivasrao D, Jayaraj Kumar K. Development and Physiochemical, in vitro evaluation of antihypertensive transdermal patches. J Pharm Sci Res 2010;2:171-2.

23. Pandit V, Khanam A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res 2009;1:799-804.

24. Bangale GS, Stephen Rathinaraj B, Rajesh KS, Gajanam Shinde V, Deepak Umalkar G, Rajveer CH, et al. Design and evaluation of transdermal films of Atenolol. J Chem Pharm Res 2010;2:595-6.

25. Bharkatiya M, Nema RK, Bhatnagar M. Designing and characterization of drug free patches for transdermal application. Int Pharm Sci Drug Res 2010;2:35-9.

26. Bharkatiya M, Nema RK, Bhatnagar M. Development and characterization of transdermal patches of metoprolol tartrate. Asian J Pharm Clinic Res 2010;3:2.

27. Anil Reddy B. In vitro characterization and evaluation of transdermal drug delivery system for metoprolol tartrate. J Pharm Res Health Care 2010;2:325-9.

28. Jayaprakash S, Halith SM, Firthouse PM, Yasmin, Nagarajan M. Preparation and evaluation of celecoxib transdermal patches. Pak J Pharm Sci 2010;23:279-83.

29. Donbrow M, Samuolo Y. Zero order drug delivery from double-layered porous films: Release rate profiles from ethyl cellulose, hydroxypropyl cellulose and polyethylene glycol mixtures. J Pharm Pharmacol 1980;32:463-70.

30. Shoail MH, Tazeen J, Merchant HA, Yousuf RI. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J Pharm Sci 2006;19:119-24.

31. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.

32. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985;60:110-1.

33. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. Pharm Tech 1996;20:64-74.

34. Patel N, Naruka PS, Chauhan CH, Modj J. Formulation and evaluation of immediate release tablet of Topiramate anti epileptic drug. JPSBR 2013;3:65-65.

35. Soul A, Panchagnub R. Role of dissolution studies in controlled release drug delivery system. STP Pharm Sci 1999;9:157-68.