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Development of Tizanidine HCl transdermal patches: *In-vitro* and *Ex-vivo* characterization

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ABSTRACT

The purpose of this work was to design and evaluate matrix type transdermal patches of Tizanidine hydrochloride using Hypromellose (HPMC E15) as polymer, dibutyl phthalate as plasticizer and citral as permeation enhancer. The DSC and FTIR results showed the compatibility of the excipients with the drug. These transdermal drug delivery systems were characterized for their thickness, folding endurance, content uniformity, tensile strength and *in-vitro* release studies of the drug from the polymeric matrix. *In-vitro* release studies and *ex-vivo* permeation were carried out with modified Franz diffusion cell using pH 5.8 & pH 7.4 phosphate buffers as receptor medium and it showed controlled release of drug. The results suggest that the formulation of TIZ may be useful in the development of a therapeutic system to deliver TIZ across the skin for a prolonged period, i.e. 24 hr.

Keywords: Tizanidine Hydrochloride, Transdermal patch, HPMC E15, *in-vitro* & *ex-vivo.*

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INTRODUCTION

Transdermal therapeutic system are defined as 'self-contained' discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery systems (TDDS) offer many advantages such as reduced side effects, elimination of first-pass metabolism and improved patient compliance. Transdermal drug delivery system is used for delivery of drugs with small molecular size, short half-life, low oral bioavailability and low dose, etc. In recent times, transdermal patches are become most acceptable approach for patients. Several drugs were administered through transdermal route by matrix-type transdermal patches which include aceclofenac, dexamethasone, terbutaline sulphate, atenolol, diltiazem, etc. Present day, transdermal patches are applied in several therapeutic regions like smoking cessation, pain management, hormone replacement and treatment of heart disease[1-5]. Tizanidine hydrochloride is a smooth muscle relaxant with half life of 2.54 hrs. It exhibits first-pass metabolism, which leads to poor bioavailability i.e.<40%. Very few studies were reported on transdermal patches using tizanidine hydrochloride. The objective of the present study was to develop and evaluate transdermal delivery systems of TIZ for *invitro* release studies, *ex-vivo* permeation studies and mechanical properties.

MATERIALS

Tizanidine hydrochloride obtained as a gift sample from Yarrow chem Ltd. HPMC E15 was supplied by BMR chemicals, HYD. Potassium dihydrogen ortho phosphate, Sodium hydroxide, Methanol, Dichloromethane and dibutyl phthalate were supplied by Merck Ltd, Mumbai. Citral were purchased from Merck Ltd. Dialysis membrane was supplied by Hi Media Laboratories Pvt Ltd, Mumbai.

Methodology:

Drug polymer interaction studies

To study the possible interaction between Tizanidine HCl and polymeric materials of the patches, Differential scanning calorimetry(DSC, Perkin Elmer 4000) and FTIR (KBR pellet method) was carried out on pure drug and drug-excipient physical mixture.

Preparation of transdermal patches

The preparation of transdermal patches of TIZ was carried out by following solvent casting technique. Weighed quantities of polymer (Table I) Hydroxy propyl methyl cellulose (HPMC E 15 LV), were taken in a boiling tube. About 20 ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set-aside for 6 hours to allow the polymer to swell. After

swelling dibutyl phthalate as a plasticizer 15-17%v/w (of dry polymer weight), permeation enhancer and weighed amount of drug was added to this polymeric mixture and mixed well. It was set-aside for sometime 10-15mins to exclude any entrapped air and was then transferred into a previously cleaned Anumbra Petri plate (72.3 sq cm). Drying of these patches were carried out at room temperature for overnight and then the polymeric films formed were removed carefully, placed in a vacuum oven and vacuum was applied for 8-12hrs to remove traces of solvent if any. They were stored in a desiccator till the evaluation tests were performed. The entire film was cut into patches of 4.9cm^2 [12].

Table I: Composition of TIZ transdermal patches

Formulation code	Drug (mg)	HPMC E15 (mg)	Citral (%)
T1	30	600	-
T2	30	800	-
T3	30	1000	-
T4	30	1200	-
T5	30	1000	12
T6	30	1000	14
T7	30	1000	16

Note: 17% v/w Dibutyl phthallate to the total polymer weight, incorporated as Plasticizer.

Each patch (4.9 cm^2) contains 2mg of TIZ. 20ml dichloromethane:methanol(1:1)

Evaluation Parameters

Thickness

The thickness of the film was measured at 5 different points using screw gauge. For each formulation, three selected films were used and average thickness was recorded.

Weight variation

Three films from each batch of an area of 4.9 cm^2 were weighed individually and the average weight was calculated.

Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at same place until it breaks. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Drug content

Films from each formulation were taken, cut into small pieces (4.9 cm^2), and were allowed to dissolve in a 100 ml phosphate buffer and kept on magnetic stirrer for 24 hrs. The solution was filtered using whatmann filter paper & diluted suitably and the absorbance of the solution was measured using UV-visible spectrophotometer at 235 nm against blank.

In-vitro release studies

The drug release studies from TIZ transdermal patches were performed using Franz diffusion cells. Commercially available water impermeable adhesive backup membrane was placed over the patches (4.9 cm^2). Then the transdermal patch was placed over a dialysis membrane (Himedia MolWt 5000) and sandwiched between the two compartments and fixed tightly using clamps. The whole set up was placed on magnetic stirrer. Samples (2 ml) were collected up to 24 hrs. Analysis was carried out using UV-Vis spectrophotometer. Phosphate buffer pH 5.8 (15 ml) was used as release media. The study was conducted at 32 ±0.5^{o}C at a speed of 500 rpm. The analysis was done at 235 nm against phosphate buffer pH 5.8 as blank. Mathematical expressions, zero order[4], First order[14] and Higuchi model were applied to analyze the release mechanism from the transdermal patches.

Preparation of rat abdominal skin

Wistar rats weighing 230-250 gm were sacrificed using anaesthetic ether (IAEC/23/Ucpsc/KU/2018). The hair of test animals were carefully trimmed short (<2 mm) with a pair of scissors and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique, which involved soaking the entire abdominal skin in water at 60^{o}C for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for *ex-vivo* permeability studies.

Ex-vivo permeation studies

Franz diffusion cell with a surface area of 4.9 cm^2 was used for *ex-vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS under test. The receiver phase 15ml of phosphate buffer saline (PBS) pH 7.4, stirred at 500 rpm on a magnetic stirrer; the whole assembly was kept at 37 ± 0.5^{o}C. The amount of drug permeated was determined by removing 2ml of sample at appropriate time intervals up to 24 hr, the volume was replenished with an equal volume of phosphate buffer saline pH 7.4. The absorbance was measured at 235 nm spectrophotometrically. Cumulative amounts of drug permeated in µg/cm^2 were calculated and plotted against time. Drug flux (µg/hr/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (4.9 cm^2)[11] and the permeability coefficient was deduced by dividing the flux by initial drug load[12].

The target flux is calculated using the following equation.

$$J_{Target} = \frac{C_{SS}\, Cl_T\, BW}{A}$$

A represents the surface area of the transdermal patch (i.e 4.9 cm^2); BW, the standard human body weight of 60 kg; C_{ss} the TIZ concentration at the therapeutic level (0.015µg/ml) and the Cl_T the total clearance (0.504L/hr/kg), the calculated target flux value for TIZ was 15.42µg/hr/cm^2.

Moisture absorption study

The films were weighed accurately and placed in a desiccator containing 100ml saturated solution of aluminum chloride (79.50% RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight[9].

Moisture content

The patches were weighed and kept in a desiccator containing calcium chloride at 40^{o}C for 24 hr. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight[5].

Measurement of mechanical properties

Mechanical properties of the fabricated films were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, and UK), equipped with 25 kg load cell. The Tensile strength (T.S) was measured using the film strip (60×10mm) free from air bubbles or any physical imperfections. The film strip (60 × 10mm) was held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm s^{-1}pulled the strips to a distance till the film broke. The force required to break the film was consider as a tensile strength and it was calculated as kg/mm^2.

$$\text{Tensile strength} = \frac{\text{Force required to break patch (kg)}}{\text{Cross-sectional area of patch (mm}^2\text{)}}$$

RESULTS AND DISCUSSION

DSC study: The DSC curve of tizanidine hydrochloride showed a single sharp endothermic peak at 279ºC corresponding to its melting point 280ºC. In optimized formulation, endothermic peak of drug was well preserved with slight changes in terms of shifting towards the lower temperature, 278ºC.

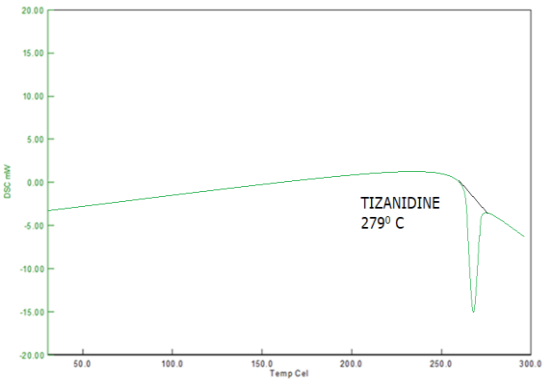

Figure 1: DSC thermogram of pure drug

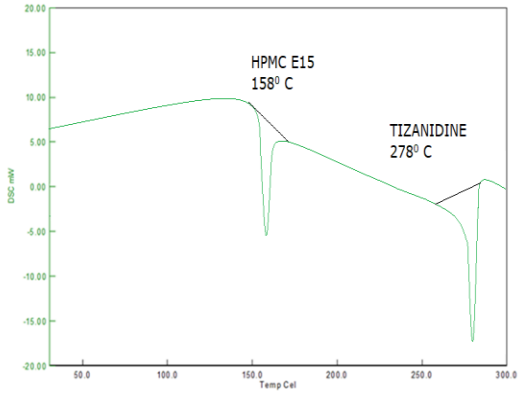

Figure 2:DSC thermogram of drug + polymer

FTIR spectra: The IR spectral analysis of TIZ HCl alone showed that the principal peaks were observed at wave numbers of 1635.69, 2931.9, 3242.95. In the IR spectra of the physical mixture of TIZ HCl and HPMC E15 the principal peaks were observed at 1635.61, 2933.93, 3443.05. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the present study.

Table II. Comparison of the Peaks of Functional Groups Observed in FTIR Spectra

Functional group	C=N Stretch	C-H Stretch	N-H Stretch
Tizanidine HCl	1635.69	2931.90	3242.95
Tizanidine HCl with HPMC E15	1635.61	2933.93	3443.05

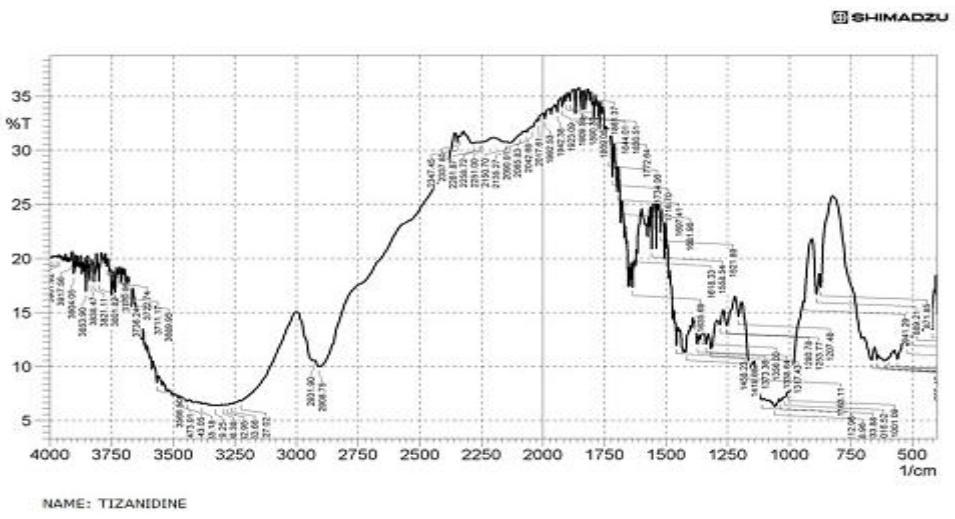

Figure 3: FTIR spectra of pure TIZ HCl

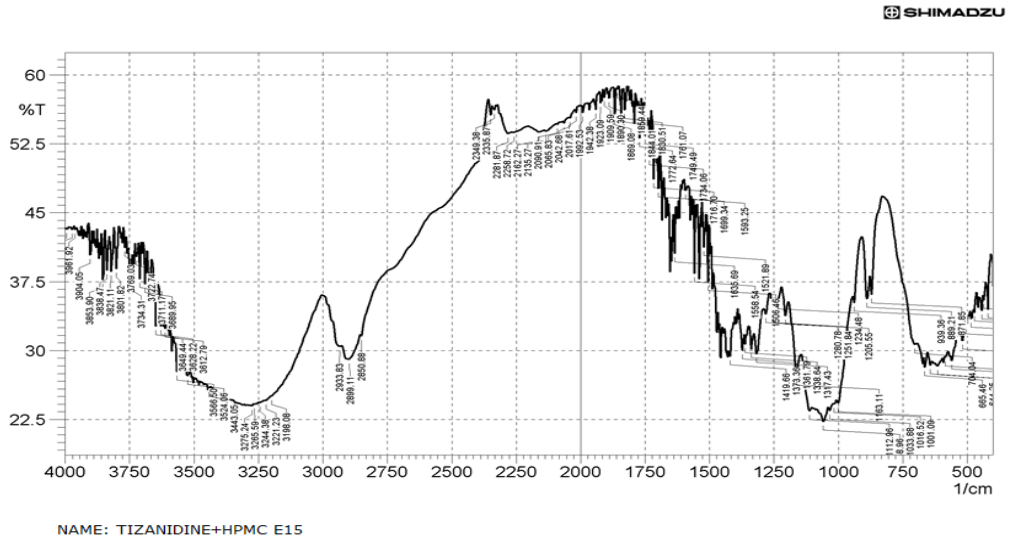

Figure 4: FTIR Graph of Pure Tizanidine HCL With HPMC

Moisture absorption and moisture content studies:

The moisture content in the patches is ranged from 4.2 ± 0.23 to 6.0 ± 0.24%. The moisture absorption in the formulations is ranged from 5.4 ± 0.35 to 6.8 ± 0.33%. The results revealed that the moisture absorption and moisture content was found to increase with increasing concentration of hydrophilic polymer (HPMC). The low moisture absorption protects the transdermal films from microbial contamination and small moisture content prevents the films from becoming brittle.

Mechanical Properties

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength (TS) and elastic modulus (EM) and elongation at break (E/B). A soft and weak polymer is characterized by a low TS, EM and E/B; a hard and brittle polymer is defined by a moderate TS, high EM and low E/B; a soft and tough polymer is characterized by a moderate TS, low EM and high E/B; where as a hard and tough polymer is characterized by a high TS, EM and E/B. The results of mechanical properties are shown in Table III. Formulation T3 and T4 exhibited greater values of tensile strength (1.63 ± 0.22 kg/mm^2 and 1.72 ± 0.25 kg/mm^2 respectively). The results revealed that as the concentration of HPMC increased, the tensile strength was found to be increased. These observations indicate that formulation T3 patches were found to be strong, not brittle and flexible, T4 patches were found to be strong but were brittle and not flexible.

Table III: Physico chemical evaluation of different formulations

Formula-tion code	Thickness (mm)	Weight variation (mg)	Drug content (mg)	Moisture content (%)	Moisture absorption (%)	Tensile strength (kg/mm^2)
T1	0.34±0.82	36.0±0.97	2.1±0.76	4.2±0.23	5.4±0.35	1.26±0.23
T2	0.36±0.80	38.2±0.93	1.98±0.74	5.3±0.23	5.8±0.34	1.50±0.24
T3	0.38±0.75	40.2±1.0	2.0±0.74	5.7±0.20	6.2±0.34	1.63±0.22
T4	0.38±0.75	40.5±0.84	1.97±0.64	6.0±0.24	6.8±0.33	1.72±0.25
T5	0.37±0.74	40.2±0.72	2.0±0.78	5.4±0.23	6.0±0.32	1.60±0.24
T6	0.38±0.86	40.1±0.87	2.1±0.76	5.3±0.22	6.3±0.35	1.63±0.25
T7	0.38±0.75	40.3±1.13	2.0±0.78	5.7±0.20	6.2±0.34	1.60±0.24

Values represent mean ± SD (n=3).

***In-vitro* release Studies**

Formulation T3 exhibited greatest (53.7±3.23) percentage of drug release without citral. In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially, however with a very nominal decrease in formulation T4 may be due to increase in the diffusional path length .

The addition of citral in different concentration to T3 formulation (Table IV) tends to enhance the release rates (Fig 5). The description of dissolution profiles by a model function has been attempted using different kinetics (zero order, first order and Higuchi square-root model) and using the equation derived by Korsmeyer *et al.*

Higuchi square route seemed to be the most appropriate model describing release kinetics from all patches (R^2=0.8874). On the other hand n values (n<0.5) indicated that amount of released drug was by Fickian diffusion.

Table IV: *in-vitro* %cumulative drug release studies

Time points (hrs)	T5 (12%)	T6 (14%)	T7 (16%)
0	0	0	0
0.5	33.0±2.36	50.6±1.53	36.5±2.65
1	34.1±2.58	54.9±1.09	40.1±2.3
2	35.7±2.46	58.4±1.12	43.6±1.06
4	38.5±2.03	65.1±1.86	56.1±1.73
6	51.9±2.76	74.2±2.08	63.3±1.13
8	58.0±1.94	80.9±2.05	66.3±1.07
12	62.4±1.73	90.7±1.78	68.8±1.54
24	74.5±1.58	101.8±1.54	78.75±2.20

Values represent mean ± SD (n=3)

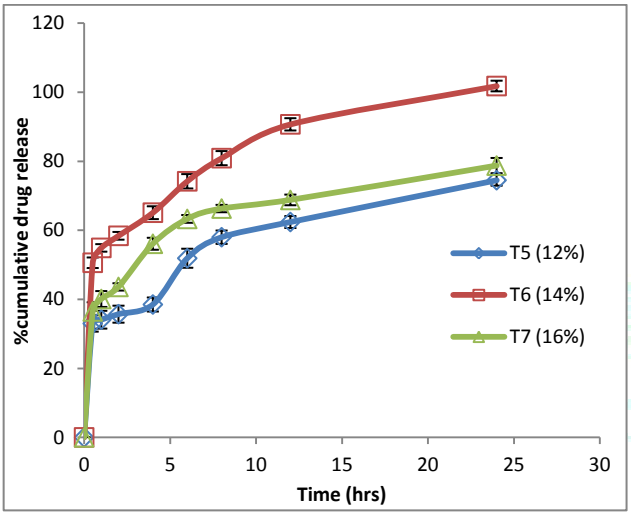

Figure 5: Comparison of % cumulative drug release of TIZ HCl from formulations with 1000 mg HPMC E 15 with varied citral concentration, T5(12%), T6(14%),T7(16%)

***Ex-vivo* permeation studies of formulations containing citral:**

The results of *ex-vivo* skin permeation of TIZ HCl from patches were shown in Fig (**6**). The cumulative amounts of drug permeated per square centimeter of patches through the rat abdominal skin when plotted against time, the permeation profiles of drug from T6 seem to follow Zero order kinetics as it is evidenced by correlation coefficient (0.9903)and Higuchi's equation (R^2=0.9460), n values (0.823) indicated that amount of released drug was by non Fickian diffusion. As the concentration of citral increased, drug permeation increased by modifying solvent nature of stratum corneum and improves drug partition coefficient into tissue and further increase in concentration, permeation was decreased, this could be attributed to the interaction between citral & drug . The required flux was higher than the targeted flux (15.42 µg/hr/cm²) with formulation T6 (14% citral 16.06µg/hr/cm²), while T5 (12%) & T7 (16%) showed lower flux than targeted flux, thus T6 formulation was optimized. The results of drug permeation from transdermal patches of TIZ HCl through the rat abdominal skin confirmed that TIZ HCl was released from the formulation and permeated through the rat skin and hence could possibly permeate through the human skin.

Table V: *Ex-vivo* skin permeation studies

Time points (hrs)	T5 (µg/cm²)	T6(µg/cm²)	T7(µg/cm²)
0	0	0	0
0.5	63.3±12.5	73.09±10.1	72.9±7.25
1	110±8.23	147.8±9.35	126±11.01
2	172±11.57	245±8.12	200±11.25
4	316±10.8	433±11.2	369±8.34
6	526±15.2	633.8±8.08	580±12.65
8	633±10.6	701±8.51	654±11.25
12	847±15.7	1109±10.02	876±10.67
24	1309±11.2	1905±11.1	1426±10.35
Flux µg/hr/cm²	11.25	16.06	12.05
Kp(cmhr^{-1}X10²)	1.14±0.150	1.63±0.0014	1.22±0.015

Values represent mean ± SD (n=3)

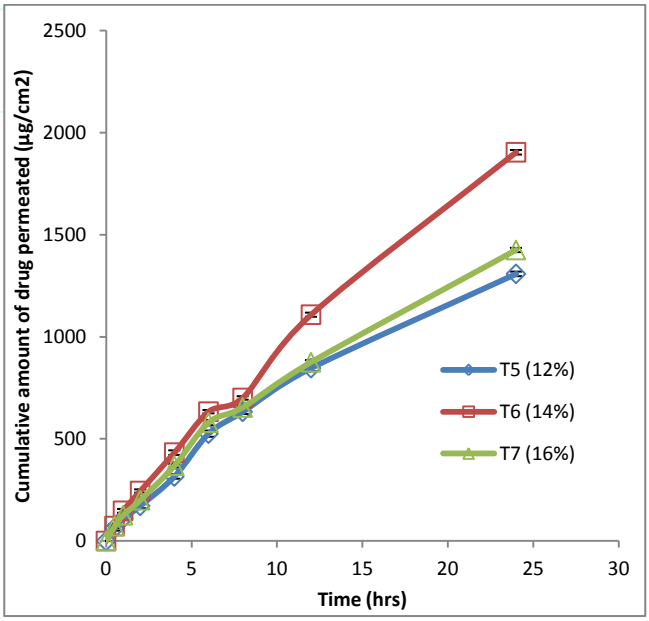

Figure 6:Comparison of cumulative drug permeated

CONCLUSION

Matrix type transdermal therapeutic systems of TIZ HCl were prepared with the required flux having suitable mechanical properties. The T6 formulation has shown good *in-vitro* release of drug and therefore chosen for further studies for optimization of concentration of permeation enhancer. T6 (14% citral) formulation showed higher flux than targeted flux. Hence TIZ HCl transdermal drug delivery system can be developed to administer TIZ HCl through transdermal route to human beings.

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CONFLICT OF INTEREST

All authors have none to declare.

REFERENCES

1. Ahlam Zaid Alkilani, Maelíosa T.C.McCrudden and Ryan F. Donnelly, Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum; Pharmaceutics J, 2015; 7:438-470.
2. Arun Raj R, Formulation Evaluation And In Vitro Permeation Studies Of Transdermal Nifedipine From Matrix Type Patches, International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(1):185-188.
3. Asha Das, Abdul Baquee Ahmed, Formulation And Evaluation Of Transdermal Patch Of Indomethacin Containing Patchouli Oil As Natural Penetration Enhancer, Asian Journal of Pharmaceutical and Clinical Research,2017; 10(11):320-325.
4. Donbrow M, Samuelov Y, J. Pharm. Pharmacol, 1980; 32:463-470.
5. Shingade G, Review on: recent trend on transdermal drug delivery system. Journal of Drug Delivery and Therapeutics, 2012; 2(1):66-75.
6. Higuchi T, J. Pharm. Sci, 1963; 52(12):1145-1149.
7. Jun Chen, Qiu-Dong Jiang, Ya-Ping Chai, Hui Zhang, Pei Peng and Xi-Xiong Yang, Natural Terpenes as Penetration Enhancers for Transdermal Drug Delivery, Molecules J, 2016; 21:1709,1-22.
8. Rahman SAU, & Sharma N, Formulation and evaluation of matrix transdermal patches of glibenclamide. Journal of Drug Delivery and Therapeutics, 2018; 8(5-s):366-371.
9. Kusum Devi V, Saisivam S, Maria G.R, Deepti P.U, Drug Dev. Ind. Pharm, 2003; 29:495-503.
10. Nuntakan Suwanpiodokkul, Phensri Thongnopnua, Kaisri Umprayan, AAPS Pharm. SciTech, 2004; 5(48):1-7.
11. Peltola S, Saarinen-Savolainen P, Kiesvaara J, Scihonen T.M, Urtti A, Int. J. Pharm, 2003; 254:99-107.
12. Ramesh Gannu, Vamshi Vishnu Y, Kishan V and Madhusudan Rao Y; Development of Nitrendipine Transdermal Patches: In vitro and Ex vivo Characterization, Current Drug Delivery, 2007; 4:69-76.
13. Robinson J.R, Lee V.H, 1987, Controlled Drug Delivery: Fundamentals and Applications, Marcel Dekker, New York, 523-552.
14. Wagner J.G, J. Pharm. Sci, 1969; 58:1253-1257.