Formulation design and *in vitro ex vivo* evaluation of transdermal patches of Cinnarizine

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Abstract: The aim of this study was to develop a Transdermal patch containing Cinnarizine using different ratios of hydrophilic and hydrophobic polymeric systems by solvent evaporation technique employing Polyethylene glycol (PEG 400) as plasticizer. The physicochemical compatibility of the drug and the polymers were studied by performing FT-IR spectroscopic analysis. Formulated patches were evaluated for physicochemical properties, skin irritation, *in vitro* drug release, *ex-vivo* permeation studies across rat abdominal skin and stability studies. The results of FT-IR studies revealed that there were no interactions between drug and polymers used. All the formulations exhibited uniformity in physicochemical properties. *In vitro* permeation studies of the formulations were performed by using Franz diffusion cells. Formulation F3 showed better permeation through rat skin (i.e., 8527.5±1.25µg/cm^2 /hr) compared to rest of formulations and followed Fick's diffusion mechanism. On the basis of in-vitro drug release and ex-vivo skin permeation performance, Formulation F3 containing the polymeric blend 19:1 Hydroxypropylmethyl Cellulose (HPMC E 50cps: Eudragit RL 100) has shown optimum release in comparison to other formulations and indicated good physical stability. So it has been demonstrated that Cinnarizine can be designed as matrix type transdermal drug delivery system (TDDS) and further *in-vivo* evaluations were required.

Keywords: Cinnarizine, transdermal patch, skin irritation study.

INTRODUCTION

Universal transfer of drugs via the Transdermal route has several possible advantages over conventional routes: avoidance of the first-pass elimination by the liver, steady drug levels in blood, fast termination of drug delivery and improved patient compliance (Chien, 1987, Kydonieus, 1987). These benefits directed to development of a number of commercial Transdermal patches.

Previous studies have shown that the Transdermal route is a potential mode of delivery of lipophilic drugs into the systemic circulation (Chien, 1992). The success of transdermal delivery depends on the ability of the drug to permeate the skin in sufficient quantities to achieve its desired therapeutic effects. However, the highly organized structure of the stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of candidates suitable for transdermal delivery (Kanikkannan *et al*, 2004). In the present study, Cinnarizine (CNZ) was used as the model drug. Cinnarizine is a lipophilic drug used for the control of vomiting due to motion sickness Chemically, cinnarizine is piperazine derivative which has short half-life (4 to 6 hrs). Related to pharmacokinetics of cinnarizine which provide anti-histaminic activity and calcium channel blocking activity by higher affinity towards H1 and calcium channel receptor. But it suffers from incomplete and variable oral absorption which occurs mainly in the proximal small intestine thus it is a good candidate to be formulated as a floating dosage form. (Ghareeb *et al*., 2012) Cinnarizine is weakly basic in nature and has a lower *pKa* value that's why it remains in ionized form at stomach pH and thereby it provides higher solubility in stomach and it remains in un-ionized form at intestinal pH so it has lower solubility in intestine (Parikh *et al*., 2006).

However in the present study, Transdermal patches containing Cinnarizine as a model drug were fabricated using various ratios of hydrophilic and hydrophobic polymers for Transdermal application and were evaluated for their physicochemical characteristics as well as for their *in vitro* drug release and *ex vivo* skin permeation potential.

MATERIALS AND METHODS

Cinnarizine was obtained from Yarrow chem. Mumbai (00028) Hydro propyl methyl cellulose (HPMC E50) cps, Eudragit RS 100, Eudragit RL 100 were obtained as gift samples from Reddy's laboratories, Hyderabad; Eudragit E 100 from Ra Chem, Hyderabad. All other chemicals used were of analytical grade. Oleic acid, tween 80, propylene glycol (Patrick, 2006), PEG-400, was buy from SD FINE chemicals. Transcutol-p, labrasol, were obtained from Natco Pharma Limited, India.

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Instruments

UV visible spectrophotometer, electrolab dissolution test apparatus, FT-IR Spectrophotometer Bruker, Hardness tester from Monsanto, Mumbai, India, Roche Friabilator Labindia, Mumbai, India.

Preparation of standard graph of cinnarizine

Standard stock solution of cinnarazine (CNZ) (1mg/ml) was prepared by dissolving 100mg of CNZ in 100ml of methanol. Diluting the standard stock solution with phosphate buffer solution pH 7.4 containing 0.5% sodium lauryl sulphate (SLS), solution of 100µg/ml concentration was prepared. From this solution, dilutions were made with phosphate buffer solution pH 7.4 containing 0.5% SLS. The absorbance of these diluted drug solutions were estimated using UV-Visible spectrophotometer at λ_{max} 250nm and standard graph of Cinnarizine was plotted (table 1). Standard stock solution of cinnarazine (CNZ) (1mg/ml) was prepared by our own in house preparation, we didn't follow any references to prepare this stock soloution, (Reference needs to describe here for this preparation). Use the full name of drug when it is used 1st time.

Preformulation studies

Solubility measurement

To determine solubility in various solvents, the drug (1gm) was dissolved in various vehicles such as oleic acid, tween 80, transcutol-p, labrasol, olive oil, PEG-400, propylene glycol (Patrick, 2006).

Partition coefficient

It was determined by shaking equal volumes of organic phase and the aqueous phase in a separating funnel. A drug solution of 1mg/ml was prepared in phosphate buffer solution, pH 7.4 containing 0.5% (SLS) and 50ml of this solution was taken in a separating funnel and shaken with an equal volume of n-octanol for 10min and allowed to stand for 24hrs with intermittent shaking (Hemangi *et al.*, 2010). Finally, the buffer solution was separated, clarified and assayed for drug content using a UV-Visible spectrophotometer at 250nm to determine partition coefficient value.

Melting point determination

It was determined by taking small amount of drug in a capillary tube closed at one end and was placed in Melting point apparatus digital melting point apparatus and temperature at which the drug melts was recorded as melting point of drug.

In-vitro drug permeation studies

The rat skin was carefully mounted between the two compartments of a Franz diffusion cell with internal diameter of 2.4cm (Gajanan *et al.,* 2011). The barrier was mounted between the donor and receptor compartments in a way that, the dermal side of the skin was facing towards receptor compartment. A 1mg/ml drug suspension was prepared in phosphate buffer solution, pH 7.4 containing 0.5% SLS and sonicated to ensure uniform drug distribution. 1ml of the above suspension was taken in the donor compartment. The receptor compartment fluid consists of 50ml of phosphate buffer solution, pH 7.4 containing 0.5% SLS. The entire setup was placed over magnetic stirrer and temperature was maintained at about 37±0.5°C. Samples of 1ml were collected at the predetermined time points from the receptor compartment and replaced with an equal volume of fresh solution and were analysed for cumulative amount permeated using UV-Visible spectrophotometer at λ_{max}250nm.

Drug-excipient compatibility study

To study the possible interaction between Cinnarizine and polymeric materials of the patches, the infrared spectra of both drug and mixture of drug and polymer was taken using FTIR- spectrophotometer to check for any possible interaction between the drug and the polymer.

Preparation of transdermal patches

Transdermal patches containing Cinnarizine were prepared using different ratios of hydrophilic (HPMC E50cps) and hydrophobic (Eudragit RL100, RS 100, E 100) polymers by solvent casting technique. The polymers were weighed in requisite ratios and dissolved in 30ml of dichloromethane: methanol solvent mixture (1:1) and allowed to stand and swell for 6hrs. To this Cinnarizine drug which was previously solubilised in oleic acid and PEG 400 (15%w/w) were added and kept aside for 2hrs to exclude any entrapped air and was then transferred to a petriplate (40cm^2) and dried at room temperature (Vijaya *et al*., 2012). The developed patches were removed carefully, cut to the size and stored in desiccators. The composition of patches was shown in table 2.

Evaluation of transdermal patches

Physical appearance

All the prepared Transdermal patches were observed for colour, clarity, flexibility, and smoothness.

Folding endurance

It was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking gave the exact folding endurance value (Ubaidulla *et al.,* 2007).

Film thickness

Patch thickness was measured at different points by using screw gauze and the average thickness was recorded (Dhawal, 2012).

Weight uniformity

Randomly selected 10 patches were individually weighed on a digital balance and average weight was calculated. The individual weight should not deviate significantly from the average weight (Suchika *et al.,* 2010).

Table 1: Standard graph of CNZ in phosphate buffer solution, pH 7.4 containing 0.5% SLS

Concentration (µg/ml)	Absorbance at 250 nm
0	0
2	0.106
4	0.223
6	0.329
8	0.450
10	0.562
12	0.675
14	0.779
16	0.864

Table 2: Formulation Design of Cinnarizine Transdermal Patches

S. No	Formulation code	Ingredients (gms)				
		Drug (mg)	HPMC E50cps	E.E100	E.RL100	E.RS100
1	F1	257	291.82	-	-	-
2	F2	257	277.23	14.59	-	-
3	F3	257	277.23	-	14.59	-
4	F4	257	277.23	-	-	14.59
5	F5	257	262.64	29.18	-	-
6	F6	257	262.64	-	29.18	-
7	F7	257	262.64	-	-	29.18
8	F8	257	248.05	43.77	-	-
9	F9	257	248.05	-	43.77	-
10	F10	257	248.05	-	-	43.77
11	F11	257	233.46	58.36	-	-
12	F12	257	233.46	-	58.36	-
13	F13	257	233.46	-	-	58.36
14	F14	257	218.87	72.95	-	-
15	F15	257	218.87	-	72.95	-
16	F16	257	218.87	-	-	72.95

Table 3: Physicochemical evaluation of CNZ patches

Code	Weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Drug content (%)
F1	473.9±1.67	0.89±1.88	292±4.72	100	101
F2	430±1.58	0.86±1.72	290±2.51	100	99
F3	486±0.89	0.81±1.55	289±3.46	100	99.64
F4	501.7±2.50	0.85±0.99	291±3.18	100	98.86
F5	468.5±1.63	0.89±1.39	290±4.72	100	99
F6	522.3±2.31	0.99±1.92	281±3.05	100	99
F7	510.8±1.8	0.86±1.67	285±3.13	100	99
F8	468.4±2.19	0.79±1.25	256±4.16	100	98
F9	432±1.51	0.82±1.18	274±4.32	100	96
F10	450.1±1.51	0.80±2.09	239±3.56	100	98
F11	539±2.50	0.85±2.13	249±4.04	100	96
F12	481.7±1.75	0.72±1.93	252±2.51	100	99
F13	477.9±1.50	0.78±1.77	230±3.21	100	98
F14	401.9±2.65	0.82±1.69	210±3.55	100	91
F15	472.3±1.60	0.85±1.53	197±3.05	100	90
F16	480.2±2.1	0.79±1.08	180±2.98	100	93

Table 4: Evaluation of Cinnarizine patches

code	%Moisture absorbed	% Moisture loss	WVTR (gm/cm^2/hr)	%cumulative drug released after 24hrs
F1	9.9±1.23	5.1±1.98	6.56× 10^{-4}	98.93±1.71
F2	9.0±1.17	4.8±1.21	6.0× 10^{-4}	95.50±2.81
F3	8.7±1.22	4.6±1.99	6.34× 10^{-4}	98.65±1.90
F4	8.8±1.54	5.0±1.09	6.21× 10^{-4}	97.21±1.02
F5	8.6±1.71	4.4±1.87	5.8× 10^{-4}	90.06±1.91
F6	8.2±3.64	4.2±0.98	6.0× 10^{-4}	93.58±1.52
F7	8.5±1.08	4.5±1.71	5.9× 10^{-4}	91.08±1.61
F8	8.0±1.45	3.8±1.32	5.2× 10^{-4}	84.89±1.61
F9	7.4±0.78	3.5±2.3	5.7× 10^{-4}	88.26±1.88
F10	7.8±1.21	4.1±1.90	5.6× 10^{-4}	87.46±1.11
F11	7.5±1.32	3.2±2.1	3.9× 10^{-4}	78.17±1.03
F12	7.1±1.12	3.0±2.06	4.7× 10^{-4}	81.48±2.04
F13	7.3±0.56	3.6±1.56	3.5× 10^{-4}	79.33±2.08
F14	6.8±1.47	2.9±1.87	3.0× 10^{-4}	72.11±1.22
F15	6.4±1.27	2.5±1.66	4.1× 10^{-4}	78.75±1.17
F16	6.5±1.87	3.1±1.22	2.8× 10^{-4}	74.81±2.70

Table 5: Regression analysis and correlation coefficient 'r' values of the *in vitro* release data according to various release kinetic model

Model fitting	R^2	K
Zero order	0.9462	3.7706
First order	0.9497	0.1153
Higuchi matrix	0.9085	10.7483
Peppas	0.9752	3.7632
Hixson -crowell	0.9836	0.0253

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Table 6: Stability studies of optimized formulations F3

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	98	285	No change in colour	97
90	97.1	281	Slight yellowish colour	96.35

Flatness

Longitudinal strips of transdermal patches were cut and lengths of each strip were measured. Variation in length due to non-uniformity of flatness was measured by determining percent constriction (Pintu *et al.*, 2011).

$$\text{Percent constriction} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}} \times 100 \quad (1)$$

Drug content determination

Selected patches from each batch was put into a 100ml standard flask containing the phosphate buffer solution, pH 7.4 containing 0.5% SLS and stirred at 400rpm for 2hrs. Then the solution was filtered and drug content was determined with the help of UV-Visible spectrophotometer at λ_{max}250nm (Vijaya *et al.*, 2011).

Percentage of moisture content

Randomly selected three films were weighed individually and kept in a desiccator containing anhydrous calcium chloride at room temperature for 24 hours. The films were weighed again after a specified interval until they show a constant weight (Anisree *et al.*, 2012).

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \quad (2)$$

Moisture absorption studies

The films were weighed accurately and placed in a desiccator containing aluminium chloride to maintain 79.50% RH (Narasimha *et al.*, 2011). After 3days, the films were taken out and weighed.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (3)$$

Water vapour transmission rate studies (WVTR)

About 1gm of fused calcium chloride was taken in previously dried empty vials having equal diameter and the polymeric patches measuring 4.52cm^2 area were fixed over the brim with the help of an adhesive. Then the vials were weighed accurately and initial weight was recorded and then kept in closed desiccators containing saturated krebs solution or potassium choloride KCl solution (what is this solution?) to maintain 63% RH. The vials were

again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through patch (Aisha *et al*., 2008).

$$WVTR = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \quad (4)$$

Water vapour transmission rate is expressed as the number of grams of moisture gained/hr/cm^2.

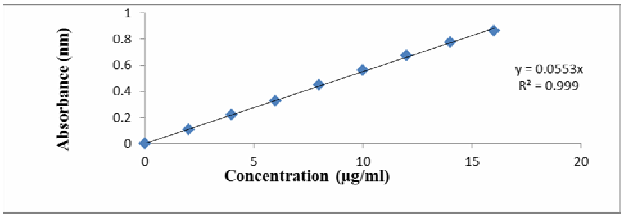

Fig. 1: Standard graph of CNZ in phosphate buffer solution, pH 7.4 containing 0.5% SLS at λ_{max}250nm.

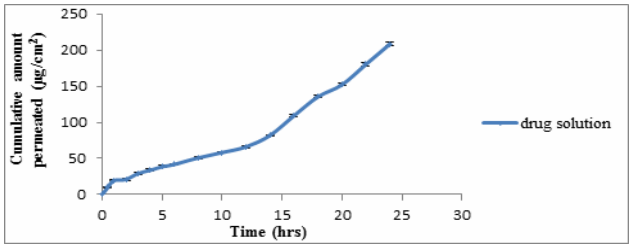

Fig. 2: *In vitro* drug permeation of CNZ through rat abdominal skin.

In-vitro release study

In-vitro drug release from transdermal patches was studied using USP type II dissolution test apparatus (Electro lab TDT-06L) thermo stated at 37±0.5°C and stirred at a rate of 25rpm (Bazigha *et al*., 2011). Patches were designed to release drug from one side only therefore the adhesive impermeable Polyester backing layer was placed on the other side of the patch. The assemble for release study were prepared by sandwiching the patch between the dialysis membrane 50Kda (Hi media). A piece of glass slide was used as a support to prevent assembly from floating. The dialysis tubing with the patch inside was secured from both ends by using dialysis closer clips and placed in dissolution apparatus containing 500ml of phosphate buffer solution, pH 7.4 containing 0.5% SLS solution. Sink conditions were maintained throughout the study. Aliquots of 5ml of samples were collected at predetermined time intervals and then analysed utilising UV-Visible Spectrophotometer at λ_{max} 250nm against blank.

Ex-vivo skin permeation study

Ex-vivo permeation of Cinnarizine patches through rat abdominal skin was studied. The rat skin was mounted between the compartments of the diffusion cell with *stratum corneum* (SC) facing the donor compartment. The SC side of the skin was kept in intimate contact with the release surface of the Transdermal drug delivery system under test (Madishetti *et al*., 2010). A dialysis membrane with molecular weight cut off 50Kg Daltons was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receptor compartment is filled with 50ml of phosphate buffer pH 7.4 containing 0.5% SLS, stirred at 400rpm on a magnetic stirrer; the whole assembly was kept at 37±0.5°C. Samples of 3ml were withdrawn from the receiver compartment at different time intervals, the volume was replenished with an equal volume of phosphate buffer solution, pH 7.4 containing 0.5% SLS. The absorbance was measured at λ_{max} 250nm in UV-visible spectrophotometer against blank.

Skin irritation studies

It was carried out on 10 healthy human volunteers in the age group of 22-26yrs (Jadhav *et al.*, 2009). About 4.52cm^2 patch containing drug was applied on right volar forearm and drug free patch was applied on left volar forearm with the help of adhesive tape USP. The portion in contact with patch was examined after 2 days for the presence of irritation, redness, itching, and edema.

Stability studies

Optimized formulation F3 is optimised formulation and is a code of formulation which was mentioned in table 2 was subjected to short term stability testing. The Transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40±2°C and 75±5% RH for 3 months as per ICH guidelines (Amit *et al.*, 2012).

RESULTS

Preformulation studies

Solubility

The drug CNZ showed maximum solubility in oleic acid. The solubility order of CNZ in various vehicles is oleic acid > tween80 > transcutol-p > labrasol > olive oil > PEG 400 > propylene glycol.

Partition coefficient and melting point determination

The partition coefficient of Cinnarizine was found to be 5.9 and melting point as 119°C respectively.

Permeation through rat abdominal skin

CNZ is practically insoluble in water, hence a release medium (phosphate buffer pH 7.4 containing 0.5% SLS) was used for solubilizing CNZ. The drug solution showed flux of 1.666µg/cm^2/hr with permeability coefficient Kp=0.00166 through rat abdominal skin (fig. 2).

Compatibility studies

FT-IR studies indicated compatibility between the drug and the excipients employed in the fabrication of TDDS, which was further confirmed by accelerated stability studies as per ICH guidelines. The results indicated that the characteristic absorption peaks due to pure Cinnarizine have appeared in the formulations, without

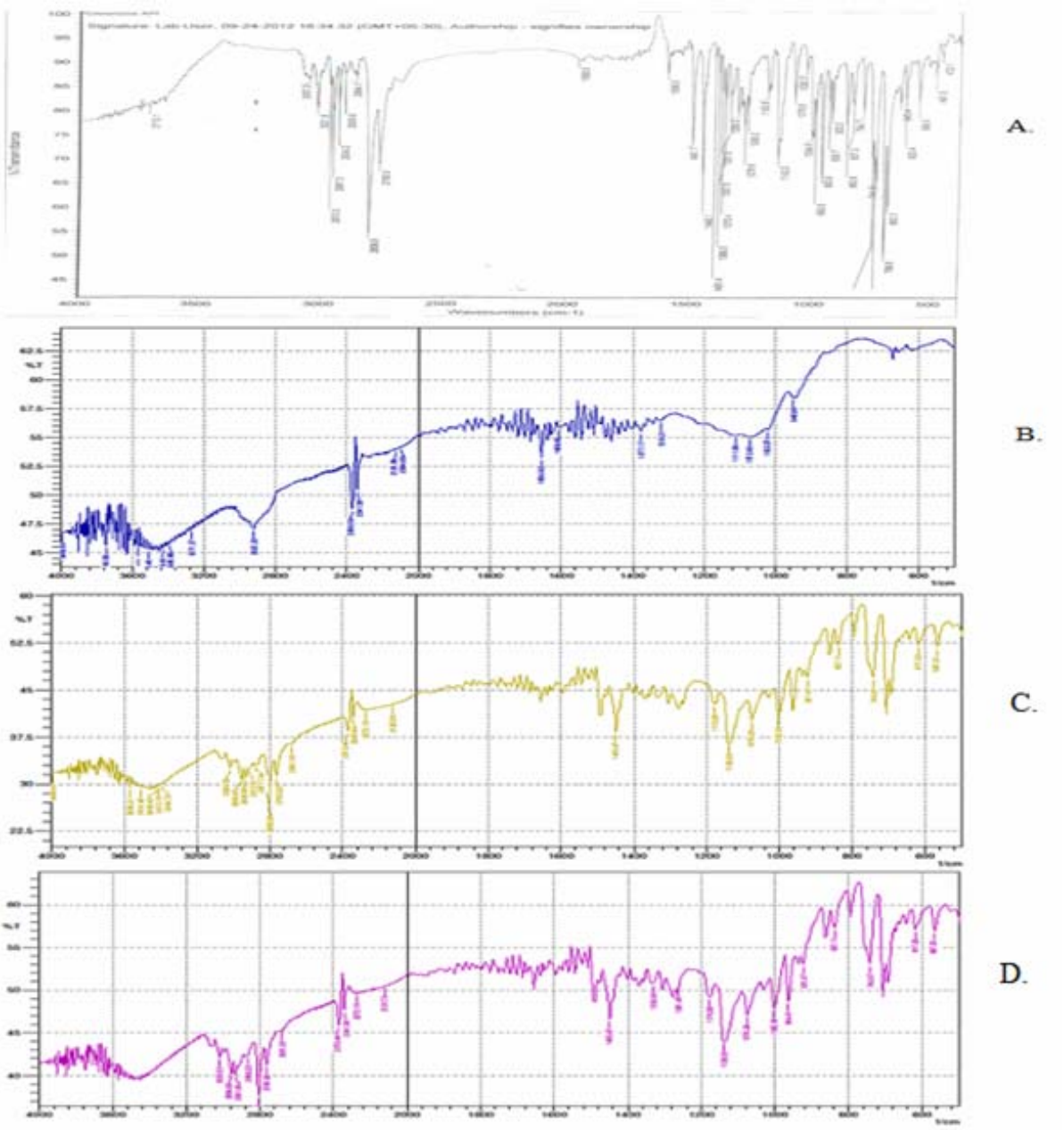

Fig. 3: FTIR studies of pure drug and physical mixture. FTIR of A) Pure drug (CNZ) B) Pure drug+HPMCE50 cps C) Pure drug +Eudragit RL100 D) Physical mixture

any significant change in their position, indicating no chemical interaction between Cinnarizine and Polymers used (fig. 3).

Preparation and Physicochemical characterization of transdermal patches

The patches preparation method yielded translucent flexible films that did not become brittle over time. 15% w/w of PEG 400 was suitable plasticizer for CNZ patches. The optimized formulations were stable at room temperature. HPMC E50 cps was kept as a parent polymer in high concentration since it has major influence on drug release.

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the CNZ patches were in the range of 180-292.The folding endurance number was increased with increasing the HPMC content.

These results indicated that the patches would not break and maintain their integrity with general skin folding when applied (table 3).

Thickness of the patch

The thickness of all the CNZ patches was in the range of 0.72-0.99mm (table 3).

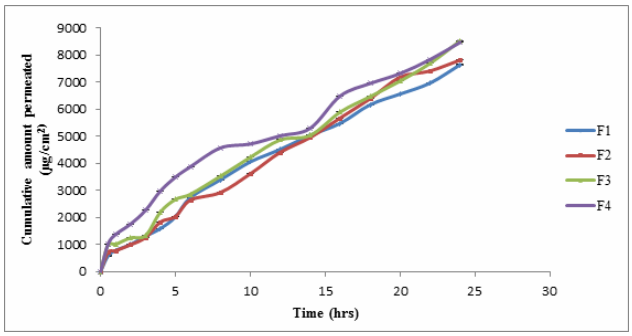

Fig. 4: Ex vivo permeation profiles of CNZ transdermal patch

Weight uniformity

The mean weights of all the prepared patches were in the range of 401.9-539 mg (table 3).

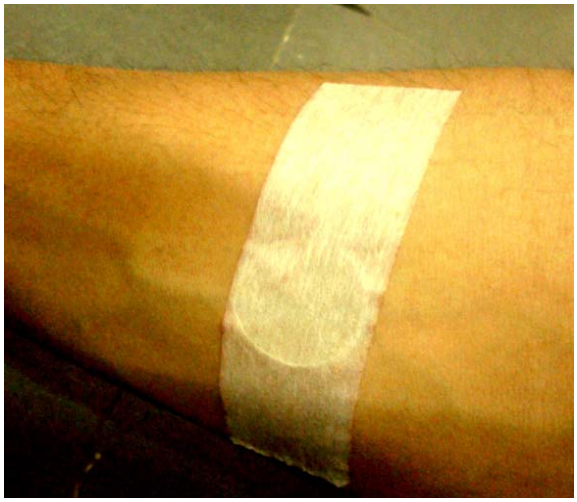

Fig. 5: Applying of CNZ patch.

Flatness

All the patches had shown the similar strip length. The percent constrictions of all patches were found to be 0%, so all patches carry 100% flatness (table 3).

Drug content

The process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90-101% (table 3).

Moisture absorption studies

The percentage of moisture absorbed ranged from 6.5% to 9.9% w/w. The moisture absorption was found to be more in formulation F1 and F2; this is because of hydrophilic nature of polymers. The moisture absorption is decreased as the concentration of hydrophobic polymer increases (table 4).

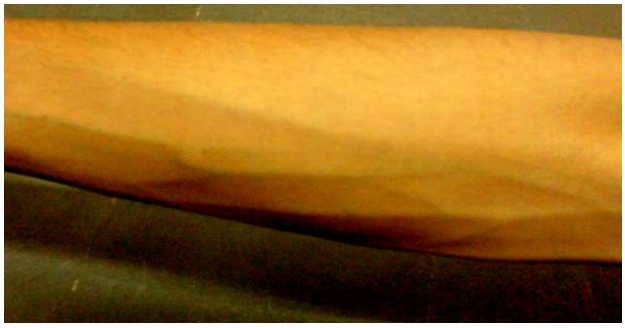

Fig. 6: After removal of CNZ patch.

Moisture loss studies

The percentage of moisture loss ranged from 2.5% to 5.1%. It was observed that the percentage moisture loss increased with increasing the hydrophilic nature of polymers (table 4).

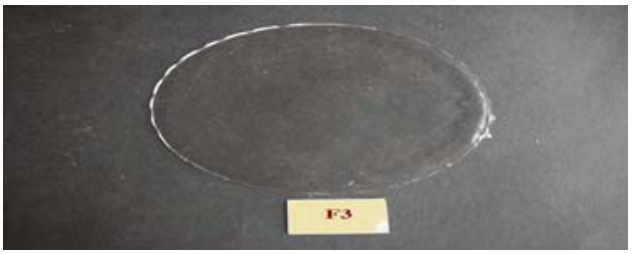

Fig. 7: Photograph of F3 formulation

Water vapour transmission rate studies

The WVTR ranged from 2.8×10^{-4} to 6.56×10^{-4} gm/cm^2/hr. Maximum WVTR was seen in F1, this was due to the hydrophilic nature of the polymer, which allowed more WVTR through this patch compared to other patches (table 4).

In-vitro drug release studies

The results of drug release profiles of CNZ patches after 24 hrs (table 4). It was clear from the release profiles of formulations that the drug release was governed by polymer nature and content. The formulations F1, F2, F3, and F4 showed the maximum release when compared with other formulations due to the high concentration of HPMC polymer. The release was decreased as the concentration of hydrophobic polymer increases.

The data obtained from dissolution profile were fitted to Zero order, first order, Higuchi, Peppas and Hixson-Crowell models (table 5). The interpretations of data were based on regression coefficient. The drug release data of formulation F3 showed good fit into Hixson-Crowell model with R^2 value 0.9836. The 'n' value for F3 formulation (0.4739) indicates that the release mechanism was fickian diffusion.

Ex-vivo skin permeation studies

The ex-vivo skin permeation studies were conducted on F1, F2, F3 and F4 formulations by virtue of their maximum drug release. The formulation F3 exhibited high cumulative amount of drug permeation (i.e., 8527.5ssµg/cm^2/hr) through rat skin when compared with other formulations. The F3 formulation showed flux of 81.5µg/cm^2/hr with permeability coefficient of 0.00326 (fig. 4).

Skin irritation studies

It's clear from the skin irritation studies that there was no erythema or oedema. This indicates skin compatibility of the polymers for topical application. The photomicrographs taken before and after the skin irritation studies were shown in (fig. 5 & 6)

Stability studies

Optimized formulations F3 (fig. 7) was selected for accelerated stability studies as per ICH guidelines. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^{0}C) maintained during the studies (table 6).

DISCUSSION

Transdermal route is one of the potent alternative routes that can improve undesirable characteristics of oral and parenteral therapy. Cinnarizine oral therapy is often associated with several problems like poor bioavailability, frequent dosing leading to patient incompliance and other systemic & local adverse effects. Transdermal drug delivery system provides a means to controlled drug release as well as reduces the intensity of action and thus reduces the side effects associated with its oral therapy. Therefore CNZ was chosen as a model drug and an attempt was made to deliver CNZ in transdermal dosage form.

Characterization of CNZ was done by performing the melting point, UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all excipients used in the study. Transdermal therapeutic systems of CNZ were prepared by solvent evaporation method by using different hydrophilic (HPMC) and hydrophobic (Eudragit) polymers. The formulated CNZ transdermal patches showed good physical properties, no drug-polymer interaction and no skin irritation. 15% w/w of PEG 400 was suitable plasticizer for CNZ patches. The optimized formulations were stable at room temperature. All the patches had shown the similar strip length and carry 100% flatness. All the patches were found to have drug content in the range of 90-101%, so the method employed i.e. solvent evaporation method is suitable for the preparation of CNZ patches. The folding endurance values indicate that the patches would not break and maintain their integrity with general skin folding when applied. It was observed that moisture absorption was high in all the cases of patches than the moisture loss. F1, F2, F3 and F4 formulations showed highest cumulative percentage drug release of 98.93%, 95.50%, 98.65% and 97.21% during *in vitro* drug release studies after 24 hrs. The release of CNZ appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data, the F1-F4 formulations showed similar drug release but upon *ex vivo* permeation studies it was found that F3 formulation showed superior drug release, therefore F3 formulation was concluded as optimized formulation. The release kinetics of F3 formulation followed Hixson-Crowell model.

CONCLUSION

From the results obtained and discussion generated there from, encouraged conclusions were drawn. On the basis of the in-vitro characterization it was concluded that Cinnarizine could be administered trans dermally through matrix type TDDS developed in our laboratory. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipient. The results suggest that the developed CNZ transdermal patches could perform better than other dosage forms, leading to improved efficacy of CNZ and better patient compliance.

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