Research Article

Formulation and Evaluation of Transdermal Patches of Cetrizine Dihydrochloride

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ABSTRACT

Cetrizine dihydrochloride belongs to the category of anti histamines used in treatment of various allergic conditions. Administration of these agents via transdermal route can bypass various disadvantages caused by oral administration and may maintain relatively consistent plasma drug level for long time therapy .The present study attempts for preparation of matrix monolithic transdermal system of Cetrizine dihydrochloride. Different polymers like hydroxy propyl methyl cellulose (HPMC), polyvinyl pyrrolidine (PVP), ethyl cellulose (EC) and methyl cellulose (MC) either individually or in combination have been tried. All the patches were prepared by adding glycerin as plasticizer. Methanol is used as a common solvent. The prepared patches were evaluated for physicochemical parameters like thickness, weight variation, folding endurance, water absorption capacity, moisture content, tensile strength, percentage elongation, drug content, in vitro and in vivo drug permeation studies. From all the patches, F7 containing 2.25%w/v of hydroxy propyl methyl cellulose and 7.5%w/v of Polyvinyl Pyrrolidone had shown good physical properties. In vitro studies indicated a drug permeation of 90.51% and in vivo studies indicated drug permeation of 85.21% in 24 hours. The in vitro and in vivo pharmacokinetic data had shown first order drug release and they followed non fickian diffusion mechanism of drug permeation.

Keywords: Cetrizine Dihydrochloride, Matrix Transdermal system, Transdermal drug delivery system.

INTRODUCTION

Cetrizine Dihydrochloride is an anti histaminic drug which is a H1 receptor antagonist. Cetrizine is used in the treatment of various allergic reactions like skin discariasis, dermatitis, itching, common cold, etc. Cetrizine dihydrochloride is used with the recommended dose of 10mg twice in a day, but it is a challenge to provide availability of drug in the body for prolonged periods in the treatment chronic skin diseases and allergic reactions. The transdermal patches of Cetrizine dihydrochloride are developed to produce controlled drug release for treatment in chronic disorders.

Cetrizine Dihydrochloride by its properties, like its dose 10mg(less than 50mg), molecular weight 388.888(less than 400D), half life 8.3hrs (10 or less than 10hrs), partition coefficient 2.8 (between 1.0-4.0), pH 1.2 (1.2-1.8) is suitable as a candidate for T.D.D.S.[1]

MATERIALS AND METHODS

Cetrizine Dihydrochloride was obtained as a gift sample from Lord Venky Pharmaceuticals Pvt Ltd Yanam. Hydroxy propyl methyl cellulose, Ethyl cellulose and Methyl cellulose manufactured by Bangalore fine chem, Poly vinyl Pyrrolidone manufactured by Loba chemie Pvt Ltd, Glycerin manufactured by FINAR Reagents, Methanol manufactured by Merck specialties Pvt Ltd. Hydrochloric acid manufactured by Reachem laboratory reagents and dialysis membrane manufactured by Himedia Pvt Ltd were used.

Preparation of drug loaded transdermal films[1-3]

Methanolic solution containing polymers as per the table 1 was performed. The glycerin (10%w/w) and Cetrizine dihydrochloride (10mg) were added into the polymeric solution and homogenized. The films were prepared on rectangular glass moulds by solvent evaporation technique. The area of film was 18cm.^{2} The polymeric solution was poured on the glass surface and covered with glass funnel to control the rate of evaporation during drying. Drying was carried out for 24hrs at room temperature. The dried films were wrapped in aluminum foil and placed in closed containers and stored at room temperature.

Standard curve for Cetrizine Dihydrochloride

100mg Cetrizine dihydrochloride was accurately weighed and dissolved in 100ml volumetric flask containing 0.1N HCl. Volume was made up to the mark and labeled as stock-I. 1ml of stock-I was taken and diluted to 100ml in a volumetric flask with 0.1N HCl and marked as stock-II. Aliquots of 2ml, 4ml, 6ml, 8ml and 10ml of stock-II solution were diluted to 10ml in a volumetric flask to get solutions containing 2µg/ml, 4µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml. Then the absorbance was measured in UV spectrophotometer at 231nm against 0.1N HCl as a blank.

Compatibility study using FT-IR

Bruker FT-IR was used for Infrared spectrums of pure drug (Cetrizine dihydrochloride) and its physical mixtures with polymers (Ethyl cellulose, Methyl cellulose, Hydroxyl Propyl methyl Cellulose, Poly vinyl Pyrrolidone) using KBr pellatisation method to investigate any possible interaction between the drug and the used polymers.

Table 1: Composition of membranes using different polymers

Formulation code	HPMC (w/v)	Methyl cellulose (w/v)	Ethyl cellulose (w/v)	Polyvinyl Pyrrolidone (w/v)	Glycerin (w/w)	Methanol For each film (ml)
F1	2%	---	---	---	10%	5
F2	3%	---	---	---	10%	5
F3	4%	---	---	---	10%	5
F4	5%	---	---	---	10%	5
F5	2.25%	0.75%	---	---	10%	5
F6	2.25%	---	0.75%	---	10%	5
F7	2.25%	---	---	0.75%	10%	5

Evaluation of Transdermal patches

The prepared Transdermal films F1 to F7 were evaluated for the following parameters

Thickness[4]

Thicknesses of all membranes were measured by using screw gauze at five different points on each membrane and average reading was noted.

Weight variation[5]

Individually 5 films of each formulation were accurately weighed and the average weight and standard deviations were calculated out.

Moisture content[6]

5 membranes of 18cm^2 of each formulation was kept in a desiccator containing fused calcium chloride and kept at room temperature. Individual membranes were weighed at different time intervals until they attained constant weight. The percentage moisture content was calculated based on initial and final weight.

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Moisture uptake[7]

5 membranes of 18cm^2 of each formulation were accurately weighed and kept in a desiccator containing water (100% Relative humidity) at room temperature for 24hrs. All the samples are weighed again after 24hrs. The percentage of moisture uptake was calculated with respect to initial weight.

$$\%\text{moisture uptake} = = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

Folding endurance[8]

A modified USP tablet disintegrating tester was used to determine the folding endurance of the membranes. It consisted of fixed and movable jaw that could move up and down at the rate of 30 strokes per minute. The distance between the two jaws at their farthest and closest was 6cm. The membrane 6cm length was clamped between the jaws in such a way that when the jaws were at the closest, the membrane folds across its middle and when the jaw was at its farthest, the membrane was in the stretched condition. Thus for every stroke of the movable jaw the membrane imparts one cycle of folding and stretching. The folding endurance was expressed as the number of strokes required to either break or develop visible cracks on the membrane. The test was conducted for a maximum of 20minutes equivalent to 600 strokes.

Tensile strength[9]

Tensile strength of the films was determined by using simulated House filed universal testing machine. The sensitivity of the machine was 1mm. It consists of two load cell jaws. The upper one was fixed and lower one was movable. The film of specific size (18 cm^2) was fixed between these grips. Weight was applied to lower jaw gradually, while measuring the strength till the films breaks. The tensile strength of the film was taken directly in kilograms and extension of film in mm.

Drug content

The drug content of the films was determined by dissolving the previously weighed film in 100ml volumetric flask containing 0.1N HCl and volume was made up to the mark. Then it was sonicated for 15mins. 1ml of this was diluted to the 100ml in a volumetric flask with 0.1N HCl. Then absorbance of the sample was determined by using elico U.V spectrophotometer at 231nm. From the reading of absorbance, the drug content per film and % drug content was calculated.

In vitro permeability studies[10]

The in vitro permeation studies were carried out in a modified Franz diffusion cell with a receptor compartment capacity of 23ml & surface area of 3.142cm^2. The diffusion cell consists of two compartments. One is donor compartment which contains transdermal film in contact with dialysis membrane. The bottom compartment contains the receptor solution. The device has a water jacket for temperature control and a sampling port. The permeation study was carried out across the dialysis membrane. The receiver compartment was filled with 0.1N HCl. The donor compartment was then placed in position such that the surface of the membrane just touches the receptor fluid surface. The assembly was placed on a magnetic stirrer. The solution in the receptor compartment was constantly

and continuously stirred at 50rpm. The temperature of whole assembly was maintained at 37±0.5^{0}C by circulating water from a constant temperature inside the water jacket, Water bath having water at 37^{0}C. The samples were withdrawn at different time intervals up to 24hours and replenished with an equal volume of 0.1N HCl at each withdrawal. The absorbance of withdrawn samples duly diluted was measured at 231nm using U.V Spectrophotometer.

In vivo studies

The film of a selected (F7) formulation has been cut into four pieces, each of them have been weighed accurately. One of these 4 pieces have been subjected to analyzing for drug content, the drug content of this expressed in % was taken as first sample at zero hours. Remaining three films have been attached to the skin of the fore arm after shaving the hair. The films are made to stick firmly to the skin by supporting them with a strip of plane cellophane ribbon. One of these three films has been separated from the skin at a time interval of 4 hours contact. From the remaining 2 films, one was separated at 8hrs contact; the other one was separated at 24hrs contact with the skin. These samples have been subjected to analysis for drug content and the percent of drug permeated has been calculated, on the basis of unabsorbed drug content of the films.

RESULTS AND DISCUSSION

Compatibility study using FT-IR

The compatibility between Cetrizine dihydrochloride and various polymers used was performed by using Fourier transform-infrared spectrophotometer (Figure 1). The samples were prepared with pure drug alone and drug with all polymers in the ratio of 1:1. The results of FT-IR study have shown the following.

The spectra of pure drug has shown O-H stretching at 3417.86cm^{-1}, C-H stretching at 3043.67 cm^{-1}, C=O stretching at 1739.78 cm^{-1}, C-Cl stretching at 1435.04 cm^{-1} and -$CH_2CH_2OCH_2$- bending at 1184.29 cm^{-1}.

The spectrum of sample containing Cetrizine Dihydrochloride with all polymers (HPMC, EC,MC and PVP) has shown O-H stretching at 3462.22cm^{-1}, C-H stretching at 2976.16 cm^{-1}, C=O stretching at 1751.36 cm^{-1}, C-Cl stretching at 1419.61 cm^{-1} and $CH_2CH_2OCH_2$ bending at 1112.93 cm^{-1}. This indicates that compatibility existed between drug and the polymers used.

Table 2: Results of physical parameters

F. code	Thickness (mm) ± SD	%Weight variation ± SD	% moisture content ± SD	% moisture uptake ± SD (RH 100%)	Folding endurance	Tensile strength (Kg/cm^2) ± SD	% elongation (mm)± SD (3×6cms film)	Drug content (mg) ± SD	% Drug content ± SD
F1	0.95±0.04	108.571±3.779	9.666±0.560	28.860±1.470	>600	0.745±0.038	4.9±0.4	9.636±0.064	96.36±0.64
F2	1.011±0.047	157.142±4.879	6.773±0.411	39.273±1.924	>600	1.145±0.072	4.18±0.51	10.441±0.080	104.41±0.80
F3	1.307±0.047	207.142±4.879	9.906±0.496	54.240±2.544	437	1.426±0.073	3.46±0.37	12.898±0.147	128.98±1.47
F4	1.635±0.035	260±5.773	7.546±0.271	61.366±4.017	189	1.479±0.091	3.93±0.25	15.778±0.191	157.78±1.91
F5	1.044±0.036	157.857±3.933	11.703±0.695	92.626±2.141	217	0.760±0.078	3.03±0.41	10.051±0.188	100.51±1.88
F6	1.041±0.034	157.142±4.879	6.876±0.316	62.023±3.539	196	0.637±0.054	3.366 ±0.513	15.117±0.884	151.17±8.84
F7	1.075±0.033	158.571±3.779	11.946±0.593	78.896±3.125	213	0.374±0.050	4.066 ±0.351	10.831±0.071	108.31±0.71

Standard deviation based on the n=5

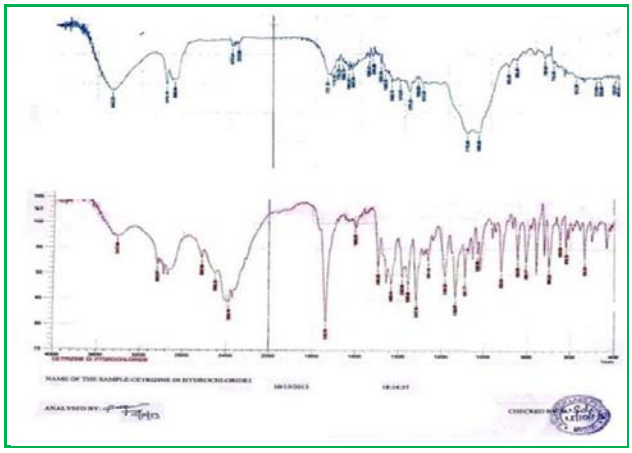

Figure 1: Compatibility studies by FT-IR

- The thickness of the film varies from one formula to the other according to the weight of polymer it contained. But the thickness variation within the films of each formulation was within the limits thus are of uniform thickness.
- The percent weight variation within the films of each formulation was also within the limits.
- The percent moisture contact in the films of all formulations was in the range of 6-12%. The least was noted in F2 (6.773±0.411) and the highest was noted in F7 (11.946±0.593).
- The percent moisture uptake of the films of formulations F1 to F4 containing HPMC alone is gradually increasing with increase in polymer concentration and F5 containing HPMC with Methylcellulose had shown highest moisture uptake i.e. (92.626±2.141), the moisture uptake in F7 containing HPMC with PVP has shown higher (78.896±3.125) than the F6 containing HPMC with Ethyl cellulose (62.023±3.539).
- F1 & F2 formulations had shown no visible cracks on the films even after 600 folds in the test for folding endurance but the films of F3 were broken at 437

folds , where as films of F4 were broken at 189 folds which was the least.

- The tensile strength of the films F1 to F4 was proportionately increasing from 0.745 to 1.479kg/sq.cm with increase in polymer HPMC concentration. But when compared with all formulations optimum strength of 0.374kg/sq.cm & elongation of 4.066 mm were observed in formulation F7. Whereas films of HPMC with 2.25% when mixed with Methyl cellulose or Ethyl cellulose have not altered the tensile strength. But PVP has reduced the tensile strength by 50%. I.e. in F7. Therefore in vitro studies were carried out for formulations F1, F2, F5 & F7 only.

In-vitro drug permeation

Table 3: *In-vitro* permeation data from F1to F7

Time (hrs)	Cumulative % drug permeated ±SD (n=5)			
	F1	F2	F5	F7
0	0	0	0	0
1	7.99±0.43	6.64±0.82	11.61±0.82	9.36±0.57
2	15.14±0.77	12.16±0.83	24.43±0.72	21.17±0.68
3	21.77±0.81	17.15±0.91	32.05±1.52	28.51±1.05
4	27.93±0.67	23.40±1.11	37.80±0.87	33.36±0.67
5	32.61±0.76	26.53±0.79	41.45±0.99	36.73±0.92
6	35.61±0.82	30.64±0.83	43.48±0.87	39.67±0.73
7	37.59±0.75	32.56±0.86	45.68±066	42.81±0.51
8	39.45±0.55	33.44±0.62	47.48±0.82	46.07±0.81
24	72.46±0.68	57.37±0.93	80.26±0.46	90.51±0.40

The data observed from the drug permeation though dialysis membrane for 24hrs, has shown that highest drug permeation was in F7 (90.51±0.40). The least drug permeation was in F2 (57.37±0.93) and the medium drug permeation was in F1&F5 (72.46±0.68 and 80.26±0.46).

Table 4: Kinetic parameters of drug permeation studies through dialysis membrane

Formulation code	First order plot(R^2)	Korsmeyer Peppas plot	
		(R^2)	N
F1	0.984	0.969	0.690
F2	0.941	0.961	0.691
F5	0.973	0.938	0.573
F7	0.988	0.962	0.671

The kinetic results obtained from the in vitro drug permeation data has shown that all the four formulations were following first order drug release kinetics and the mechanism of drug permeation was non-fickian diffusion.

The in vitro studies indicated 90.51% drug release is likely to be the best formulation and therefore subjected to in vivo studies.

In-vivo studies

The studies were performed on F7 by attaching them to the skin of human fore arm. The permeation data obtained is given in table 5.

The kinetic results obtained from the in vivo drug permeation data has shown that it following first order and non Fickian diffusion mechanism of drug release.

Table 5: Permeation data

Time (hrs)	Log (time)	Square root of time	Cumulative % drug permeated ± SD	Log % drug unabsorbed	Log % drug permeated
0	----	0	0	2	----
4	0.60205	2	31.52±1.40	1.835	1.498
8	0.90308	2.8284	43.34±0.75	1.753	1.636
24	1.38021	4.8989	85.21±0.96	1.169	1.930

Standard deviation is based on n=5

Table 6: Kinetic parameters of *in-vivo* drug permeation

Formulation code	First order plot(R^2)	Peppas plot	
		(R^2)	N
F7	0.996	0.995	0.585

CONCLUSION

Finally, from all the results the formulation F7 prepared with 2.25% HPMC, 0.75% PVP as rate controlling polymers and 10%w/w glycerin as plasticizer and methanol as a solvent has fulfilled the required physicochemical parameters. Formulation F7 when subjected to in vitro and in vivo studies, the results indicated a close correlation i.e. 90.51% and 85.21% drug release. So this is considered as the optimized formulation in the study and needs further investigation to improve in order to meet the mandatory standards of transdermal drug delivery system.

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