Page 692 to 701

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Development and Evaluation of Transdermal Patches of Cinnarizine for the Treatment of allergy

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Abstract

The objective of the present study was to develop transdermal matrix patch of cinnarazine and assess its feasibility for transdermal application. Cinnarizine is a medication derivative of piperazine, and characterized an antihistamine and a calcium channel blocker, it is also known to promote cerebral blood flow, and so is used to treat cerebral apoplexy, post-trauma cerebral symptoms, and cerebral arteriosclerosis. The results of cinnarazine transdermal matrix patch showed that the most promising formulation was HE1 (formulation containing Drug: HPMC:EC:Span:PG; (1:(2:8)). Thus optimized transdermal matrix patch of cinnarazine using polymers such as HPMC and EC with Span & PG as permeation enhancers demonstrated their ability to give sustained release, because of excellent release and permeation of drug and its influence on efficacy on allergy. The developed formulation of cinnarazine is expected to improve the patient compliance, form better dosage regimen and provide maintenance therapy to patients suffering from allergy. These promising results showed the feasibility of delivering cinnarazine through transdermal matrix patch. The developed transdermal patches of cinnarazine may prove to be a better alternative to conventional dosage forms in allergy as revealed by the results.

Keywords: *Cinnarazine; Transdermal Patch; Allergy*

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Introduction

At present, the most common form of delivery of drugs are the oral route because it has advantage of easy administration. But it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce fluctuation in plasma dug concentration due to the frequency in dosing which can be both cost prohibitive and inconvenient. The continuous intravenous (I.V.) infusion has been recognized as a suitable mode of systemic drug delivery that can maintain a constant and sustained drug levels within therapeutic window for a long period of time throughout the treatment period. But this mode of drug administration have certain health hazards like accidental needle sticks and needle pain especially for patients requiring multiple administrations on a daily basis. Therefore necessitates of continuous hospitalization during treatment and under medical supervision. It has been realized later that the benefits of I.V. infusion could be closely duplicated without its hassles by using skin as the port of entry of drug. This is known as transdermal

administration and the drug therapy systems are known as the transdermal therapeutic systems or transdermal drug delivery systems or popularly known as transdermal patches [1-3]. Cinnarizine is a medication derivative of piperazine, and characterized an antihistamine and a calcium channel blocker, it is also known to promote cerebral blood flow, and so is used to treat cerebral apoplexy, post-trauma cerebral symptoms, and cerebral arteriosclerosis. However, it is more commonly prescribed for nausea and vomiting due to motion sickness or other sources such as chemotherapy, vertigo, or Ménière's disease [4,5]. The objective of the present study was to develop transdermal matrix patch of cinnarazine and assess its feasibility for transdermal application.

Material and Method

Preformulation studies

Preformulation studies are needed to ensure the development of a stable, therapeutically effective and safe dosage form. It is a stage of development during which the physical pharmacist characterizes the physicochemical properties of drug substance and its interaction with various formulation components.

Identification of drug

Physical Appearance

Through visual inspection, the physical appearance of pure drug was carried out as per Indian Pharmacopoeia.

Determination of melting point

Melting point of was determined using digital melting point apparatus by capillary fusion method. A capillary was taken and its one end sealed with the help of burner. The open end of the capillary tube was pushed into a small plug of the powder and tube was tapped gently, so that collected material settled down. The process was repeated several times. Then the capillary tube was placed in the melting point apparatus. The temperature at which drug starts to melt was noted.

Determination of UV absorption maxima

The accurately weighed quantity 10 mg of Cinnarazine drug sample was dissolved in 0.01N HCL and volume make upto 100 ml with methanol in a 100 ml volumetric flask to obtain a stock solution 100 µg/ml. Then 1 ml of this stock solution was pipetted out in a 10 ml volumetric flask and volume was made upto the mark with methanol to obtained the concentration 10 µg/ml. The resulting solution was then scanned between 200-400 nm using UV-visible spectrophotometer (Model-1700, Shimadzu, Japan). The UV spectrum sample (fluoxetine) was recorded and obtained λmax was matched with the UV spectrum as reported in official monograph.

Fourier transform infrared (FT-IR) spectroscopy

The infrared spectroscopy of the pure drug sample was carried out to identity the drug. A pellet of drug was prepared by compressing of the drug with IR grade potassium bromide by applying of 5.5 metric ton of pressure in KBr press. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan).

Determination of solubility

The dissolution and diffusion fluid for drug release and permeation studies respectively were selected based on solubility data of cinnarazine in various fluids. The solubility of drug sample was determined by adding 100 mg of drug sample in successively increasing amount in various fluids like methanol, chloroform, phosphate buffer solution pH 7.4 (PBS pH 7.4) and buffer containing 5%, 10% and 20% (v/v) of methanol as co-solvent. The volume of solvent required to dissolve the drug was recorded [6].

Determination of partition coefficient

The partition coefficient of drug was determined in n-Octanol as a non-aqueous phase and phosphate buffer solution pH 7.4 (PBS pH 7.4) as an aqueous phase. These two phases were mixed in equal quantities and kept for saturation with each other in separating

funnel. After mixing the system remain undisturbed for 30 minutes. The partition coefficient was determined by taking 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.4. The separating funnels were shaken on mechanical shaker for 24h. Two phases were separated and aqueous phase was filter through Whatman filter paper and the amount of the drug in aqueous phase was determined, after appropriate dilution by spectrophotometrically at λmax 227 nm by using phosphate buffer solution pH 7.4 as a blank.

Preparation of standard curve

Preparation of cinnarazine standard stock solution (100µg/ml) in 0.01N HCL

Cinnarazine was accurately weighed 10 mg of cinnarazine in 10ml volumetric flask. The volume was then made upto 100 ml by using 0.01N HCL solution to obtain the solution of 100 µg/ml. From the Cinnarazine stock solution (100 µg/ml) 1ml was pippeted and diluted to 10ml by using 0.01N HCL solution into different volumetric flask and made upto 10ml with 0.01N HCL solution so as to get concentration of 1.0 to 10.0 µg/ml

Calibration curve of cinnarazine in 0.01 N HCl solution

From the Cinnarazine stock solution (100 µg/ml) 1ml was pippeted and diluted to 10ml by using 0.01N HCL solution. From the solution appropriate aliquuots was taken into different volumetric flask and made upto 10ml with 0.01N HCL solution so as to get concentration of 1.0 to 10.0 µg/ml

Formulation of Cinnarazine transdermal patches

Matrix patches were casted on a glass mould by solvent casting methods. Seven types of polymer patches were prepared. First three formulation were prepared by using HPMC alone having drug and polymer 1:2, 1:3, 1:4 using distilled water as a solvent and one more formulation is formulated using HPMC with permeation enhancer Span 80 (1%) having drug polymer ratio 1:4. Next two formulations were prepared by using HPMC and EC in combination having drug and polymer in the ratio 1:(2:8), 1:(1:9) using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC and EC by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8). Propylene glycol (3%) used as a plasticizer [7-9].

Ingredients	HF1 (1:2)	HF2 (1:3)	HF3 (1:4)	HF4 (1:4)	HE1 (1:(2:8)	HE2 (1:(1:9)	HE3 (1:(2:8)
Drug (Cinnarazine)	525	525	525	525	525	525	525
HPMC	1050	1575	2100	2100	1050	525	1050
EC	-	-	-	-	4200	4725	4200
Span 80 (%)	-	-	-	1	-	-	1
Propylene glycol (%)	3	3	3	3	3	3	3

Table 1: *Formulation of matrix transdermal patches of Cinnarazine.*

Note: All the reading is in mg

Physicochemical evaluation of Cinnarazine patches

Physical appearance

All formulated transdermal patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness, which on a large part determines patient acceptability of the patch and also therapeutic efficacy [10].

Thickness

Thickness of transdermal patch was measured by using digital thickness gauge (Muttato Japan). Thickness of rectangular patch (2 x 2 cm) was determined with a four different points and average thickness was taken. Same was performed for other patches also [10].

Weight variation

Weight variation study of transdermal patches was performed by individually weighing 10 randomly selected patches of sizes 4.52 cm^2 on digital weighing balance and average weight was calculated. The individual weight of patches should not deviate significantly from the average weight [11].

Drug content

To determine the drug content of transdermal patch, known amounts of patch was cut from casted film and dissolve in chloroform in 100 ml volumetric flask and placed in shaking incubator for 4h. The solution was filtered through membrane filter (0.45 µm) and 1 ml solution was taken and diluted with chloroform to 10 ml. The absorbance of solution was measured at 227 nm by using UV/visible spectrophotometer (Model-1700, Shimadzu, Japan). The chloroform was used as a blank. The average reading of three patches was taken as the content of drug in one patch [49].

Moisture content

To determine moisture contents of transdermal patches, they were weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24h. The transdermal patches were weighed repeatedly until they showed a constant weight. The moisture content was calculated by given below formula [12].

%MC = FW-IW/IW*100

Moisture uptake

Transdermal patches were kept in desiccators at room temperature for 24h with silica gel and weighed (ws) and transfer to other desiccators to expose of 75% RH using a saturated solution of sodium chloride at 25^0C and patches were reweighed again and again, until a constant weight (wm) was obtained. The moisture uptake capacity was calculated according to the given formula [13].

%MU = Wm-Ws/Ws*100

Flatness

Longitudinal strips from the 5 randomly selected transdermal films of each formulation were cut out. One from the center and one from the other side of patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0% constriction was considered to be 100% flatness. Flatness was calculated by measuring constriction of strip using given formula [14].

%C=I1-I2/I2*100

Where,

I1 = Initial length of each strip, I2 = Cutted film length

Folding endurance

The folding endurance of patch was expressed as the number of folds (number of times the patch folded at the same place), either to break the preparation or to develop visible cracks. This test was performed to determine the stability of sample to withstand folding and brittleness. Folding endurance of patches was determined by repeatedly by folding a small strip of patches (approximately 2 × 2 cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gave the value of folding endurance and it was recorded [15].

Tensile strength

The formulated patches were evaluated for its tensile strength to measure their mechanical properties. The tensile strength of the patches was determined by using a self designed assembly (Department of Pharmacy). Assembly consists of a pan hanged by using a strong thread and the other end of the thread was attached with the centre of the patch. The whole assembly was held like a beam balance and weights were kept on the pan. Weights required to break the patch was noted. Tensile strength was then calculated using the following formul [16].

Tensile Strength= Break Force/a.b (1+ ΔL/L)

Where,

a = Width of the patch,

b = Thickness of the patch

L = Length of the patch,

ΔL = Elongation of patch at break point

Break Force = Weight required to break the patch (Kg)

pH Measurement

The pH of the film-forming solutions was determined using a pH meter which was calibrated before use with buffered solutions at pH 4, 7 and 10 [17].

***In Vitro* drug release studies**

The dissolution studies were performed by using dissolution rate test apparatus (USP-II) for the assessment of the release of the drug from the transdermal patches (3.14 cm^2). The commercially available water impermeable adhesive backing membrane was placed over the patch and it was further fixed on glass slide (2.3 x 2.3 cm) using cyanoacrylate adhesive. Then the transdermal patch was covered with a dialysis membrane and placed at the bottom of dissolution vessels with the release surface facing upward. The apparatus was equilibrated to 32 ± 0.5^0C and the dissolution medium was 0.01N HCl in PBS pH 7.4. The paddle speed was kept constant at 50 rpm. The samples were withdrawn at appropriate time intervals upto 24h and analyzed by UV spectrophotometer at 252 nm. After each sampling, an equal volume of fresh dissolution fluid was added to the dissolution vessel to maintain a sink condition [18,19].

The drug release data of all formulations were fitted to various mathematical models such as zero order as cumulative % of drug released vs. time, first order as log cumulative % of drug remaining vs. time and Higuchi's model as cumulative % drug released vs. square root of time. To determine the mechanism of drug release from formulations, the data were fitted into Korsmeyer Peppas equation as log cumulative % of drug released vs. log time [20].

Results

The preformulation study was performed in order to assure the authenticity of sample drug and determination of some parameters for development of formulation. Preformulation studies of Cinnarazine including identification of drug, determination of melting point, UV absorption maxima and identification of drug sample by FT-IR spectroscopy and other studies were carried out, the observed results were presented. The physical appearance, melting point and UV absorption maxima of drug sample (Cinnarazine) were characterized and obtained results are reported in Table 1. The supplied powder of Cinnarazine was a crystalline, white or almost white in color powder of odorless and bitter in taste. The melting point (Table 2) of drug sample (Cinnarazine) was found to be 118-122^0C indicated that the drug sample was pure. The drug sample was also identified by UV scanning (Model-1700, Shimadzu, Japan) and FTIR spectroscopy (Model-8400 S, Shimadzu, Japan). The maximum absorbance of drug in methanol was found to be at λmax 252 nm which shown in Figure 1. The infrared spectroscopy of the pure drug sample was carried out to identity the drug sample. Potassium bromide was used for preparing the sample for I.R. spectroscopic study. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FTIR spectrophotometer (Model-8400S, Shimadzu, Japan). The IR spectrum of cinnarazine drug sample is presented in Figure 2.

USP – XV Standard	Sample
White to off white crystalline powder	white powder

Table 2: *Physical Appearance of Cinnarazine.*

USP – XV Standard	Sample
118-122^{0}C	118-122^{0}C

Table 3: *Determination of Melting Point of Cinnarazine.*

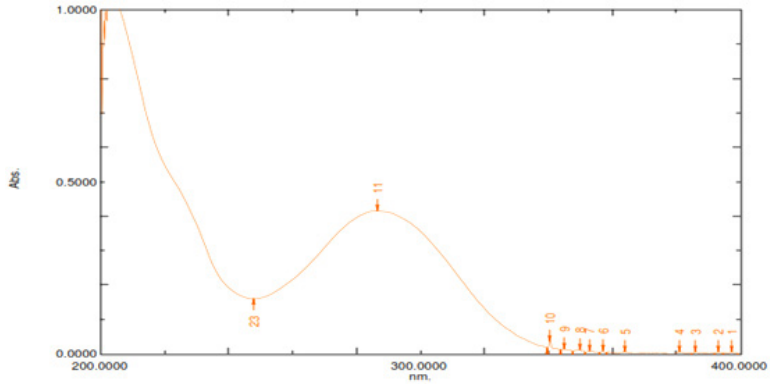

Figure 1: *Absorption Maxima of Cinnarazine in 252 nm.*

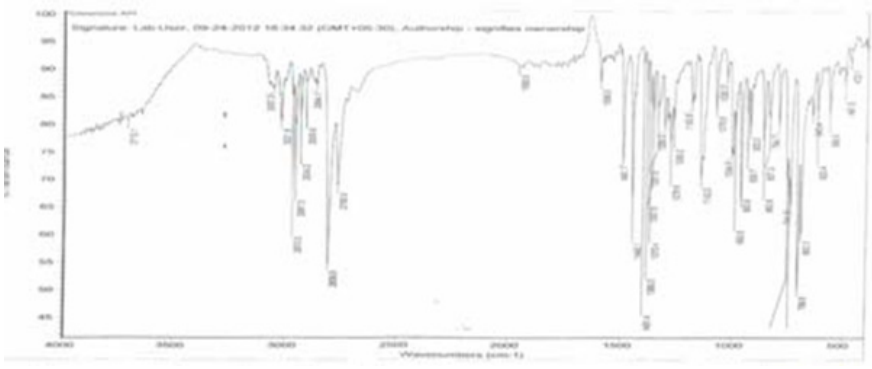

Figure 2: *FTIR Spectra of Cinnarazine.*

The calibration curve of Cinnarazine in 0.1 N HCl was prepared with dissolving accurately weighed 100mg of Cinnarazine in 100ml volumetric flask. The volume was then made upto 100ml by using 0.1N HCL solution to obtain the solution of 100µg/ml and was scanned in UV spectrophotometer and the sample obeys the beer-lamberts law.

S/No.	Conc. (µg/ml)	Absorbance
1.	1	0.453
2.	2	0.846
3.	3	1.019
4.	4	1.572
5.	5	1.942

Table 4: *Calibration Curve of Cinnarazine in 0.1 N HCl (pH 1.2).*

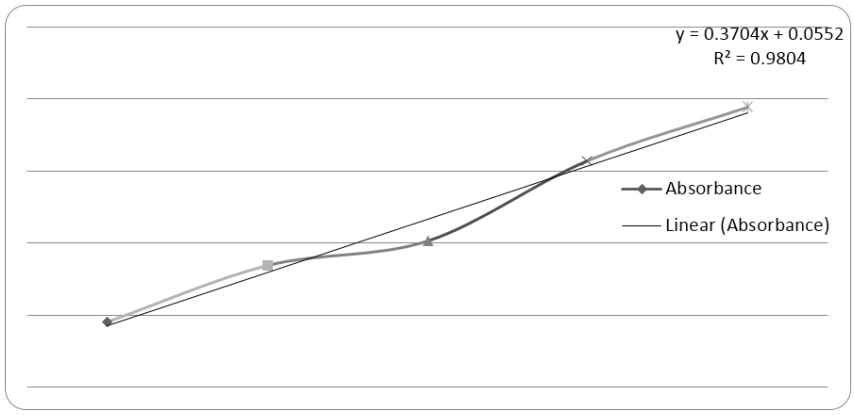

Figure 3: *Standard Curve of Cinnarazine in 0.1 N HCl (pH1.2) at 252 nm.*

Solubility study of drug sample (Cinnarazine) was determined for selection of dissolution and diffusion medium in different solvents at room temperature. The volume of solvent required to dissolve the drug was recorded in Table 4. The solubility study revealed that the drug sample was freely soluble in methanol, soluble in chloroform and 20% methanol in phosphate buffer solution (PBS) 7.4, sparingly soluble in 10% methanol in PBS pH 7.4, slightly soluble in 5% methanol in PBS pH 7.4 and very slightly soluble in PBS pH 7.4. The partition coefficient value of in n-Octanol/PBS pH 7.4 was found to be 3.72 ± 0.14.

S/No.	Solvent	Solubility
1	0.1 N HCl	Soluble
2	0.1 N NaOH	Soluble
3	Ethanol	Soluble
4	Water	Insoluble
5	Ether	Soluble
6	Dioxane	Soluble

Table 5: *Determination of Solubility of Cinnarazine.*

USP - XV Standard	Sample
Log P (dioxane/water), 9.85	Log P(dioxane/water), 9.80

Table 6: *Determination of Partition Coefficient of Cinnarazine.*

The transdermal patches were prepared by using different ratio of polymers as mentioned in Chapter 5. Various ratio of HPMC, EC, Span 80 and Propylene glycol were used to formulate 7 different batched of patches. Different batches of formulation were prepared and drug polymer ratio used were (1:2), (1:3), (1:4), (1:4), (1:(2:8), (1:(1:9) and (1:(2:8) respectively for HF1, HF2, HF3, HF4, HE1, HE2 and HE3. The prepared transdermal patches were evaluated for their physiochemical characteristics like physical appearance, thickness, weight uniformity, drug contents, moisture contents, moisture uptake, flatness, folding endurance, tensile strength and pH. The results of physicochemical characteristics are given in Table 6.The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble. The moisture content and moisture uptake of various formulations showed that with increasing in concentration of polymer both percentages of moisture content and moisture uptakes were increases. The percentage of moisture contents and moisture uptake were found in the range from 1.14 ± 0.23 to 5.29 ± 0.97 and 2.10 ± 0.20 to 8.46 ± 0.19 respectively. The results indicated that the hydrophilicity of the polymers is directly proportional to the

percent of moisture contents and moisture uptake. The low percentage of moisture content in formulations could help them to remain stable and prevents them from being completely dried. Also, low moisture uptake protects the material from microbial contamination and bulkiness of the patch. The dissolution studies of transdermal patches are very crucial to ensure sustained release pattern. One need to maintain concentration of drug on the stratum corneum surface consistently and subsequently morrmke than concentration of drug in the plasma to obtain a constant permeation drug release rate. The modified paddle over disc assembly using 20% methanol in PBS pH 7.4 as a dissolution medium at 32 ± 0.5^{0}C was used to conduct dissolution studies. The result of in vitro dissolution studies of prepared transdermal patches are presented in Table 7 and Figure 4.

FC	Thickness (mm)	Weight Variation (mg)	Drug Content (%)	Flatness	Folding Endurance	Tensile Strength (kg/mm^2)	pH
HF1	0.254 ± 0.017	169.61 ± 2.33	95.03 ± 1.56	100	43 ± 2.43	0.352 ± 0.03	5.8
HF2	0.268 ± 0.011	164.40 ± 1.89	96.20 ± 1.11	100	48 ± 4.82	0.404 ± 0.03	6.3
HF3	0.272 ± 0.014	169.61 ± 2.33	96.20 ± 0.61	100	46 ± 2.29	0.352 ± 0.03	5.9
HF4	0.267 ± 0.012	165.20 ± 2.08	97.64 ± 1.04	100	45±4.85	0.346 ± 0.05	6.1
HE1	0.242± 0.17	164.07±1.18	98.12±0.94	100	35±3.17	0.381±0.04	6.2
HE2	0.246 ± 0.027	166.76± 2.76	97.64 ± 1.04	100	37±4.73	0.370 ± 0.07	5.7
HE3	0.248 ± 0.031	172.01 ± 2.77	96.20 ± 0.61	100	38±4.23	0.372 ± 0.03	5.9

Table 7: *Physiochemical evaluation of cinnarazine transdermal Patches.*

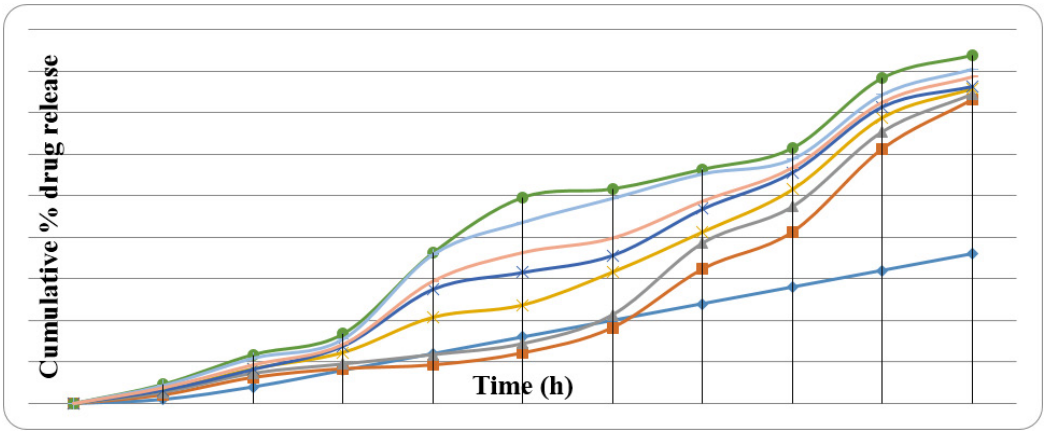

Figure 4: *Cumulative % drug release.*

Time (h)	Cummulative % of drug release						
	HF1	HF2	HF3	HF4	HE1	HE2	HE3
0	0	0	0	0	0	0	0
1	2.10	2.71	3.18	3.16	4.62	4.32	3.78
4	6.28	7.29	8.38	8.22	11.78	10.90	9.29
8	8.38	9.51	12.29	13.83	16.77	15.48	14.22
12	9.29	11.77	20.76	27.49	36.28	35.83	29.41
16	12.18	14.42	23.72	31.54	49.62	43.61	36.26
20	18.29	21.39	31.65	35.65	51.66	49.36	39.75
24	32.38	38.61	41.29	46.83	56.39	55.26	48.61

28	41.29	47.39	51.52	55.62	61.48	58.81	56.66
32	61.28	65.39	68.81	71.44	78.38	74.33	72.38
36	73.10	74.41	75.77	76.34	83.83	80.43	78.48

Table 8: *In vitro dissolution profile of cinnarazine transdermal patches.*

Conclusion

The objective of the present study was to develop transdermal matrix patch of cinnarazine and assess its feasibility for transdermal application. Cinnarizine is a medication derivative of piperazine, and characterized an antihistamine and a calcium channel blocker, it is also known to promote cerebral blood flow, and so is used to treat cerebral apoplexy, post-trauma cerebral symptoms, and cerebral arteriosclerosis. However, it is more commonly prescribed for nausea and vomiting due to motion sickness or other sources such as chemotherapy, vertigo, or Meniere's disease. Low dose maintenance therapy of cinnarazine has the capability to reduce potential side effects and improved patient compliance which are more common with conventional drug delivery.

The results of cinnarazine transdermal matrix patch showed that the most promising formulation was HE1 (formulation containing Drug: HPMC: EC: Span: PG; (1:(2:8)). Thus optimized transdermal matrix patch of cinnarazine using polymers such as HPMC and EC with Span & PG as permeation enhancers demonstrated their ability to give sustained release, because of excellent release and permeation of drug and its influence on efficacy on allergy. The developed formulation of cinnarazine is expected to improve the patient compliance, form better dosage regimen and provide maintenance therapy to patients suffering from allergy.

These promising results showed the feasibility of delivering cinnarazine through transdermal matrix patch. The developed transdermal patches of cinnarazine may prove to be a better alternative to conventional dosage forms in allergy as revealed by the results.

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