International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2016.669.674

Research Article
Transdermal Local Anaesthetic Films of Tetracaine in Comparison to the Conventional Gel in Effective Management of Pain

[1]Hong Lin, [2]Yan Zhang, [1]Ming Hou and [1]Yue-lan Wang

[1]Department of Anesthesiology, Qianfoshan Hospital of Shandong Province, 250012 Shandong, People's Republic of China
[2]Department of Anesthesiology, Qilu Hospital of Shandong University, 250014 Shandong, People's Republic of China

Abstract

Background: Tetracaine hydrochloride is a topical local anaesthetics used in the treatment of pain associated with minor surgical procedures it also gives relief from pain associated with various localized muscle, joint, post-herpetic neuralgia, arthritis and haemorrhoids. **Objective:** The present study is designed to prepare and evaluate transdermal patches of tetracaine hydrochloride to deliver drug for a longer period of time to circumvent severe pain after surgical procedures. **Methodology:** Transdermal patches of tetracaine hydrochloride were prepared by solvent casting method. The prepared patches were evaluated for the various evaluation parameters like thickness, surface pH, weight uniformity, content uniformity, folding endurance, swelling index, *in vitro* drug release study, *in vitro* test for mucoadhesion and *in vivo* studies. **Results:** All the formulations exhibited acceptable physical properties. In *ex vivo* drug diffusion study the patches exhibited controlled release upto 24 h. The formulation Th3 (containing EC, SCMC and PVP) showed the best performance in the *ex vivo* drug diffusion with 92.02±1.21% drug release after 24 h. In the clinical study on the patients suffering from the post operative pain it was observed that the Th3 decreased the pain score from 9.89±0.08 to 4.05±0.21 while the gel could decrease the same from 9.80±0.01 to 7.09±1.10 at the end of 24 h post application. **Conclusion:** It was concluded that the prepared transdermal patches of the tetracaine were having significant effect as compared to the tetracaine gel used conventionally.

Key words: Analgesia, swelling, tetracaine, anaesthesia, pain score, transdermal

Received: December 24, 2015 Accepted: June 21, 2016 Published: July 15, 2016

Citation: Hong Lin, Yan Zhang, Ming Hou and Yue-lan Wang, 2016. Transdermal local anaesthetic films of tetracaine in comparison to the conventional gel in effective management of pain. Int. J. Pharmacol., 12: 669-674.

Corresponding Author: Yue-lan Wang, Department of Anesthesiology, Qianfoshan Hospital of Shandong Province, 66, Jingshi Road, Jinan, 250014 Shandong, People's Republic of China Tel/Fax: 0086-0531-82968900

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Transdermal Drug Delivery System (TDDS) is topically applied drug delivery system which involves incorporation of drug in the form of inert polymeric films or patch[1,2]. It is one of the most promising methods for topical drug application. Transdermal drug delivery systems bypass the hepatic first pass metabolism, maintain the desired plasma level consistently for prolonged period, require the dosing less frequently and minimizes the adverse effects. Apart from these advantages over the conventional oral dosage forms the TDDS can easily be removed, if any sign of irritation or other kind of side effects are observed. The TDDS shows the better patient compliance and almost free from inter subject variability (associated with the pathophysiological conditions of the patients). The more and more drugs (specially with short biologiocal half life) are being investigated for transdermal drug delivery soas to achieve fluctuation free plasma drug levels (which is often associated with the adverse effects)[3-10].

The topical anaesthetic agents and analgesic are used in the treatment of pain associated with minor surgical procedures. It also gives relief from pain associated with various localized muscle, joint, post-herpetic neuralgia, arthritis and haemorrhoids[11,12]. Topical anaesthetic agents are also used for dealing with chronic pain or for diagnostic purposes[13]. In particular it may also be useful for child and adult patients for post-surgical management of pain. The various dosage forms like creams, gels aerosols are available for achieving topical analgesia. As compared to other routes of administration the topical anaesthesia has proven to be effective, safer and more acceptable[14]. Topical anaesthesia is a very good alternative specially for the patients after minor surgical operation. Sometimes when it is very difficult to tolerate the intense pain in the elderly patients suffering from postoperative pain, arthritis, gout and osteoartheritis topical local anaesthetic application may resolve the problem[13,15].

Tetracaine HCl is a local anaesthetic of ester type. It is applied topically to produce local anaesthesia. Tetracaine shows the short duration of action so gel like formulateions are needed to be applied many times in a day to show the prolonged analgesia. Therefore, it was thought that the transdermal films of tetracaine might show the effective analgesia for prlonged period of time.

The objective of this study was to prepare and evaluate transdermal drug delivery system of tetracaine hydrochloride. The transdermal patches were evaluated for various physicochemical and biological evaluation parameters including *ex vivo* diffusion study and *in vivo* study.

MATERIALS AND METHODS

Materials: Tetracaine Hydrochloride (TH), Ethyl Cellulose (EC), hydroxypropyl methyl cellulose (HPMC) and Poly Vinyl Pyrrolidone-K30 (PVP-K30) were purchased from Sigma Aldrich, US. All other chemicals were of analytical grade.

Method of preparation of transdermal patches: Solvent casting method was adopted for the fabrication of transdermal films of tetracaine hydrochloride (Table 1). Fabrication was done by combining the polymers in different ratio. The EC, SCMC and PVP films were prepared first by dissolving EC and SCMC in a measured volume of ethanol. Then PVP was added and mixed properly to get a homogeneous mixture. Specific quantity of dibutylphthalate and isopropyl myristate was added. An accurately weighed amount of drug was dissolved in a suitable solvent and dispersed in polymer mixture it was poured in to the glass mould placed on the uniform surface. Inverted positioned funnel was used to control the solvent evaporation. After 24 h the patches were removed, cut into circular disc with 3 cm diameter and kept in a desiccator for further studies.

Physiochemical evaluation: Patch thickness for all the formulations of transdermal patches was determined by using digital micrometer at different points and the average thickness of the prepared patch was calculated and reported. For weight uniformity a specified area (5 cm^2) of patch was cut from different parts of the circular cast and weighed in digital balance. The average weight and standard deviation values were calculated from the individual weight. Folding endurance for the formulations were measured by taking a small strip of patch (5 cm^2) and it was cut evenly and folded repeatedly at the same place till it breaks. Count the number of times the film could be folded at the same place. A point where it breaks will give the value of the folding endurance. Percentage elongation break test was performed by noting the length just before the break point, the percentage elongation can be determined from the equation:

$$\text{Elongation (\%)} = \frac{\text{L1-L2}}{\text{L2}} \times 100$$

Table 1: Composition of transdermal patches of tetracaine hydrochloride

Ingredient	Th1	Th2	Th3	Th4
TH (mg)	50	50	50	50
EC (mg)	200	150	100	150
SCMC (mg)	250	200	150	300
PVP-K30	-	100	200	50
Ethanol (mL)	20	20	20	20

where, L1 is the final length of each strip and L2 is the initial length of each strip.

Percent moisture content and water vapour permeability: The preweighed films were kept in a desiccators (containing fused calcium chloride at room temperature) for 24 h. After 24 h the films were reweighed and then percentage moisture content was determined. For water vapour permeability, 1 g of fused calcium chloride was added into the properly washed and dried glass vials (5 mL) about. The prepared transdermal films were applied to the brim with the help of adhesive tape. Then again the vials were weighed and kept in a humidity chamber (85% RH) for 24 h. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24 h to note down the weight gain[16].

Drug content: A specified area of patch was dissolved in methanol. The resulted solution is filtered by using filter medium. Sample is taken, diluted and analyzed spectrophotometrically at 310 nm.

***Ex vivo* drug diffusion studies:** Franz diffusion cell was used to carry out the diffusion study using the abdominal rat skin[17]. The apparatus consists of two compartments, the donor and the receptor compartment. The abdominal skin was kept on the bottom opening of donor compartment as it touches the receptor medium (phosphate buffer pH 7.4, 15 mL) throughout the study and both the compartments were held together tightly with the help of clamps. The temperature was maintained at 37±0.5°C and receptor compartment was provided with sampling port. The temperature was maintained at 37±2°C and the receptor medium was agitated at 400 rpm by placing the apparatus on the top of a magnetic stirrer with hot plate. The diffusion study was carried out up to 24 h and 1 mL sample was withdrawn at different intervals of time. Immediately after withdrawal of samples the same volume of fresh phosphate buffer pH 7.4 was replaced. The samples were analyzed UV spectrophotometrically at 310 nm.

Animals: The healthy male Wistar rats (150-225 g) used for the study were kept in standard environmental conditions of light and temperature. The rats were allowed drinking water and standard diet *ad libitum*. After acclimatization period of 2 days the rats were used for the study. The animal study protocols were approved by the Institutional Ethical Committee of Shandong University, Shandong.

Primary skin irritation test: The patches were applied to the Wistar albino rats at a high dose of 4% w/w and observed for any sign of edema or erythema at the site of application after 48 h of application.

***In vivo* analgesic activity of tetracaine transdermal patch**

Hot plate method: The rats were placed on hot plate analgesiometer at 55±1°C. The transdermal patch was placed on the shaved dorsal surface of rat with TH dose (1.0 mg kg^{-1}) 30 min before the beginning of the test. The hot plate method (thermally induced algesia) was used for assessing the analgesic activity of the prepared patches. The time taken to the start of jumping or licking forepaw by the rat was observed (measured at various time intervals) and it was called the reaction time. The Maximum Response (MR) to the tetracaine loaded patches in terms of the reaction time in seconds which reflects the intensity of drug action, the Time of the Maximum Response (TMR) and the duration of Drug Action (DA) were used as the parameters.

Writhing method: Acute analgesia produced by the drugs was assessed by the acetic acid induced writhing method in rats. Rats were divided in three groups of 6 rats each. The control group: Control (received non medicated transdermal films) the Test group II: Received transdermal films (Th3, 10 µg kg^{-1} body mass), the standard group received TH gel, 50 µg kg^{-1} body mass. Ten hours after treatment, 0.6% (V/V) acetic acid solution (10 mL kg^{-1}) was injected to rats intraperitoneally. Total number of writhes, which was a parameter of chemically induced pain (i.e., constriction of abdomen, turning of trunk and extension of hind legs) was counted for 20 min. The analgesic effect was expressed as percent reduction of writhes in comparison with the control[18].

Statistical analysis: Results were expressed as Mean values±Standard Deviations and the significance of the difference observed was analyzed by the Student's t-test.

RESULTS

The transdermal drug delivery systems of tetracaine hydrochloride were prepared by solvent casting method. The EC SCMC and PVP-K30 were used as a polymer and dibutyl phthalate and isopropyl myristate were added as a plasticizer to enable elasticity in the formulation. All the preparations were evaluated for its physical properties such as uniformity of drug content, thickness, weight uniformity, folding endurance, percentage moisture content,

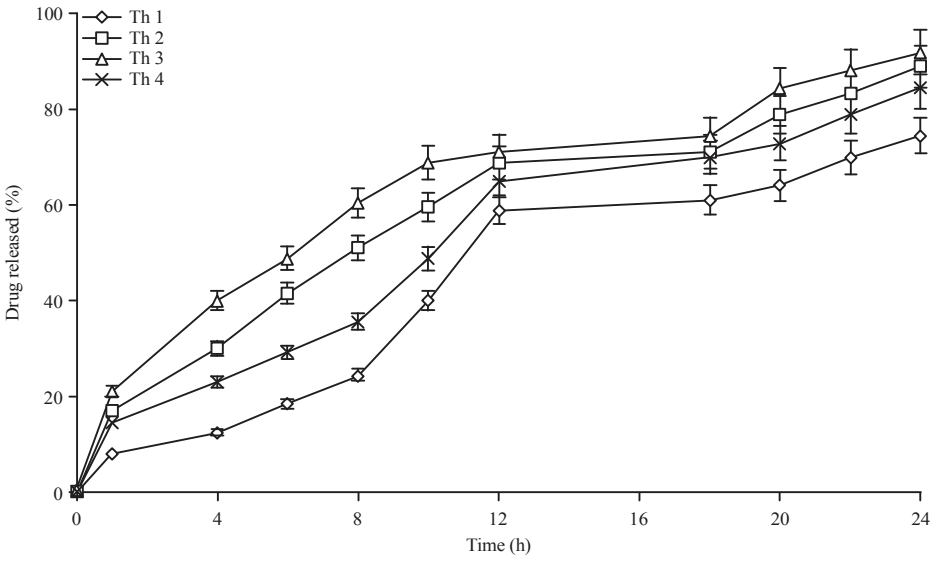

Fig. 1: *Ex vivo* permeation study of the prepared tetracaine transdermal patches

Table 2: Physicochemical properties of transdermal patches of TH

Formulae code	Drug content (%)	*Thickness (mm)	Weight uniformity (mg)	*Folding endurance	*Moisture content (%)	*Percent elongation break	*Water vapor permeability
Th1	82.02±0.2	0.153±0.024	93±5.110	132	2.01±0.057	74.0	0.24±0.023
Th2	84.12±0.1	0.160±0079	100±3.04	170	2.43±0.038	91.3	0.36±0.021
Th3	87.01±0.2	0.221±.0240	106±2.50	130	2.25±0.073	100.4	0.51±0.032
Th4	83.20±0.2	0.192±0.009	112±3.05	131	3.85±0.031	82.16	0.34±0.011

±SD: *Standard deviation

Table 3: *In vivo* analgesic activity (hot plate method) of transdermal patch of TH

Formulation	MR (s)[a]	TMR (h)	DA (h)
Th gel (2%)	5.00±0.01	1.50	6
Th3	8.00±0.12	1.75	>12

[a]All values are Means±SE of 6 determinations, MR: Maximum analgesic response, TMR: Time of maximum analgesic response and DA: Duration of analgesic action

water vapour permeability and percentage elongation break test (Table 2). Drug content for all the formulations was determined UV spectrophotometrically. The formulation Th3 showed the highest drug content value of 87.01±0.2% while the formulation Th1 showed the lowest drug content of (82.02±0.2%) thickness was measured with the help of digital micro meter. Thickness was highest (0.221±0.024 mm) for Th3 and lowest (0.153±0.024 mm) for Th1. The average weight of transdermal patches was highest for Th4 (112±3.05 mg) and lowest (93±5.110 mg) for Th1. Folding endurance for preparations were calculated by repeatedly folding the patch at the same place till it breaks. The values for the same were within the range of 131-170.

Percent moisture content in the formulations was determined by weighing the patches before and after keeping the films into the desiccator. Percent moisture content for formulation ranged from 2.01±0.057% (Th1) to 3.85±0.031 (Th4). Result showed that water vapour permeability was found to be in the range of 0.24±0.023 to 0.51±0.032. The *ex vivo* diffusion study was performed in phosphate buffer (pH 7.4) by using Franz diffusion cell. In the *ex vivo* diffusion study the percentage drug release was 74.48±1.02 to 92.02±1.21% at the end of 24 h. Formulation Th3 showed the best diffusion profile might be due to higher concentration of PVP-K30 in the formulation as compared to the other formulations.

There was no sign of edema or erythema in the Wistar rats even with the high doses containing patches.

The *in vivo* analgesic activity of the best formulation Th3 was performed by hot plate method and writhing method (Table 3 and 4). It was observed that the Th3 showed more than 12 h of duration of action while the tetracaine gel showed only 6 h duration of action. The writhing method reported 67.95% of analgesia with Th3 patch while on the other hand the standard gel showed 62.82% of analgesia at the end of 12 h post application. It also to be noted the gel could reach upto the above mentioned effectiveness only after applying it twice a day. The tetracaine gel could not pace up with the analgesic effectiveness of the patch (Fig. 1).

Table 4: *In vivo* analgesic activity (writhing method) of transdermal patches of TH

		Analgesic activity	
Drug	Dose (μg kg^{-1})	No. of writhes[a]	Analgesia (%)
Control (blank films)	-	78±3	-
Th gel (standard)	2	29±2[b]	62.82
Th3	5	25±3[b]	67.95

[a]Mean±SEM, n = 6 and [b]p<0.05 vs control

DISCUSSION

The TDDS is a topical drug delivery system which provides the prolonged drug delivery for local as well as systemic effects. The drug release from the transdermal patch is well governed by the nature of drug, polymer, type of delivery system (matrix, reservoir etc.), pathophysiology of skin barrier etc. The drug molecule interact physically with the network polymeric chains of the deleivry matrix. The flexibility of the polymeric chain and other physical properties like swelling, moisture uptake etc. play the vital role in controlling the diffusion of drug across the polymeric matrix and then the skin[19-22].

Topical local aesthetics are basically used to relief patient from the severe pain associated with the post operative surgery, patients suffering from arthritis or osteoarthritis[23]. Tetracaine hydrochloride is the only topical anaesthetic drug which is very widely used and well tolerated as compared to the other local anaesthetics. Present study deals with the preparation of transdermal patches of tetracaine hydrochloride and its comparison with the standard marketed gel. The prepared formulations were of good physical appearance smooth surface with no visible cracks on the surface. It was found to be satisfactory as maximum 87% of drug was loaded in formulation Th3, rest three formulations also showed good results with minor variations. The results of water vapour permeation indicated that increase in PVP concentration increases values of water vapour permeation which may be due to irregular arrangement of molecules in the amorphous state. It usually causes the molecule to be spaced apart as compared to crystal state.

Thickness of patches reflects the release characteristics as formulations with maximum thickness of the patch gave more sustained release drug profile as compared to the other formulations. The moisture content in the formulations was found to be increaseing by increase in the concentration of PVP-K30 and also with increasing the contents of SCMC. Percent moisture content reflects the amount of water retained in the patches which provides the required surface wetting for better absorption of the drug. Significant values of moisture content in all the formulations suggested and supported good results of *ex vivo* diffusion study. In another study, the transdermal patches of donepezil[24] were prepared. The *in vitro* release data was treated with kinetic equations and it followed zero order release. The diffusion study was carried out using rat skin showed 89% drug was released within 72 h. It can be stated that the process of drug release in most of the controlled release delivery system is by diffusion control mechanism and polymer matrix showed the important role on thediffusion of the drug[25]. The *ex vivo* diffusion profile for the present study did not fit to zero order pattern as it was aimed[26-28]. Practicality, it followed Higuchi's model which is indicative of matrix diffusion as the release mechanism. It may be the second best mechanism of release because the matrix diffusion provides slow release.

The *in vivo* study reported a very significant analgesic activity by formulation Th3 as compared to that of standard gel with higher analgesia with prolonged duration of action. In a present study also, the local anaesthetic transdermal films of lidocaine were prepared for effective management of severe postoperative pain especially for the use in children and elderly patients[18].

CONCLUSION

Therefore, it can be concluded that the transdermal local anaesthetic films oftetracaine may be quite effective in comparison to the conventional gel ineffective management of pain. The films showed effective and prolonged analgesia in rats. The prepared tetracaine transdermal films may be effective alternative analgesia in postoperative pain especially for children and elderly patients.

ACKNOWLEDGMENT

Authors humbly acknowledge the kind support and facilities provided by Qianfoshan Hospital of Shandong province. Thanks are due to all the staff members of Department of Anesthesiology of Qianfoshan Hospital of Shandong province and of Qilu Hospital of Shandong University for their kind cooperation.

REFERENCES

1. Jung, E., E.Y. Lee, H.K. Choi, S.J. Ban and S.H. Choi *et al*., 2015. Development of drug-in-adhesive patch formulations for transdermal delivery of fluoxetine: *In vitro* and *in vivo* evaluations. Int. J. Pharmaceut., 487: 49-55.
2. Lefevre, G., G. Sedek, H.L.A. Huang, M. Saltzman, M. Rosenberg, B. Kiese and P. Fordham, 2007. Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: Relative effects of body site application. J. Clin. Pharmacol., 47: 471-478.

3. Keleb, E., R.K. Sharma, E.B. Mosa and A.A.Z. Aljahwi, 2010. Transdermal drug delivery system-design and evaluation. Int. J. Adv. Pharmaceut. Sci., 1: 201-211.
4. Jana, S., A. Manna, A.K. Nayak, K.K. Sen and S.K. Basu, 2014. Carbopol gel containing chitosan-egg albumin nanoparticles for transdermal aceclofenac delivery. Colloids Surf. B: Biointerfaces, 114: 36-44.
5. Kerimoglu, O., E. Keskin, B. Dortunc and S. Anah, 2013. Matrix type transdermal therapeutic system containing captopril: Formulation optimization, *in vitro* and *ex vivo* characterization. Acta Poloniae Pharmaceutica-Drug Res., 70: 291-300.
6. Cha, B.J., E.D. Lee, W.B. Kim, S.J. Chung, M.H. Lee and C.K. Shim, 2001. Enhanced skin permeation of a new capsaicin derivative (DA-5018) from a binary vehicle system composed of isopropyl-myristate and ethoxydiglycol. Arch. Pharmacal Res., 24: 224-228.
7. Cho, Y.A. and H.S. Gwak, 2004. Transdermal delivery of ketorolac tromethamine: Effects of vehicles and penetration enhancers. Drug Dev. Ind. Pharm., 30: 557-564.
8. Santos, P., A.C. Watkinson, J. Hadgraft and M.E. Lane, 2012. Influence of penetration enhancer on drug permeation from volatile formulations. Int. J. Pharmaceut., 439: 260-268.
9. Batheja, P., L. Sheihet, J. Kohn, A.J. Singer and B. Michniak-Kohn, 2011. Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and *in vitro* and *in vivo* skin distribution studies. J. Controlled Release, 149: 159-167.
10. Wang, Y., X.P. Zhao and J.W. Ruan, 2015. Transdermal drug delivery system of aceclofenac for rheumatoid arthritis and the effect of permeation enhancers: *In vitro* and *in vivo* characterization. Int. J. Pharmacol., 11: 456-462.
11. Lexicomp, 2013. Drug Information Handbook. 22nd Edn., Lexicomp, Hudson, OH., ISBN: 9781591953197, Pages: 2193.
12. Neal, J.M., 2003. Effects of epinephrine in local anesthetics on the central and peripheral nervous systems: Neurotoxicity and neural blood flow. Regional Anesthesia Pain Med., 28: 124-134.
13. Amin, S.P. and D.J. Goldberg, 2005. Topical anesthetics for cosmetic and laser dermatology. J. Drugs Dermatol., 4: 455-461.
14. Huang, W. and A. Vidimos, 2000. Topical anesthetics in dermatology. J. Am. Acad. Dermatol., 43: 286-298.
15. Rajesh, N., G. Siddaramaiah, D.V. Gowda and C.N. Somashekar, 2010. Formulation and evaluation of biopolymer based transdermal drug delivery. Int. J. Pharm. Pharmaceut. Sci., 2: 142-147.
16. Mukherjee, B., S. Mahapatra, R. Gupta, B. Patra, A. Tiwari and P. Arora, 2005. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on *in vitro* skin permeation. Eur. J. Pharmaceut. Biopharmaceut., 59: 475-483.
17. Gairola, A., U. Chaurasia, A. Singh and V.A. Saharan, 2014. Development and evaluation of transdermal patches of aceclofenac. Thai J. Pharmaceut. Sci., 38: 90-97.
18. Mao, S.S., W.J. Zhang, W.J. Li and J. Ma, 2015. Transdermal drug delivery of lidocaine as patient compliant local anesthesia in effective management of postoperative pain. J. Biomater. Tissue Eng., 5: 499-503.
19. Kesarwani, A., A.K. Yadav, S. Singh, H. Gautam, H.N. Singh, A. Sharma and C. Yadav, 2013. Theoretical aspects of transdermal drug delivery system. Bull. Pharmaceut. Res., 3: 78-89.
20. Djordjevic, J., B. Michniak and K.E. Uhrich, 2003. Amphiphilic star-like macromolecules as novel carriers for topical delivery of nonsteroidal anti-inflammatory drugs. AAPS PharmSci, 5: 1-12.
21. Saxena, M., S. Mutalik and M.S. Reddy, 2006. Formulation and evaluation of transdermal patches of metoclopramide hydrochloride. Indian Drugs, 43: 740-745.
22. Patel, H.J., J.S. Patel, B.G. Desai and K.D. Patel, 2010. Permeability studies of anti hypertensive drug amlodipine besilate for transdermal delivery. Asian J. Pharmaceut. Clin. Res., 3: 31-34.
23. Roberts, J. and J. Hedges, 1998. Procedures in Emergency Medicine. 3rd Edn., WB Saunders, London, UK., pp: 457-473.
24. Madan, R., N.S. Argade and K. Dua, 2015. Formulation and evaluation of transdermal patches of donepezil. Recent Patents Drug Delivery Formul., 9: 95-103.
25. Manvi, F.V., P.M. Dandagi, A.P. Gadad, V.S. Mastiholimath and T. Jagadesh, 2003. Formulation of a transdermal drug delivery system of ketotifen fumarate. Indian J. Pharmaceut. Sci., 65: 239-243.
26. Ozguney, S., H.Y. Karasulu, G. Kantarci, S. Sozer, T. Guneri and G. Ertan, 2006. Transdermal delivery of diclofenac sodium through rat skin from various formulations. AAPS PharmSciTech, 7: E39-E45.
27. Verma, P.R.P. and S.S. Iyer, 2000. Transdermal delivery of propranolol using mixed grades of Eudragit: Design and *in vitro* and *in vivo* evaluation. Drug Dev. Ind. Pharm., 26: 471-476.
28. Gupta, S.P. and S.K. Jain, 2004. Development of matrix-membrane transdermal drug delivery system for atenolol. Drug Delivery, 11: 281-286.