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DESIGN AND EVALUATION OF TOLTERODINE TARTARATE TRANSDERMAL DELIVERY SYSTEMS: ENHANCEMENT OF PERMEABILITY VIA PHYSICAL AND CHEMICAL TECHNIQUES

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ABSTRACT
The aim of the present investigation was to develop transdermal patches of Tolterodine tartarate(TT) and improve the permeation using physical (Iontophoresis) and chemical (d-Limonene) permeation enhancement techniques.The matrix type transdermal patches of TT were prepared using solvent casting technique. Ten formulations(composed of Hydroxy propyl methyl cellulose(HPMC) in the ratios of 1:12.5,1:10 and 1:15 in the formulations F1,F2 & F3, HPMC and Eudragit RL100 in the ratios of 4:4, 5:3, 6:2 and 7:1 in the formulations F4, F6, F7 & F9 and HPMC and Eudragit RS 100 in the ratios of 5:3, 6:2 & 7:1 in the formulations F5, F8 & F10)were prepared. In all formulations 17% PEG 400 was used as plasticizer. All formulations were evaluated for *in-vitro* release studies, water absorption, water content, water vapor transmission rate studies (WVTR) and Mechanical properties. The physicochemical interaction between TT and polymers were investigated by Differential Scanning Calorimetry (DSC).Effect of different concentrations of d-Limonene (6%, 8% and 10%), different current densities (0.075, 0.15 & 0.3 mA/cm^2) and combination of both the techniques on the optimized formulations were studied through *ex-vivo* permeation studies.The maximum drug release was obtained in the formulations F1 (72.72% in 12 hrs), F9 (81.69% in 24hrs) and F10 (73.95% in 24hrs). These formulations were used in further experiments for the improvement of flux. Little improvement in the flux (F1 (Control: 30.79µg/hr/cm^2, d-Limonene: 46.36 µg/hr/cm^2), F9 (Control: 28.02 µg/hr/cm^2, d-Limonene:53.24µg/hr/cm^2) and F10 (Control:25.60µg/hr/cm^2, d-Limonene:39.44 µg/hr/cm^2)was observed with 8% of d-Limonene. Significant improvement in flux was obtained with iontophoresis using 0.15mA/cm^2 (F1:167.12 µg/hr/cm^2, F9:114.34 µg/hr/cm^2 & F10:55.72 µg/hr/cm^2). Required flux (260 µg/hr/cm^2) was obtained with combination of both the techniques in the formulations F1: 253.28 µg/hr/cm^2 & F9: 177.50 µg/hr/cm^2.

KEYWORDS: Tolterodine tartarate, iontophoresis, d-Limonene, transdermal patch.

INTRODUCTION
Iontophoretic drug delivery systems form a major group of the relatively few physical enhancement transdermal delivery systems that have been successfully developed and commercialized. The electrically driven penetration enhancement provided by this method has succeeded in overcoming the formidable barrier presented by the stratum corneum has shown to be a promising technique for various agents including macromolecules.[1,2] The combined use of iontophoresis and other techniques are likely to yield useful and interesting data which will intensify the efforts to more fully explore other techniques as a means of transdermal drug delivery.[3-5]

Overactive bladder (OAB) disorder is a condition characterized by frequent urination, an urge to urinate immediately and urinary incontinence due to involuntary detrusor contraction. It often requires long term treatment. Tolterodine tartarate (TT) with anti cholinergic and direct spasmolytic effect on bladder smooth muscle is widely used for treatment.[6]

TT is available as conventional and extended release capsules. However, it's oral administration is limited on account of its adverse effects & extensive first pass metabolism. TT extensively metabolized following oral administration (BA: 17-74%, varies from extensive to slow metabolisers), and its major metabolite acts similar to the parent substance on receptors, which restricts its application in patients with liver cirrhosis. Its partition coefficient (log P) is 1.51 at pH 7.4 with higher solubility in water (12mg/ml).[7-10] Transdermal route could be alternative route to avoid first pass metabolism, adverse effects and to increase patient compliance. Enhancement techniques (chemical& physical) used to deliver an effective dose of drug through skin to reversibly reduce

barrier function of skin and TT, positively charged molecule of relatively little higher molecular weight (475.6g/mol) with a low daily dose, suitable for iontophoretic transdermal delivery.[11,12]

Previous studies, reported the enhancement effects of different o-acyl menthol derivatives by formulating drug in adhesive patches with different pressure sensitive adhesives(PSA) and concluded that M-OA is the most promising enhancer among all other with good *in vitro-in vivo* correlation. More over as esterases are present in the human and animal epidermis, the ester linkage of o-Acyl menthol offers the possibility of degradation by skin esterases in living epidermis which increased enhancer safety. Terpenes present in natural occuring substances appear to be acceptable enhancers clinically. In the present study d-Limonene was used as penetration enhancer as reported earlier for someother drugs.[13]

The present objective of the present study was divided into three objectives. One of those to develop and evaluate transdermal delivery systems of TT for *invitro* release studies and mechanical properties. Second objetive was to study the effect of d-Limonene and Iontophoresis on permeation of TT through *ex-vivo* permeation studies using rat abdominal skin. During this study different concentrations of d-Limonene and different current densities of iontophoresis evaluated for enhancement effect. And the third objective was to study the synergestic effect of physical and chemical techniques and comparing the three respective permeation enhancement studies.

MATERIALS AND METHODS

Materials

Tolterodine tartarate obtained as a gift sample from Aurabindo pharma ltd. HPMC E15 was supplied by BMR chemicals, HYD. Eudragit RL100 & RS100 were kindly supplied by Evonik Degussa India Pvt Ltd, Mumbai. D-Limonene was supplied by Gagia Chemical industries pvt ltd. Potassium dihydrogen ortho phosphate, Sodium hydroxide, Methanol, Dichloromethane and PEG 400 were supplied by Merck Ltd, Mumbai. Dialysis membrane was supplied by Hi Media Laboratories Pvt Ltd, Mumbai.

Drug polymer interaction studies

To study the possible interaction between tolterodine tartarate and polymeric materials of the patches, Differential scanning calorimetry(DSC) was carried out on pure drug and drug- excipient physical mixtures.The differential thermal analyzer (DSC 822, Mettler Toledo, Switzerland) was used for this purpose.

Preparation of transdermal patches

The preparation of transdermal patches of TT with and without enhancer (d-limonene) was carried out by following solvent casting technique. Weighed quantities of polymers (Table I) Hydroxy propyl methyl cellulose (HPMC E 15 LV), Eudragit RS 100 and Eudragit RL 100, 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 Poly ethylene glycol 400 as a plasticizer 15-17%v/w (of dry polymer weight), 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 Petri plate. Drying of these patches was 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 desiccators till the evaluation tests were performed. The entire film was cut into patches of 2.89cm^2.

In vitro release studies

Drug release from TT transdermal patch was studied by using Diffusion cells e.g. Franz Diffusion cell. Patches with an area of 2.89cm^2 were cut and diffusion assembly prepared by adhering the patch onto the synthetic membrane (dialysis) using an adhesive tape USP. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the reservoir compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals up to 24hrs, the samples were withdrawn for analysis and replaced with same volume of fresh medium. The concentrations in the samples were determined spectrophotometrically at 283nm. pH 7.4 phosphate buffer was used as release media. The release studies were performed in three replicates and mean values were considered. Optimized formulations had been selected from above studies to *ex-vivo* permeation studies.

Measurement of Mechanical Properties

Mechanical properties of the films were evaluated using a microprocessor based advanced force guaze (Ultra Test, Mecmesin, UK) equipped with a 25 kg load cell. Film strip with dimensions 60 x 10 mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm/s pulled the strips to a distance till the film broke. The force and elongation were measured when the film broke. The mechanical properties were calculated according to the following formulae [14]. Measurements were run in three replicates for each formulation. Results were shown in Table.III.

$$\text{Tensile strength (Kg.mm}^{-2}\text{)} = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation at break} = \frac{\text{Increase in Length (mm)} \times 100}{(\%\ \text{mm}^{-2})\ \text{Original length (mm)}\ \text{Cross sectional area (mm}^2\text{)}}$$

Preparation of skin for permeation studies: Albino rats weighing 150-200 gm were sacrificed using anesthetic ether. 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° C for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for *ex vivo* permeability studies.[15]

***Ex vivo* Permeation Studies**

Franz diffusion cell 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. A dialysis membrane (Himedia) with molecular weight cut off of 5000 was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receiver phase is 16 ml of phosphate buffer saline (PBS) pH 7.4, stirred at 100 rpm on a magnetic stirrer; the whole assembly was kept at 37 ± 0.5°C. The amount of drug permeated was determined by removing 1 ml of sample at appropriate time intervals up to 24 hr, the volume was replenished with an equal volume of PBS pH 7.4. The absorbance was measured at 283 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 (2.89 cm^2). The target flux is calculated using the following equation.[16,17]

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

A represents the surface area of the transdermal patch (i.e 2.89 cm^2), BW the standard human body weight of 60 kg, C_{ss} the TT concentration at the therapeutic level (2.2µg/L) and the CL_T the total clearance (5.7 L/hr/kg) [4], the calculated target flux value for TT was 260.34 µg/hr/cm^2.

Effect of different concentrations of d-Limonene as chemical permeation enhancer on *ex-vivo* permeability of TT from transdermal patch through rat abdominal skin

The aim of this study is to optimise the concentration of permeation enhancer. For this study d-Limonene at different concentrations of 6%, 8% and 10% v/w of polymer weight was used in the TT polymeric film formulation (Table II) containing complete hydrophilic polymer (HPMC) (F1) and permeation study was conducted.

After optimization, studies conducted to observe the effect of optimised concentration of d-limonene on permeability of drug from different (HPMC & Eudragits) optimised transdermal patches. All the experiments were conducted in triplicates.

Preparation of iontophoretic electrodes, optimisation of process parameters and study the effect of iontophoresis on permeation of TT from transdermal patches

Silver /Silver chloride (Ag/AgCl) electrodes were used for the application of iontophoretic current. Silver wire of 0.5mm diameter (about 5cm) was rinse with concentrated HCl and followed by water to remove traces of surface contaminants. The wire electrode was then immersed in a molten silver chloride for 30min. A grey silver chloride layer was gradually coated on the silver wire. The evenly coated wire was used for iontophoretic experiments.[18] Iontophoretic experiments were conducted using Franz diffusion cells. The excised skin was clamped between two halves of the diffusion cell so as to face the stratum corneum towards the donor compartment, anodal chamber of the cell in which 3ml (4mg) of the drug solution was placed. A power supply was used to deliver a constant direct current via Ag/AgCl electrodes. The receptor solution (cathodal chamber) was 16 ml of phosphate buffer of pH 7.4 and was magnetically stirred. The preliminary trials were conducted for optimisation of iontophoretic process parameters like current density (high current density (0.3mA/cm^2) to low current density (0.075mA/cm^2)) and duration of time (0.5 hr to 2hrs).Optimised current density and duration of application were further used to study the effect of iontophoresis on permeation of TT from different optimised transdermal patches. All the experiments were conducted in triplicates.

Table I. Composition of TT transdermal patches.

Formulation ingredients	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
TT(mg)	4	4	4	4	4	4	4	4	4	4
HPMC E15(mg)	50	40	60	31.25	31.25	25	37.5	37.5	43.75	43.75
ERL100(mg)	_	_	_	18.75	_	25	12.5	_	6.25	_
ERS100(mg)	_	_	_	_	18.75	_	_	12.5	_	6.25

Table II. Formulation of TT polymeric films with chemical enhancer (d-Limonene).

Formulation ingredient	Formulation code		
	F11	F11	F11
TT(mg)	4	4	4
HPMC E 15(mg)	50	50	50
d-Limonene	6%	8%	10%

Formulation ingredient	Formulation code		
	F11	F12	F13
TT(mg)	4	4	4
HPMC E 15(mg)	50	43.75	43.75
ERL 100 (mg)	-	6.25	-
ERS 100 (mg)	-	-	6.25
d-Limonene	8%	8%	8%

* 17%v/w PEG 400 was used as a plasticizer. Solvent mixture 25ml of Dichloromethane and Methanol in 1:1 ratio was used.

Table III. Mechanical properties of Tolterodine tartarate transdermal patches.

Formulation	Tensile strength (kg/mm²)		Elongation at break (%mm²)	
	Mean	SD	Mean	SD
F1	1.96	0.014	7.68	0.24
F9	2.42	0.002	11.29	0.13
F10	2.69	0.019	13.46	0.12

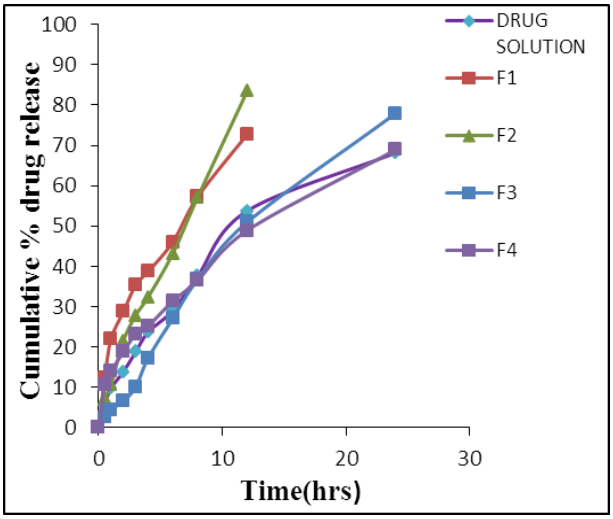

Fig 1. *in vitro* drug release profile of tolterdine tartarate transdermal patches (F1-F4).

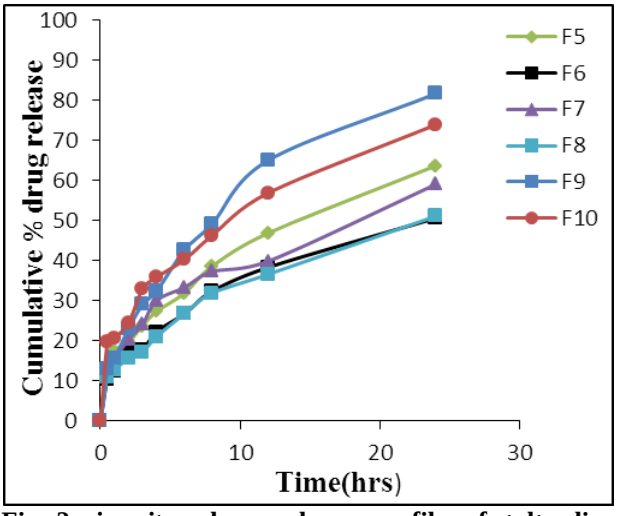

Fig 2. *in vitro* drug release profile of tolterdine tartarate transdermal patches (F5-F10).

Effect of combination of physical and chemical enhancement techniques on *ex-vivo* permeability of TT from transdermal patch through rat abdominal skin

The aim of this study was to identify the effect of combination of physical and chemical enhancement techniques on permeability of drug from transdermal patches through rat abdominal skin. For this purpose d-limonene of 8% v/w concentration of polymer weight was incorporated in the formulation and the permeation study was conducted through iontophoretic delivery. All the experiments were conducted in triplicates.

RESULTS AND DISCUSSION

In vitro release studies

Figure.1& 2 shows the drug release profiles of different transdermal patches of Tolterodine tartarate. Formulations F1(72.72% in 12hrs), F9(81.69%) & F10(73.95%) containing HPMC E15, HPMC E15 & ERS100, HPMC E15 & ERL100 respectively showed maximum release have chosen as optimized formulations for further studies. It was clear that as the concentration of hydrophilic polymer (HPMC E15) increases drug release from patch decreased. This is because HPMC forms a water swellable gel like structure that decrease further penetration of medium thus decreases the drug release. In case of formulations F1, F2 & F3, F2 of 1:10 ratio of drug to polymer released almost 90% drug within 12 hrs, there was significant difference in drug release from F1 and F3. Release order was like F2>F1>F3. For a controlled delivery of drug from patches F1 selected for further study. In case of polymeric films with Eudragits and HPMC, patches with lower concentration of Eudragits showed good release. This may be because of hydrophobic nature of Eudragits. As the permeability of Eudragits towards water is in order of ERS100 < ERL100, the release from ERL 100 patches is faster compared to ERS 100.

The description of release 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*.It was evident from correlation coefficients that except F1 & F3 follow Higuchi rate release kinetics and "n" value indicating the transport of drug from patches governed by Fickian diffusion where as F1 follows zero order release kinetics with Fickian diffusion and F3 follows first order release kinetics governed by Non-fickian transport.[19-21]

Mechanical properties

Results of mechanical properties had shown in Table.III. From the results it has been revealed that as the concentration of Eudragit increased, the tensile strength and elastic modulus were found to be increased but elongation at break values decreased. A direct proportional relation was observed between tensile strength and elongation at break.Tensile strength more in films formulated with ERL 100. The % Elongation break was found to be highest in F10 compared to F1&F9.

***Ex-vivo* permeation studies**

Effect of chemical enhancer d-Limonene on permeation of Tolterodine tartarate from patches through rat abdominal skin

The cumulative % drug permeated after 24hrs from transdermal patch, F1 (HPMC E15) without permeation enhancer was found to be 48.83% and flux 30.79µg/cm^2/hr. After incorporation of chemical enhancer of 6%, 8% and 10% *ex-vivo* studies showed increase in %drug permeation with increase in concentration (71.02%, 85.96% and 86.73% after 24 hrs). Cumulative amounts of drug permeated were calculated and flux was found to be 33.21µg/cm^2/hr, 46.36µg/cm^2/hr and 44.29µg/cm^2/hr respectively.But there is a slight decrease in flux with 10% compared to 8%, it may be due to saturation effect. 8% was selected as optimized concentration. Results were shown in Table IV & Figure 3.

Table IV. Effect of different concentrations of d-Limonene on permeation of TT through rat abdominal skin

Concentration of permeation enhancer	Q_{24}[a] (µg/cm^2)	Flux (µg/hr/cm^2)
Control*	675.84±34.12	30.79±2.12
6%	955.29±45.98	33.21±0.15
8%	1189.75±23.78	46.36±0.98
10%	1200.41±12.64	44.29±0.11

[a]Cumulative amount (µg) of drug permeated per cm^2, results are mean ± SD of triplicate observations.
*Formulation F1

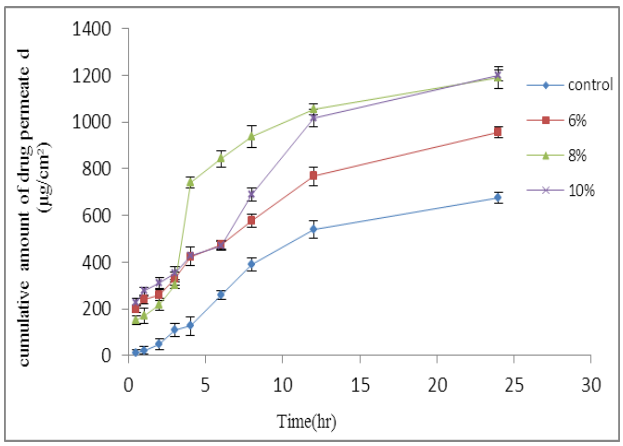

Fig 3: Effect of different concentrations of d-Limonene on permeation of TT through rat abdominal skin (using F1 formulation as control).

The cumulative % drug permeated after 24hrs from transdermal patches, F9 (HPMC-Eudragit RL100) and F10 (HPMC-Eudragit RS100) was found to be 91.42% and 79.7%. Flux was calculated as 53.24µg/cm^2/hr and 39.44µg/cm^2/hr respectively. (Table V & Fig.4).

Table V: Effect of chemical permeation enhancer (d-limonene) on *ex-vivo* permeation of TT transdermal patches through rat abdominal skin.

Formulation	Q_{24} (µg/cm^2)	Flux (µg/hr/cm^2)
Control(F9)	793.49±23.97	28.02±1.89
F12	1265.32±34.19	53.24±0.97
Control(F10)	582.56±21.78	25.60±2.34
F13	1103.11±42.68	39.44±1.67

Values are expressed as mean ± SD; n=3

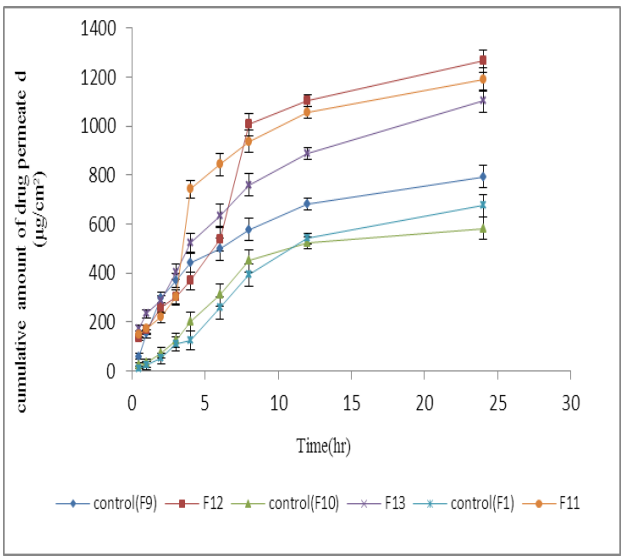

Fig 4: Effect of d-Limonene on *ex-vivo* permeation of TT from transdermal patches through rat abdominal skin.

Effect of different direct current densities and duration of time on iontophoretic delivery of TT drug solution through rat abdominal skin.

Iontophoretic experiments conducted using Franz diffusion cells. Drug solution of 3ml was used in donor compartment. During the experimental trials to optimize the duration of application of current, current applied from 0.5 to 4hrs in different trials using minimum current density 0.075mA/cm^2. After 3hours it was observed that skin damaged, so 2hrs was selected as maximum safe duration of time for the present iontophoretic experiment. And the studies conducted to optimize current density using 0.075-0.31mA/cm^2, have shown that iontophoresis, at current densities of 0.31mA/cm^2 can electroporate the skin to a certain degree, by causing transient pores, and these act as transport route during iontophoresis. Further increase in current density caused damage to skin. An increase in the drug permeation and flux of TT was found with increase current density, (102.51% after 6hrs & 258.76µg/cm^2/hr) with 0.15mA/cm^2 for 2hrs current application; however

the amount of TT released with the use of 0.075mA/cm^2 was not found significant (78.47% for 24hrs & 72.36µg/cm^2/hr) in comparison with amount released with 0.15mA/cm^2 when compared with control (45.51% for 24hrs & 27.68µg/cm^2/hr) and flux obtained with 0.15mA/cm^2 is near to required flux.(Table VI & Fig.5). These conclusions were drawn after preliminary trials and 0.15mA/cm^2 for 2hrs was selected as experimental conditions (parameters) for further experimentation.

Table VI. Effect of different current densities on iontophoretic delivery of TT drug solution through rat abdominal skin.

Current densities (mA/cm^2)	Q*(µg/cm^2)	Flux (µg/hr/cm^2)
Control	629.89±25.40(24hrs)	27.68±2.67
0.075	1086.09±12.98(12hrs)	72.36±3.78
0.15	1418.82±34.98(6hrs)	258.76±2.56
0.31	1493.84±43.12(3hrs)	576.95±4.90

*Q is the cumulative drug released per cm^2
values are expressed as mean ±SD; n=3

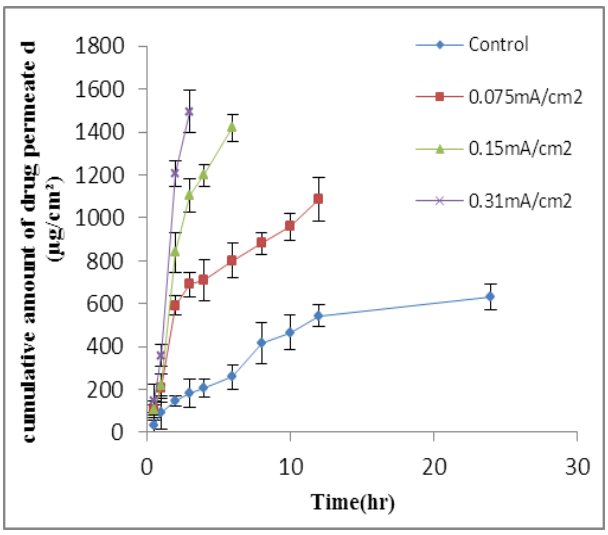

Fig 5: Effect of different current densities on *ex vivo* permeation of TT through rat abdominal skin.

Effect of iontophoretic delivery as physical enhancer on *ex-vivo* permeation of Tolterodine tartarate from transdermal patches through rat abdominal skin

An increase in the drug permeated and flux from TT transdermal patches observed to be significant compared to control without any penetration enhancer. The cumulative % drug permeated and flux was found to be increased i.e., 99.65% in 10hrs, 100.77% in 12hrs and 92.65% after 24hrs and 167.12, 114.34 and 55.72µg/cm^2/hr for F1, F9 &F10 respectively. When the iontophoresis was not applied the drug permeated was found to be 48.83%, 57.33% and 42.09% with achieved flux of 30.79, 28.02 and 25.60µg/cm^2/hr for F1, F9& F10 respectively. (Cumulative amounts were calculated and shown in Table VII & Fig.6).

Table VII. Effect of iontophoresis as penetration enhancer on permeation of TT from transdermal patches through rat abdominal skin.

Formulation	Q* (µg/cm^2)	Flux (µg/hr/cm^2)
Control (F1)	675.84±34.12(24hrs)	30.79±2.12
F1(0.15mA/cm^2)	1379.23±27.09 (8 hrs)	167.12±3.12
Control (F9)	793.49±23.97(24hrs)	28.02±1.89
F9(0.15 mA/cm^2)	1394.74±24.08(12hrs)	114.34±2.12
Control(F10)	582.56±21.78(24hrs)	25.60±2.34
F10 (0.15 mA/cm^2)	1282.53±34.09(24hrs)	55.72±2.43

*Q is the cumulative drug released per cm^2
values are expressed as mean ±SD; n=3

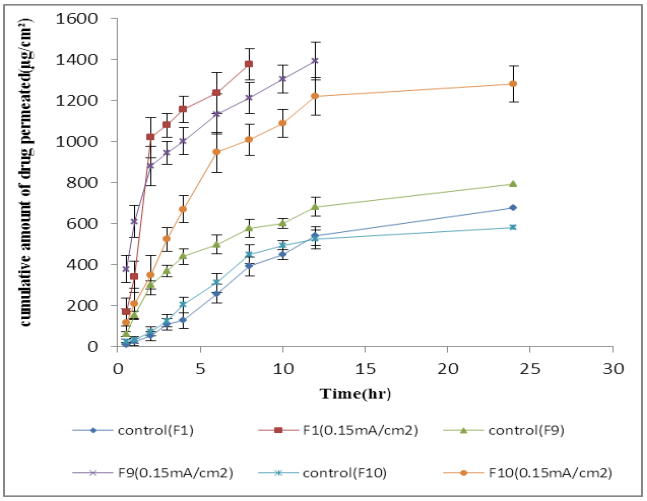

Fig.6 Effect of iontophoretic delivery on *ex vivo* permeation of TT from transdermal patches through rat abdominal skin.

Effect of combination of physical and chemical enhancement techniques on *ex-vivo* permeability of TT from transdermal patches through rat abdominal skin

To improve the effect of iontophoresis, chemical penetration enhancer d-Limonene was incorporated in to the patches of interest. The cumulative % drug permeated across rat abdominal skin using both the chemical and physical enhancement techniques was found to be 99.87% in 6hrs for F1 and 97.54% in 8hrs for F9 with achieved flux of 253.28 and 177.50µg/cm^2/hr respectively. The results are shown in Table VIII & Figure 7. It was evident that compared to individual effect, their combined effect increased the flux significantly.

Table VIII: Effect of combination of physical and chemical enhancement techniques on *ex vivo* permeability of TT from transdermal patches through rat abdominal skin.

Formulation	Q*(µg/cm^2)	Flux (µg/hr/cm^2)
F1 IONTO+CHEM	1382.28±57.98(6hrs)	253.28±4.56
F9 IONTO+CHEM	1350.03±63.07(8hrs)	177.50±3.89

*Q is cumulative of drug released per cm^2.
Values are expressed as mean ± SD; n=3.

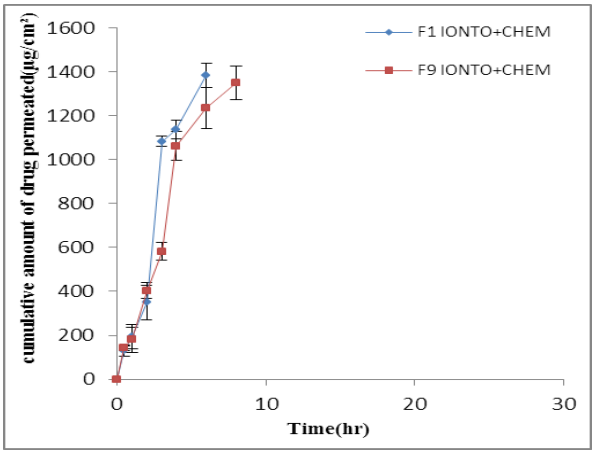

Fig.7 Effect of d-limonene in combination with iontophoresis on *ex vivo* permeation of TT through rat abdominal skin.

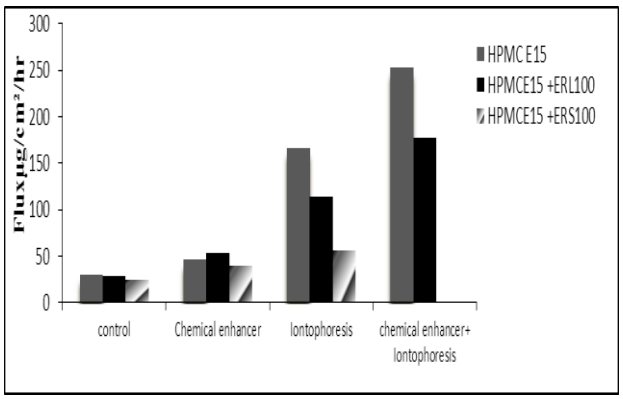

Fig. 8: Comparison of cumulative % drug permeated and flux achieved by TT transdermal patches through various enhancement techniques.

Drug polymer interaction studies(DSC)

The DSC curve of Tolterodine tartarate showed a single sharp endothermic peak at 216.11^{o}C corresponding to its melting point 206-211^{0}C. In optimized formulations, endothermic peak of drug was well preserved with slight changes in terms of shifting towards the lower temperature. These minor changes in the melting endotherm of drug could be due to the mixing of drug and exicipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. Thus, it was concluded that TT is compatible with all the excipients (HPMC & EUDRAGITS) used in the formulation.

CONCLUSION

The work was designed to support the development of devices for transdermal delivery & present project work shows that iontophoretic delivery of Tolterodine tartarate has increased its transdermal permeation from its transdermal films significantly. Hence the development of a transdermal iontophoretic system for Tolterodine tartarate may be a promising one as the required flux may attain and oral side effects will be reduced. The results can be considered for further study to support and confirm the efficacy claims by pharmacokinetic and pharmacodynamic studies through *in-vivo* studies in human beings.

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