Design and Evaluation of Transdermal Patches of Labetalol Hydrochloride

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Abstract— *β-blockers like labetalol hydrochloride (LHCl) are potent and highly effective antihypertensive agents. The main drawback associated with β-blockers is extensive first-pass metabolism, variable bioavailability requiring frequent dose administration. This makes them an ideal candidate for transdermal therapeutic systems. β-blockers formulated as transdermal therapeutic system should enhance the bioavailability as well as improve patient compliance. Constant innovations and improvement in this field have potential that large-scale commercialization of transdermal dosage forms can be done.*

Aim: *The aim of the present work was to develop and evaluate matrix type transdermal patches containing new polymeric combination to enhance the bioavailability as well as improve patient compliance.*

Materials and Methods: *In present work development and evaluation of matrix-type transdermal patches containing a new polymeric combination of HPMC, carbopol934, ethyl cellulose, propylene glycol, polyethylene glycol, and isopropyl myristate for labetalol (LHCl) HCl (LBHCl). Film casting technique has been used in preparing patches. The patches were characterized for physical, in vitro release studies and ex vivo permeation studies using human cadaver skin.*

Result: *F_6 was found to be better than the other formulations and hence selected as the optimized formulation on the basis of results of evaluating parameters such as thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content, formulation. The optimized patch was assessed for its pharmacokinetic, pharmacodynamic, skin irritation test and stability studies.*

Conclusion: *Successful development of sustained release matrix type of transdermal patches which can show greater patient compliance in treating hypertension has been done.*

Keywords— Drug delivery, labetalol hydrochloride, penetration enhancer, skin permeation, transdermal.

I. INTRODUCTION

Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. Hypertension is the most common cardiovascular disease worldwide. Its global occurrence is estimated to be around 1 billion individuals, and approximately 7.1 million deaths occur per year. Therefore, cost- effective approaches to optimally control blood pressure are need of the hour.

Management of hypertension with conventional dosage forms requires long-term treatment leading to poor patient compliance due to greater frequency of administration. Although there is the availability of

a plethora of therapeutically effective antihypertensive molecules, inadequate patient welfare is observed. It has provided a good platform for design and development of new formulations using different routes. Ever since the transdermal drug delivery has came into existence, it has offered great advantages including non-invasiveness, prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance, and easy termination of drug therapy. Attempts have been made to develop the transdermal therapeutic system for various antihypertensive agents, including β-blockers, an important antihypertensive class.[1-4]

The first-pass metabolism is a phenomenon, whereby the concentration of a drug is significantly reduced before it reaches the systemic circulation. One of the ways to avoid first-pass metabolism in case of antihypertensive drugs is formulating them in transdermal patch. The transdermal patch for labetalol hydrochloride (LHCl) can be prepared by different techniques using natural, semi-synthetic, and synthetic polymers.

A transdermal patch is a medicated adhesive patch that is positioned on the skin to transport a specific dose of medicine through the skin into the bloodstream. The major advantages provided by transdermal drug delivery system (TDDS) include enhanced bioavailability, more homogeneous plasma levels, longer duration of action leading to reduction in dose regularity, reduced side effects and enhanced therapeutic effect due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. TDDS avoid the GIT absorption and provide multi-day therapy with a single use, quick notification of medication in urgent situation and termination of drug therapy is rapidly possible through patch removal in case of side effects, can be easily applied and simply removed from the skin, it is the simple delivery system.[5-13]

Labetalol hydrochloride (LHCl) is an antihypertensive drug belonging to the class of β blockers. It has a low biological half-life of 2–5 h and undergoes extensive pre-systemic metabolism ranging from 14% to 89%. It has a low-molecular-weight (364.9), with no reported skin irritation history. It also has a favorable partition coefficient (7.08). With all these characteristics we propose LHCl to be an ideal drug candidate for the development of TDDS.[13-18]

II. MATERIALS AND METHODS

2.1 Chemicals and reagents

Chemicals and reagents for experimental work were procured as follows, LHCl was procured as gift samples from Cipla Ltd, HPMC procured from Loba Chemie, Mumbai, sodium lauryl sulfate and glycerine was procured from Merck, Mumbai, ethyl cellulose, dimethylsulfoxide, isopropyl myristate, and propylene glycol were procured from Molychem, Mumbai.

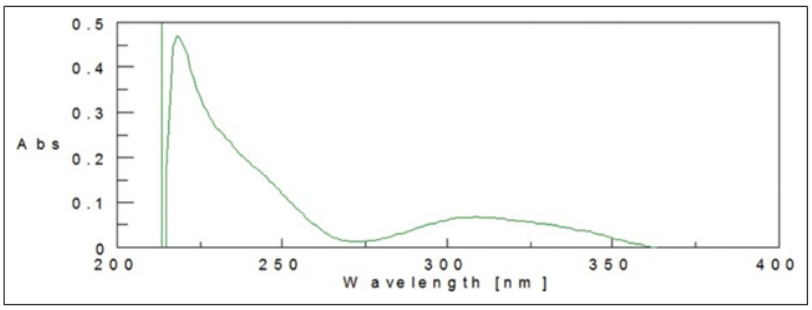
2.2 Experimental work

2.2.1 Validated analytical method development for determination of LHCl

2.2.1.1 Determination of λ max

The first important step in any analytical method development is a determination of λ max. Using this wavelength further validation has to be done. The result is presented in Figure 1.

FIGURE 1: Determination of λ max



2.2.1.2 Linearity

Several aliquots of LHCl hydrochloride were prepared separately at strength of 100 µg/ml, which were further diluted to prepare solutions in the concentration range of 2–10 µg/mL. Results of linearity, slope intercept, and correlation coefficient are shown in Tables 1 and 2, and Figure 2.

FIGURE 2: Calibration of labetalol hydrochloride

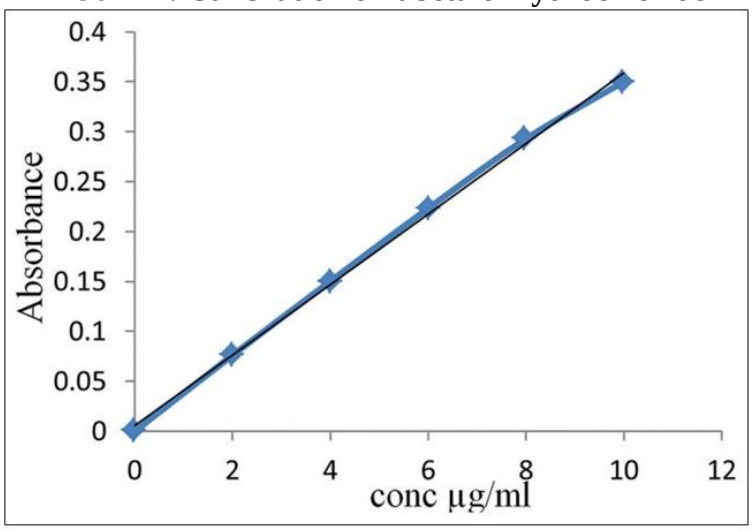


TABLE 1
RESULT OF LINEARITY RANGE

Concentration (µg/ml)	Absorbance
2	0.0762
4	0.1503
6	0.2233
8	0.2931
10	0.3502

TABLE 2
RESULT OF SLOPE INTERCEPT AND CORRELATION COEFFICIENT

Parameter	Methanol: water
Slope	0.035
Intercept	0.005
R2	0.998

2.2.1.3 Precision

Precision of the method was studied by making three different concentrations, namely, 2, 6, and 10 µg/mL and relative standard deviation was calculated. Results of intraday precision are shown in Table 3 and interday in Table 4.

2.2.1.4 Accuracy

Accuracy was determined by spiking a known concentration of pure drug in a mixture of marketed formulation solutions. The recovery of drug in the presence of marketed formulation was found to be in between the predefined acceptance criteria. Results of accuracy were shown in Table 5.

2.2.2 Compatibility study of drug and polymers

The compatibility study for drug and polymer was conducted by exposing the physical mixture of drug and polymer to X-ray diffractometry (Philips PW-3710) and DSC (Pyris Diamond TG/DTA, Make-PerkinElmer). Results shown in Figure 2.1, 2.2, and 2.3 indicate that there is no interaction.

2.2.3 Formulation of transdermal patches with different polyme

A 3^2-randomized full factorial design was used in the present study. In this design, two independent factors were evaluated, each at three levels and experimental trials were performed for all nine possible combinations. The compositions of HPMC and ethyl cellulose were chosen as independent variables. F1 to F9 batches were prepared using the factorial design and were analyzed for thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content.

The drug-free patches were prepared using polymers such as HPMC, Carbopol 934, ethyl cellulose, sodium lauryl sulfate, dimethyl sulfoxide, propylene glycol, polyethylene glycol, isopropyl myristate, methanol, and chloroform.

For the preparation of transdermal patches of LHCl were prepared using solvent evaporation method on aluminum foil. Accurately weighed quantity of 100 mg HPMC, 100 mg sodium lauryl sulfate and 400 mg ethyl cellulose were taken in a clean dry beaker. Solution of 30 mg LHCl was prepared by dissolving it in sufficient quantity of a mixture of methanol: chloroform. The solution was added to a beaker and mixed well.

Polymeric solution of remaining 70 mg of LHCl hydrochloride was prepared using 100 mg HPMC dissolved in chloroform and was kept for evaporation. Polymeric powder thus obtained was added to the beaker with constant stirring along with a small quantity of solvent. The gel-like formulation was obtained. It was poured on aluminum foil in Petri dish and kept in an oven at 37°C for 12 h.[13-18]

2.2.4 Characterization of transdermal patches [22-32]

The characterization of transdermal patches was done by evaluating parameters such as thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content. Comparative results are mentioned in Table 6.[20,21]

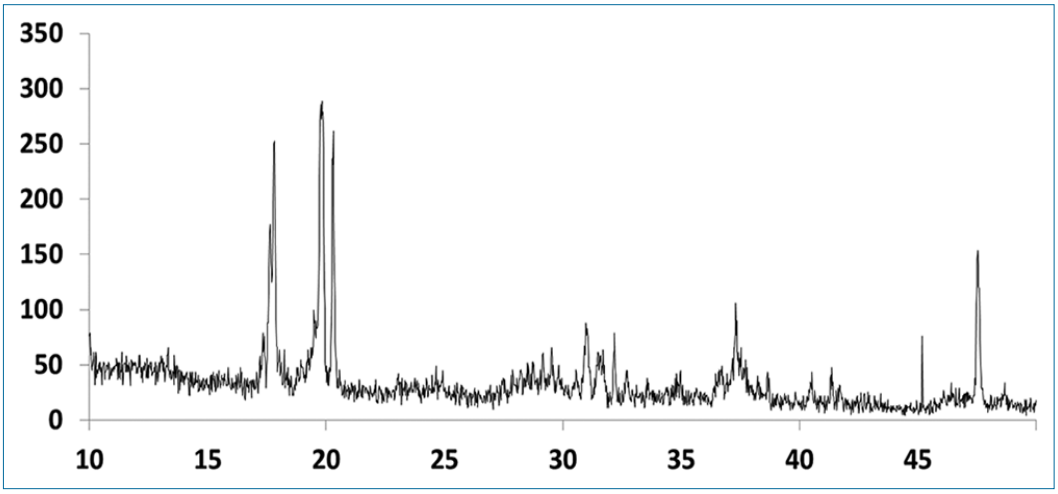
TABLE 3
RESULTS OF INTRADAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	102	0.4
	6	105	
	10	94.3	
Afternoon	2	100.05	0.6
	6	109.1	
	10	90.1	
Evening	2	120.1	1.1
	6	118.4	
	10	114.1	

TABLE 4
RESULTS OF INTERDAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	114.5	0.5
	6	115.02	
	10	101.14	
Afternoon	2	115.03	0.6
	6	119.08	
	10	98.04	
Evening	2	120.2	0.8
	6	118.1	
	10	96.03	

FIGURE 2.1: X-ray diffractometer of formulated patch



2.2.5 Thickness

Patch thickness was measured using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the mean value was calculated.

2.2.6 Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm × 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value of that prepared transdermal film.

TABLE 5
RESULTS OF ACCURACY

Level of recovery	Amount added (mg)	Concentration recorded (mg)	% Recovery	% RSD
80	8	7.55	94.3	0.87
	8	7.48	93.5	
	8	7.74	96.7	
100	10	9.74	97.4	1.23
	10	9.65	96.5	
	10	10.22	102.2	
120	12	11.71	97.5	1.41
	12	12.4	103.3	
	12	11.85	98.7	

TABLE 6
RESULTS OF THICKNESS, FOLDING ENDURANCE, TENSILE STRENGTH

Batch code	Folding		Mean±SD		
	Tensile strength kg/cm2)		%	Thickness (mm)	% Drug
F1	177±3.2	0.528±0.007	41.2±0.015	0.1645±0.019	100.02±0.59
F2	179±5.2	0.535±0.009	38.8±0.014	0.1704±0.013	98.23±2.38
F3	170±3.8	0.520±0.015	37.1±0.012	0.1695±0.014	102.30±1.69
F4	170±3.8	0.548±0.013	40.2±0.013	0.2015±0.017	104.51±3.9
F5	177±3.2	0.551±0.016	39.6±0.017	0.1849±0.001	100.02±0.59
F6	175±1.2	0.540±0.005	35.8±0.012	0.1645±0.019	101.18±0.57
F7	172±1.8	0.542±0.007	39.2±0.013	0.1704±0.013	99.37±1.24
F8	175±1.2	0.537±0.002	28.9±0.015	0.1695±0.014	98.65±1.96
F9	170±3.8	0.525±0.010	30.1±0.015	0.2015±0.017	104.23±3.62

2.2.7 Tensile strength

The tensile strength was determined using a modified pulley system. The strip of the patch (2×1 cm^2) was cut and hold between the two clamps present on pulley system. Weights were increased gradually in pan. The force required to break the film was considered as a tensile strength and was calculated as kg/cm^2.

2.2.8 Percentage of moisture content

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. Films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated using formula and is presented in Table 7.

$$\text{Percentage of moisture content} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

TABLE 7
RESULT OF MOISTURE CONTENT

Batch no	% Moisture content
F1	5.20±1.81
F2	4.05±0.66
F3	4.25±0.86
F4	2.30±1.09
F5	2.78±0.61
F6	3.09±0.30
F7	2.87±0.52
F8	2.93±0.46
F9	2.50±0.29

2.2.9 Percentage of moisture uptake

The prepared patches were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage moisture content from the below-mentioned formula and are presented in Table 8.

$$\text{Percentage of moisture content} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

TABLE 8
RESULTS OF % MOISTURE UPTAKE

S. No	% Moisture uptake
F1	10.60±0.63
F2	9.39±0.58
F3	11.54±1.57
F4	10.47±0.50
F5	9.09±0.88
F6	10.35±0.38
F7	10.25±0.28
F8	8.55±1.42
F9	9.55±0.42

2.2.10 Determination of drug content

A 5 cm^2 patch was cut into small pieces, put into a 100 ml phosphate buffer pH 7.4 and shaken continuously for 24 h. The whole solution was ultrasonicated for 5 min. The drug concentration was analyzed using ultraviolet spectrophotometer at a wavelength of 218 nm. The results are presented in Table 9.

TABLE 9
RESULTS OF DRUG CONTENT

Batch No.	Drug content
F1	100.02±0.59
F2	98.23±2.38
F3	102.30±1.69
F4	104.51±3.9
F5	97.05±3.56
F6	101.18±0.57
F7	99.37±1.24
F8	98.65±1.96
F9	104.23±3.62

FIGURE 3: Drug release profile of different formulation

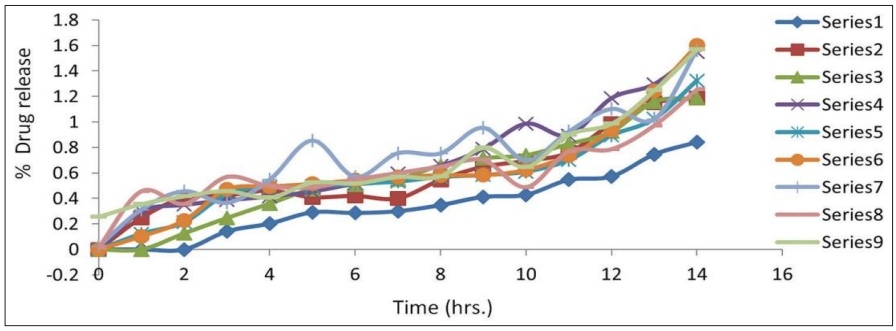


FIGURE 2.2: DSC results of formulated polymeric patch (without drug)

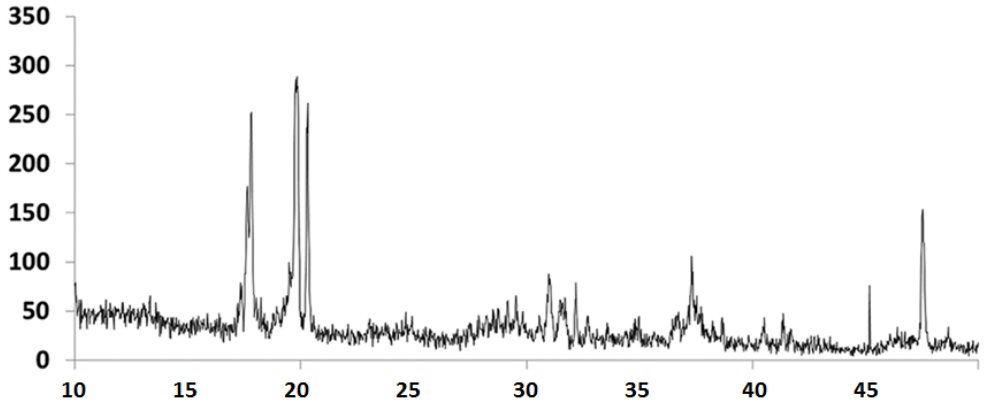
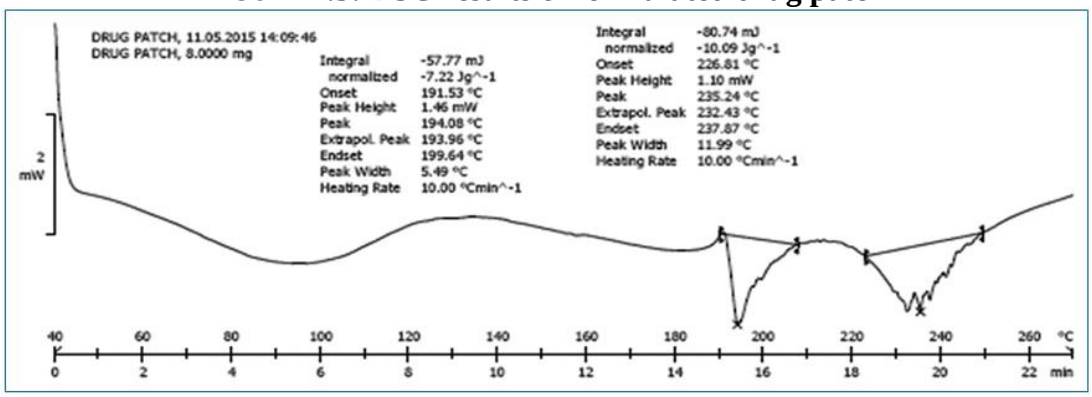


FIGURE 2.3: DSC results of formulated drug patch



2.2.11 In Vitro Diffusion Studies

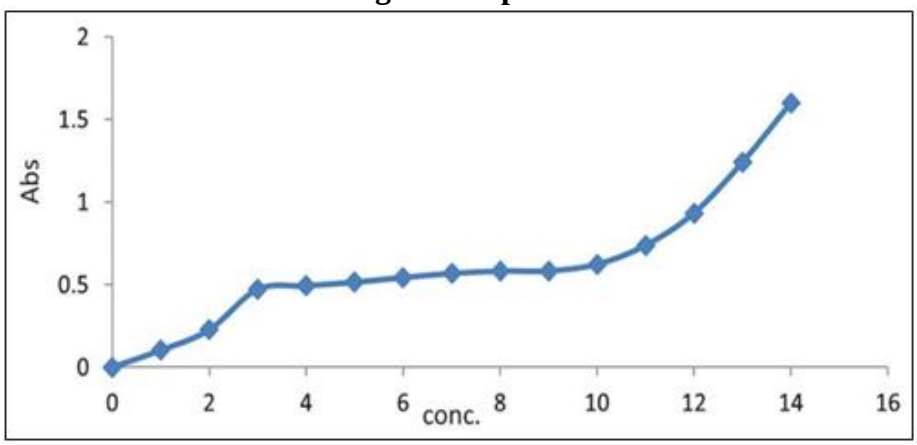
The diffusion studies were conducted to get an idea of permeation of drug through barrier from the transdermal systems. The Franz and Keshary Chien (K-C) type of horizontal diffusion cells with a receptor compartment capacity of 22 ml was utilized. The cellulose acetate membrane (pore size 0.45 µ) was mounted between the donor and receptor compartment of the diffusion cell. The transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil.

The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly stirred using magnetic beads, and the temperature was maintained at 32 ± 0.5°C. The diffusion study was carried out for 12 h, and 1 ml sample was withdrawn at an interval of 1 h. The samples were analyzed for drug content at 218 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. Results are presented in Table 10 and Figure 3. The result of drug release from optimized formulation batch F6 has been presented separately in Table 10 and Figure 4.

TABLE 10
RESULT OF IN VITRO DRUG RELEASE

Time (h)	% Drug release
1	2.79
2	6.33
3	13.33
4	13.94
5	14.55
6	15.37
7	16.08
8	16.48
9	16.51
10	17.66
11	20.93
12	26.52
13	35.34
14	45.59

FIGURE 4: Drug release profile of ideal batch



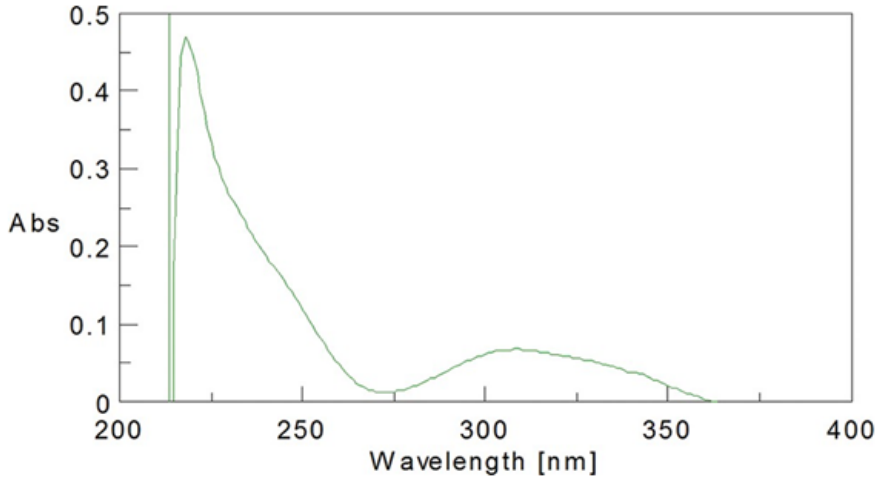
2.2.12 Stability Study

According to the ICH guidelines 257, the TDDS samples were stored at 40 ± 0.5°C and 75 ± 5% relative humidity (RH) for 3 months. The samples were withdrawn at 0, 30, 60, 90, and 180 days and analyzed for physicochemical parameters as well as drug diffusion. If a significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition, i.e. 30°C and 75% RH. The stability studies were carried out for F6 formulation which was optimized formulation.[19]

III. RESULT AND DISCUSSION

3.1 Determination of λ max

From fig. it was found that the λ max for labetalol hydrochloride in methanol: water system was found to be 218nm.



3.2 Calibration related result and discussion.

3.2.1 Linearity

TABLE 11
RESULTS OF LINEARITY

Concentration (µg/ml)	Absorbance
2	0.0762
4	0.1503
6	0.2233
8	0.2931
10	0.3502

Experimentally the linearity for labetalol hydrochloride in methanol: Water system at 218 nm was found to between 2-10 µg/ml.

3.2.2 Precision

3.2.2.1 Intraday Precision

TABLE 3.1
RESULTS OF INTRADAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	102	0.4
	6	105	
	10	94.3	
Afternoon	2	100.05	0.6
	6	109.1	
	10	90.1	
Evening	2	120.1	1.1
	6	118.4	
	10	114.1	

3.2.2.2 Interday Precision

TABLE 3.2
RESULTS OF INTERDAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	114.5	0.5
	6	115.02	
	10	101.14	
Afternoon	2	115.03	0.6
	6	119.08	
	10	98.04	
Evening	2	120.2	0.8
	6	118.1	
	10	96.03	

From the experimental procedure % RSD values for interday and intraday precision were found to be within limits.

3.2.2.3 Accuracy

TABLE 3.3
RESULTS OF ACCURACY

Level of recovery	Amount Added (mg)	Concentration recorded (mg)	Recovery %	RSD %
80	8	7.55	94.3	0.87
	8	7.48	93.5	
	8	7.74	96.7	
100	10	9.74	97.4	1.23
	10	9.65	96.5	
	10	10.22	102.2	
120	12	11.71	97.5	1.41
	12	12.4	103.3	
	12	11.85	98.7	

From experimental procedure the % recovery of drug in the developed formulation was found to be with in acceptance criteria on the basis of values of % RSD.

3.2.3 Characterization of transdermal films

3.2.3.1 Thickness

TABLE 3.4
RESULTS OF THICKNESS

Batch No.	Thickness	Batch No.	Thickness
F1	0.1645±0.019	F6	0.1910±0.007
F2	0.1704±0.013	F7	0.1712±0.012
F3	0.1695±0.014	F8	0.2135±0.029
F4	0.2015±0.017	F9	0.1862±0.002
F5	0.1849±0.001		

3.2.3.2 Folding endurance

TABLE 3.5
RESULTS OF FOLDING ENDURANCE

Batch No.	Folding endurance
F1	177±3.2
F2	179±5.2
F3	170±3.8
F4	170±3.8
F5	177±3.2
F6	175±1.2
F7	172±1.8
F8	175±1.2
F9	170±3.8

3.2.3.3 Tensile strength

TABLE 3.6
RESULTS OF TENSILE STRENGTH

Sr.No	Tensile strength kg/cm^2
F1	0.528 ± 0.007
F2	0.535
F3	0.520 ± 0.015
F4	0.548 ± 0.013
F5	0.551 ± 0.016
F6	0.540 ± 0.005
F7	0.542 ± 0.007
F8	0.537 ± 0.002
F9	0.525 ± 0.010

3.2.3.4 Percentage of moisture content

TABLE 3.7
RESULT OF MOISTURE CONTENT

Batch no	Moisture Content %	Batch No.	Moisture Content %
F1	5.20±1.81	F6	3.09±0.30
F2	4.05±0.66	F7	2.87±0.52
F3	4.25±0.86	F8	2.93±0.46
F4	2.30±1.09	F9	2.50±0.29
F5	2.78±0.61		

3.2.3.5 Percentage moisture uptake

TABLE 3.7
RESULT OF MOISTURE UPTAKE

Sr. No.	Moisture Uptake %	Sr. No.	Moisture Uptake %
F1	10.60±0.63	F6	10.35±0.38
F2	9.39±0.58	F7	10.25±0.28
F3	11.54±1.57	F8	8.55±1.42
F4	10.47±0.50	F9	9.55±0.42
F5	9.09±0.88		

3.2.4 Drug Content

3.2.4.1 Results of drug content

TABLE 3.8
RESULTS OF DRUG CONTENT

Batch No.	Drug Content	Batch No.	Drug Content
F1	100.02±0.59	F6	101.18±0.57
F2	98.23±2.38	F7	99.37±1.24
F3	102.30±1.69	F8	98.65±1.96
F4	104.51±3.9	F9	104.23±3.62
F5	97.05±3.56		

3.2.4.2 In-vitro drug release profile

TABLE 12
***IN VITRO* DRUG RELEASE PROFILE FOR F6 FORMULATION THE OPTIMIZED FORMULATION [19]**

Time (hrs)	Drug Release %
1	2.79
2	6.33
3	13.33
4	13.94
5	14.55
6	15.37
7	16.08
8	16.48
9	16.51
10	17.66
11	20.93
12	26.52
13	35.34
14	45.59

From the experimental procedure carried out for thickness folding endurance, tensile strength, percentage of moisture content, percentage of Moisture Uptake and determination of drug Content the values were found to be within acceptance criteria.

3.2.5 Stability testing

The present work of stability study was carried out for optimized formulation (F6) at 40 ± 0.5°C and 75 ± 5% RH for 1 month using programmable environmental test chamber (Remi, India). The sample was evaluated for drug content uniformity, and it was found to be 98.54%.

IV. DISCUSSION

A successful development and evaluation of transdermal patches of LHCl prepared by solvent evaporation method have been done. All the patches prepared were subjected to evaluation parameters such as thickness (0.1910±0.007), % moisture uptake (10.35±0.38), % moisture content (3.09±0.30), tensile strength (0.540±0.005), folding endurance (175±1.2), drug content (101.18±0.57), and *in-vitro* diffusion study and stability study. A successful analytical method was also developed for formulated preparation. On the basis of results of various tests carried out for F1 to F9 formulations, F6 was found to be optimized formulation.

V. CONCLUSION

The prepared TDDS of patches of LHCl using different grades of HPMC and ethyl cellulose has shown promising results for all the evaluated parameters. It can be concluded use of HPMC K100 and ethyl cellulose can be done successfully in preparation of sustained release matrix type of transdermal patches which can show greater patient compliance in treating hypertension successfully.

REFERENCES

[1] Ahad A, Al-Jenoobi FI, Akhtar N, Raish M, Aqil M. Systemic delivery of b-blockers via trans-dermal route for hypertension. Saudi Pharm J 2014;23:587-602.

[2] Allen LV, Popovich NG, Howard C. Ansels Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2005. p. 298-315.

[3] Dezfuli AR, Aravindram AS, Manjunath M, Ganesh NS, Shailesh T. Development and evaluation of transdermal films loaded with antihypertensive drug. Int J Pharm Bio Sci 2012;3:559-69.

[4] Gaikwad AK. Trans-dermal drug delivery system: Formulation aspects and evaluation. Compr J Pharm Sci 2013;1:1-10.

[5] Kumar JA, Pullakandam N, Prabu SL, Gopal V. Trans- dermal drug delivery system. Int J Pharm Sci Rev Res 2010;3:49-54.

[6] Barry BW. Novel mechanisms and devices to enable successful trans-dermal drug delivery. Eur J Pharm Sci 2001;14:101-14.

[7] Baykara T, Yapar EA. Physical properties and in vitro release studies on sotalol monolithic films prepared by eudragit polymers. Turk J Pharm Sci 2010;7:255-66.

[8] Bracht S. Trans-dermal therapeutic systems: A review. Drug Deliv Innov Pharm Technol 2001;11:92-8.

[9] Chien YW. Trans-dermal Controlled Systemic Medications. USA: Marcel Dekker, Inc.; 1987. p. 1-21.

[10] Finnin BC, Morgan TM. Transdermal penetration enhancers: Applications, limitations, and potential. J Pharm Sci 1999;88:955-8.

[11] Hanumanaik M, Patil U, Kumar G, Patel SK, Singh I, Jadatkar K. Design, evaluation and recent trends in trans-dermal drug delivery system. Int J Pharm Sci Res 2012;3:22-8.

[12] Jain AK, Thomas NS, Panchagnula R. Transdermal drug delivery of imipramine hydrochloride. I. Effect of terpenes. J Control Release 2002;79:93-101.

[13] Jani RK, Patel JK. A review on delivery of antihypertensive drugs through trans-dermal systems. Int J Pharm Clin Sci 2012;1:1461-74.

[14] Ezhumalai K, Ilavarasan P, Mugundhan PM, Sathiyaraj U, Rajalakshmi AN. Trans-dermal patches in novel drug delivery system. Int J Pharm Technol 2011;3:2402-19.

[15] Kandavilli S, Nair V, Panchagnula R. Polymers in trans-dermal drug delivery systems. Pharm Technol 2002;73:62-80.

[16] Kusumdevi V, Asha AN, Agadi SS, Mathew D. Optimization of Trans-Dermal Delivery of Selected Antihyperlipidaemic Agents-Statin 2013;2(3):92-8.

[17] Lee WR, Shen SC, Lai HH, Hu CH, Fang JY. Transdermal drug delivery enhanced and controlled by erbium: YAG laser: A comparative study of lipophilic and hydrophilic drugs. J Control Release 2001;75:155-66.

[18] Lin W, Cormier M, Samiee A, Griffin A, Johnson B, Teng C, et al. Trans-dermal delivery of antisense oligonucleotides with projection patch (Macroflux®) technology. Pharm Res 2001;18:1789-93.

[19] Selvam RB, Singh AK, Sivakumar T. Trans-dermal drug delivery systems for antihypertensive drugs - A review. Int J Pharm Biomed Res 2010;1:1-8.

[20] Ramachandran C, Fleisher D. Trans-dermal delivery of drugs for the treatment of bone diseases. Adv Drug Deliv 2000;42:197-223.

[21] Mehdizadeh A, Toliate T, Rouini MR, Abashzadeh S, Dorkoosh F. Design and in vitro evaluation of new drug-in-adhesive formulations of fentanyl trans-dermal patches. Acta Pharm 2004;5:301-17.

[22] Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification in vitro. Eur J Pharm Biopharm 2001;52:103-12.

[23] Murthy SN, Hiremath SR. Physical and chemical permeation enhancers in trans-dermal delivery of terbutalinesulphate. AAPS PharmSciTech 2001;2:1-5.

[24] Patel D, Kavitha K. Formulation and evaluation aspects of trans-dermal drug delivery system. Int J Pharm Sci Rev Res 2011;6:83-90.

[25] Puglia C, Filosa R, Peduto A, de Caprariis P, Rizza L, Bonina F, et al. Evaluation of alternative strategies to optimize ketorolac transdermal delivery. AAPS PharmSciTech 2006;7:64.

[26] Rathbone MJ, Hadgraft J, Roberts MS, editors. Modified Release Drug Delivery Technology. Vol. 126. New York: Marcel Dekker, Inc.; 2004. p. 471-619.

[27] Premjeet S, Bilandi A, Sahil K, Akanksha M. Trans- dermal drug delivery system (Patches), applications in present scenario. Int J Res Pharm Chem 2011;1:1139-51.

[28] Sharma K, Singh V, Arora A. Natural biodegradable polymers as matrices in trans-dermal drug delivery. Int J Drug Dev Res 2011;2:85-103.

[29] Vanbever R, Lecouturier N, Préat V. Transdermal delivery of metoprolol by electroporation. Pharm Res 1994;11:1657-62.

[30] Vishwakarma SK, Niranjan SK, Irchhaiya R, Neeraj K. A novel trans-dermal drug delivery system. Int Res J Pharm 2012;3:39-44.

[31] Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. 1st ed. New Delhi: Vallabh Prakashan; 2002. p. 411-47.

[32] Walters KA. Dermatological and Trans-dermal Formulations. New York: Marcel Dekker, Inc.; 2002. p. 1-39.