Volume 2, Issue 4, 2023, Page 488-504

International Journal of Pharma Research and Technology

Formulation and Invitro Evaluation of Transdermal Patches of Nebivolol Hydrochloride

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Abstract

Nebivolol is a highly cardio selective β1 -receptor blocker with nitric oxide -potentiating vasodilator effect and used in 50 mg dose for the treatment of the hypertension. Moreover, it is a long-acting antihypertensive agent preferred for treating chronic heart failure in high-risk patients. Transdermal drug delivery systems (TDDS) are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the intact skin at a preprogrammed rate. The biopharmaceutical classification system (BCS) has categorized nebivolol under class II (low solubility and high permeability), suggesting that the non-oral route can be a feasible alternative. Therefore, the present research work was aimed to develop sustain release transdermal patch of Nebivolol utilizing different polymers such as HPMC E50, PVP, Eudragit RS100, and ethyl cellulose and plasticizers such as PEG-400 and Dibutyl phthalate and DMSO as a penetration enhancer via solvent casting method for a low dose of the drug. According to *in-vitro* drug study, Nebivolol loaded with polymers HPMC E50-EC with PEG-400 as a plasticizer was shown to be the optimum formulation, with drug release of 4.66 mg/cm^2 /12 h. The patches of Nebivolol concentration remained steady for three months, and their physicochemical and drug release properties did not alter significantly. The formulation was help to avoid first pass metabolism and provide sustained release of the drug and avoid non-compliance with the tablet dosage form. The results indicated that the strategy adopted, viz, preparation of Nebivolol transdermal patch, was successful in enhancing the permeation of drug.

Keywords: Nebivolol, Vasodilator, Biopharmaceutical classification, Transdermal patch, Transdermal drug delivery systems.

Introduction

A transdermal patch, also known as a flesh patch, is a therapeutic sticky pad (a thin mass of soft substance utilized for safety, filling, and convenience) put on the skin to administer a particular quantity of drugs into the blood circulation via the skin. The patch offers a managed discharge of drug into the patient, typically through a permeable membrane designed to cover a reservoir of drug or through body temperature melting a thin coating of medication incorporated in the sticky tape, which is a benefit of transdermal drug delivery over other types of delivery of drug such as oral, topical, i.v, intramuscular, and so on[1].

Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery with around 40% of the drug candidates being under clinical evaluation related to transdermal or dermal systems[2]. Transdermal drug delivery systems (TDDS) are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the intact skin at a preprogrammed rate. Transdermal delivery of drug is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance. The physicians have a wide choice for treatment from transdermal formulations [3].

Transdermal drug delivery systems that can delivers medicine via the skin portal to the systemic circulation at a predetermined rate and maintain clinically effective concentrations for prolonged period of time[4]. This route of drug administration represents an attractive alternative to oral delivery of drugs and avoids the hazards and discomfort associated with parenteral therapy. The treatment can also be terminated rapidly by simply removing the patch when need arises. Transdermal delivery may also eliminate side effects of that drugs cause when presented in conventional forms[5].

Materials and Methods

Materials

Nebivolol Hydrochloride was obtained as gift sample from Gift Sample from Alkem Laboratories Ltd; Goa HPMC K4M was obtaied from Blue Cross Laboratory, Ltd, Nashik. Ethyl cellulose, Polyethylene glycol 400, PVP K15, Eudragit RS 100, ect was purchased from Modern Industries. All chemicals used were analytical grade.

Methods

Preformulation Study

Organoleptic Properties:

The sample of Nebivolol was studied for Organoleptic characteristics such as color, odor and appearance.[7]

Melting Point

Melting point of Nebivolol was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and average value was noted[7].

Determination of solubility[8]

Solubility of nebivolol was determined in different solvents. All solutions were prepared and 10 mg of nebivolol was added to 10 ml of each solution placed in the 10 ml volumetric flask and kept aside for 24 hr. After 24 h of shaking, 1 ml of aliquot was taken out from each sample and filtered through Whatman filter paper. After suitable dilutions, absorbance was measured at 282 nm and calculations for solubility were done.

Partition coefficient[7]

The partition coefficient of the drug was determined by taking equal volumes of n-octanol and aqueous phases in a separating funnel. 20 mg of drug was added to n-octanol: water (20:20) and was taken in a separating funnel and shaken for 10 minutes and allowed to stand for 2 h. The aqueous phase was separated from organic phase. The aqueous phase was assayed using UV

Spectrophotometer at 284 nm and amount of drug in organic phase was determined using difference to get partition coefficient.

Loss on drying[7]

Weighed a glass Stoppard shallow weighing bottle that has been drying under same conditions that has been employed in the determination.1gm of the sample was transferred to the bottle. Covered it and accurately weighed the bottle and the contents. Distributed the sample evenly by gentle sidewise shaking of the bottle. Dried the substance in the hot air oven at 105^0 C for 2 h and after allowed it to cool. Weighed the contents and the bottle. Calculated the difference in the initial and final weight of the substance.

UV Method Development of Nebivolol

Linearity (Calibration curve)

The developed method validates as per ICH guidelines. The plot of absorbance verses concentration is shown in Figure in results for pH 7.4 phosphate buffer. It can be seen that plots are linear in the concentration range of 10-50 µg/ml with correlation coefficients (r^2) of 0.997.

Accuracy (recovery study)

Recovery studies were carried out by adding a known quantity of pure drug to the reanalyzed formulations and the proposed method was followed. From the amount of drug found, percentage recovery was calculated as per ICH guidelines.

Precision (repeatability)

Intraday and interday precision was determined by measurement of the absorbance for three times on same day and on three different days. The relative standard deviation for replicates of sample solutions should less than 2 % to meet the acceptance criteria for established method.

LOD

LOD was determined using the relation 3.3 σ/s where 'σ' is the standard deviation of the response and s is the slope of the calibration curve. LOQ Similarly, LOQ was determined using the relation 10 σ/s.

FTIR interpretation of drug [9, 10, 11]

The infra-red spectrum of drug and polymers was recorded with BRUKER OPUS 7.5 over wave number of 4000 to 400 cm^{-1} by using Infra-red spectroscopy.

DSC interpretation of drug

The study was carried out using a Mettler Toledo differential scanning calorimeter equipped to a computerized data station. The sample of drug and polymer was weighed individually and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow.

Compatibility Study by Fourier Transform Infrared Spectroscopy

FTIR study was carried on pure drug and physical mixture of drug and polymers. Physical mixtures were prepared and samples kept for 1 month at 40^0C. The infrared absorption spectrum of Nebivolol and physical mixture of drug and polymers was recorded with the wave number 4000 to 400 cm^{-1}.

Differential scanning calorimetric studies

Thermal analysis was performed using a differential scanning calorimeter equipped with a computerized data station. The sample of pure drug, physical mixture of drug and polymer were weighed and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow.

Formulation of Nebivolol Loaded Transdermal Patches

The patches were cast in a glass mould with a diameter of 9.6 cm and a surface area of 72.34cm^2. By assessing the complete area of the petri dish in which the patch will be cast, the entire quantity of medicine to be placed into the patch was determined. 52.39 mg of the drug were added in each formulation in order to get 10 mg per small circular patch respectively.

Table No.1: Composition of formulations as per 3^2 full factorial design

Formulation code	Nebivolol	HPMC E50 (X1)	Ethyl Cellulose (X2)	PEG-400	DMSO	Methanol
F1	10 mg	800 mg	600 mg	5 ml	5 ml	10 ml
F2	10 mg	800 mg	500 mg	5 ml	5 ml	10 ml
F3	10 mg	800 mg	400 mg	5 ml	5 ml	10 ml
F4	10 mg	700 mg	600 mg	5 ml	5 ml	10 ml
F5	10 mg	700 mg	500 mg	5 ml	5 ml	10 ml
F6	10 mg	700 mg	400 mg	5 ml	5 ml	10 ml
F7	10 mg	600 mg	600 mg	5 ml	5 ml	10 ml
F8	10 mg	600 mg	500 mg	5 ml	5 ml	10 ml
F9	10 mg	600 mg	400 mg	5 ml	5 ml	10 ml

Evaluation of Transdermal Patches [12, 13]

1. Physical Appearance

Colour, clarity, flexibility, and smoothness of all produced patches were visuallyevaluated.

2. Thickness

Using a vernier caliper, the thicknesses of the drug-loaded patches were measured at three distinct places, and the mean value was computed.

3. Folding Endurance

For the prepared patches, the folding durability was carefully measured. The drug-filled patches were folded until they broke or developed cracks.

4. Drug Content

The produced patches are chopped into pieces and put in 100ml buffer (pH 7.4), which is then agitated for 2 hours on a mechanical shaker to get a homogenous solution, which is then filtered. The resultant solution is quantitatively transferred to volumetric flasks, and pH 7.4 phosphate buffer is used to make suitable dilutions. The resultant solutions were filtered and tested for drug content in a UV spectrophotometer at 205 nm. The average reading of three patches was used to determine the drug content of one patch.

5. Weight Uniformity

Separately weighing the patches is used to perform the weight variation test. Average of three patches was calculated.

6. Percentage Moisture Absorption

The test is carried out by weighing the films precisely. The weighted films are stored in a desiccator with 100 ml of aluminum chloride solution, which keeps the RH at 79.50

percent. After three days, the films were removed and weighed. The moisture absorption % is computed.

7. Percentage Moisture Loss

The films were precisely weighed and stored in an anhydrous calcium chloridedesiccator. The films were removed and weighed after three days. It was determined how much moisture was lost.

8. Swellability

The patches of a specified region were weighed and placed in a Petri dish with 10 ml of double distilled water to absorb. The weight of the patch was measured at certain intervals until it reached a consistent weight.

9. *In-Vitro* Drug Release Study

A Franz diffusion cell was used to investigate the *in-vitro* release patterns. The prepared patches were knotted around the cell's entrance and inserted into the donor and receptor cells. Egg shell membrane was used as a barrier membrane in the procedure. The patch is positioned in such a way that the medicine is released into the receptor compartment. The receptor compartment was filled with phosphate buffer (pH 7.4) and stirred with a magnetic bead, with the temperature maintained at 37°C. At predefined intervals, a 5 mL sample was taken and replaced with equal quantities of the elution medium. This was done for a total of 24 hours. The aliquot's medication concentration is measured and computed.[14]

10. Drug release Kinetic Study

To examine the drug release kinetics and mechanism from the patches, release data was assessed using the zero-order model, first order model, Higuchi model, and Korsmeyer-Peppas model. The drug release from TDDS patches created followed zero order kinetics, according to analysis using zero order and first order kinetic models.

11. Steady State Flux (Permeability Study)

After the lag phase, when the quantity continues to grow, steady state flux (Jss) is the amount of permeant traversing the membrane at a constant rate. This is known as steady state when the amounts recorded at repeated sample intervals are not appreciably different.

12. Stability Study

The stability study of optimized formulation was carried out according to ICH guidelines Q1C in humidity chamber (40°C ± 2°C/75 ± 5% RH). The samples were withdrawn at, 1, 2, and 3 months for given temperature condition. The formulations were evaluated mainly for drug content and % drug release at the predetermined intervals[14].

Results and Discussions

Preformulation study

All the physical properties of the drugs were within the limit of reported standards which assures the purity of the drug samples

Organoleptic Properties

Table No.2: Organoleptic Properties of Nebivolol

Identification test	Result of sample obtained	Reported standards
Colour	White	White
Odour	Odourless	Odourless
Melting point	223-227^{0}C	223-228^{0}C
Partition coefficient	3.20	3.29
Loss on drying	0.01 % w/v	NMT 0.5 % w/v

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Solubility

Table No.3 : Solubility in different solvents

Sr. No	Solvent	Observation
1	Water	Insoluble
2	Phosphate buffer pH 7.4	Soluble
3	Dimethyl Sulphoxide	Soluble
4	Methanol	Soluble

Ultraviolet - Visible Spectroscopy Study

Determination of λ_{max} in phosphate buffer pH 7.4

After studying the UV spectra of Nebivolol, it was found that drug shows maximum absorbance at 233 nm when solution (100 µg/ml) is prepared in phosphate buffer pH 7.4.

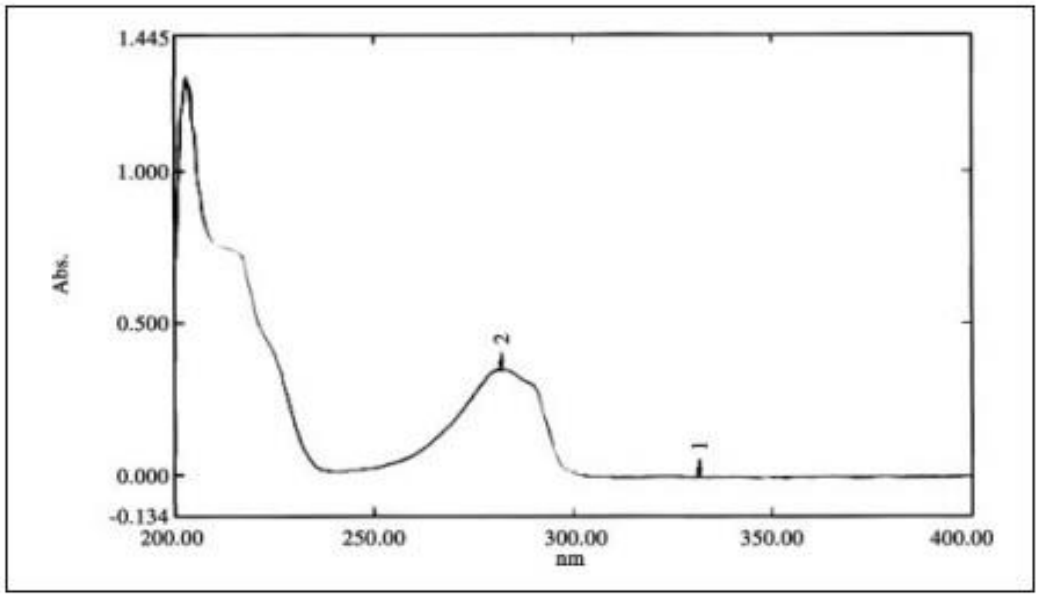

Figure No.1 : UV-Visible spectrum of Nebivolol in pH 7.4 phosphate buffer

Calibration curve of Nebivolol in pH 7.4 phosphate buffer -

The calibration curve was found to be linear in the concentration range of 10-50 µg/ml (Table 8.3) having coefficient of regression value R^2 = 0.993 and Slope y = 0.015

Table No.4: Absorbance of Nebivolol in 0.1 N HCl at 233 nm

Sr. No.	Concentration (ppm)	Absorbance
1	10	0.160
2	20	0.324
3	30	0.489
4	40	0.638
5	50	0.824

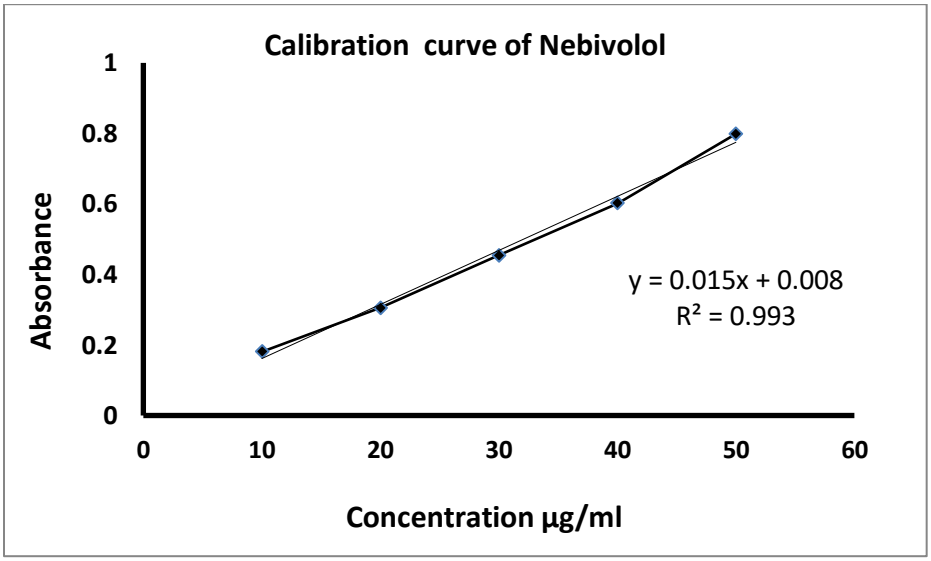

Figure No.2: Calibration curve of Nebivolol pH 7.4 phosphate buffer

UV method development

Intraday precision study

The method was developed for the drug Nebivolol using co-solvent in ethanol: pH6.8 phosphate buffer. Method was validated for linearity, accuracy and precision. The intraday and interday precision was carried out for 10-50 µg/ml shows better results.

Table No.5: Intraday precision study

Conc. (µg/ml)	Absorbance			Mean	S. D.	%RSD
	Trial 1	Trial 2	Trial 3			
10	0.1594	0.1580	0.2089	0.1754	0.02899	1.652
20	0.3667	0.3845	0.4118	0.3876	0.02271	0.586
30	0.4923	0.5270	0.5506	0.5233	0.02933	0.560
40	0.6844	0.6902	0.6890	0.6878	0.00306	0.445
50	0.8637	0.8841	0.8641	0.8706	0.01166	1.332

Interday precision study

Table No.6 : Interday precision study

Conc. (µg/ml)	Absorbance			Mean	S.D.	%RSD
	Day 1	Day 2	Day 3			
10	0.1726	0.1591	0.1180	0.1754	0.02843	1.521
20	0.3194	0.2825	0.2538	0.3876	0.03288	0.848
30	0.4281	0.3927	0.3628	0.5233	0.03268	0.624
40	0.5931	0.5863	0.5256	0.6878	0.03716	0.540
50	0.7400	0.7146	0.6985	0.8706	0.02092	0.240

Accuracy study

Accuracy study was carried out by adding known amount of standard drug 5, 10, 15 mg in reanalyzed formulations and the % recovery was found to be 100%.

Table No.7: Accuracy study

Sr no	Label claim (mg/tablet)	Amount of standard added (mg)	Total amount recovered (mg)	% recovery	S. D.	% RSD
1	50	5	54.95	99.90 %	0.00121	0.6275
2	50	10	60.16	100.2 %	0.00275	0.3519
3	50	15	66.42	102.1 %	0.00136	0.6056

Infra-Red Spectrum of Nebivolol

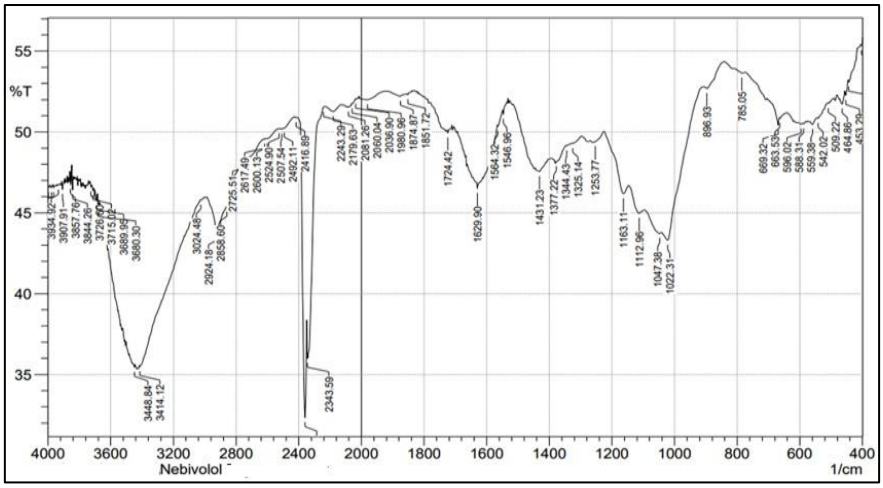

Figure No.3: FTIR Spectrum of Nebivolol

The FTIR spectra of pure Nebivolol showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug and confirms the identity of pure drug.

Differential Scanning Calorimetry

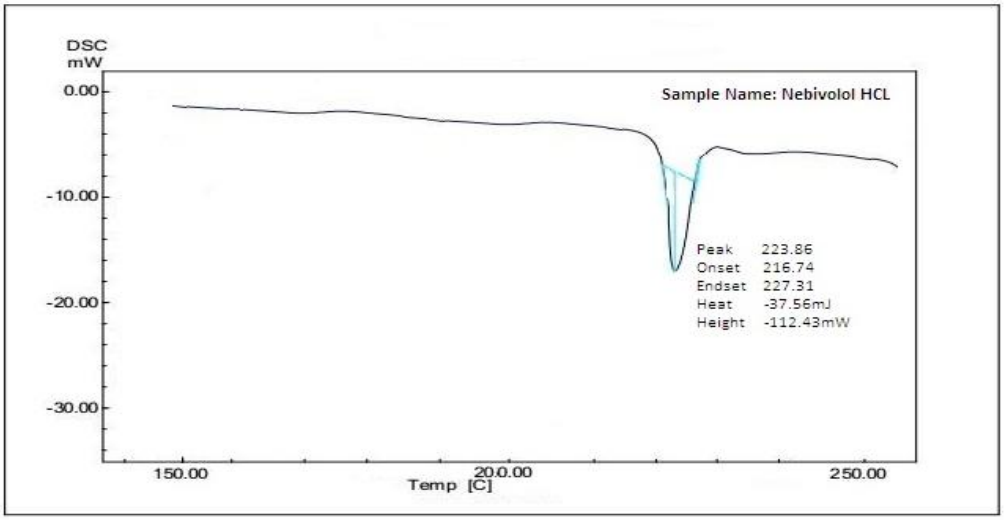

Figure No.4: DSC Thermogram of Nebivolol

Table No.8: DSC Thermogram of Nebivolol was interpreted

DSC Analysis	
Reported Standard in literature	**Observed**
223-228^{0}C	223.86^{0}C.

The DSC curve of Nebivolol showed a sharp endothermic peak at 223.86^{0}C corresponding to its melting, which confirm that purity of the drug. The drug did not decomposed followed by its melting[42].

Compatibility study

Fourier Transform Infrared Spectroscopy The characteristic absorption peaks of drug Nebivolol was remained unchanged in drug-polymer admixture which indicates that there is no prominent chemical reaction between drug and polymer mixture, proving compatibility of drugs with selected excipients for the study .

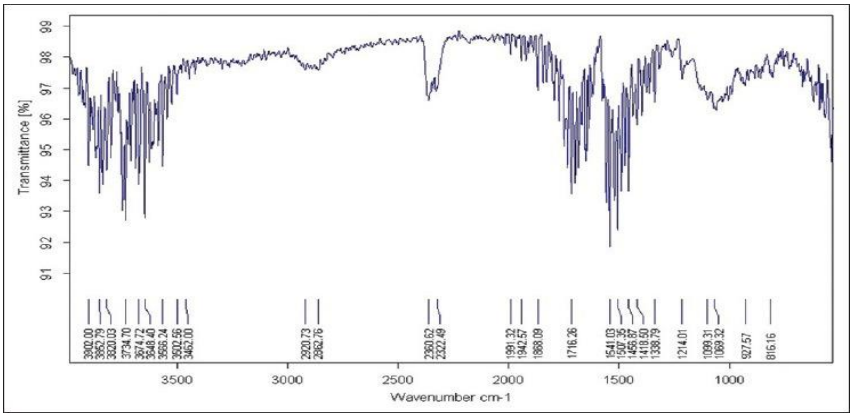

Figure No.5: IR Spectrum of Physical mixture of drug and excipients

Differential Scanning Calorimetry

DSC thermogram of drug exhibited characteristic peak at 223.86^{0}C and physical mixture exhibited characteristic peak at 223.46^{0}CFor physical mixtures, in all the cases melting endotherm of drug was well preserved with little or no change in enthalpy value of drug indicating compatibility of both drugs with selected excipients in the study shown in fig. The polymers HPMC K4M and ethyl cellulose have been reported to be compatible with a number of drugs.

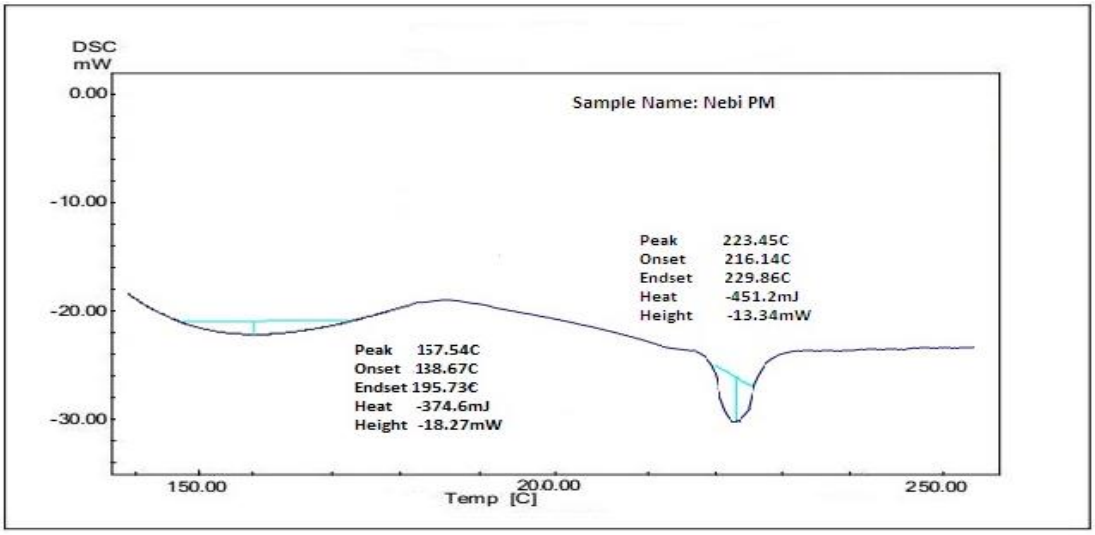

Figure No.6: DSC Thermogram of physical mixture of drug and excipients

Formulation of Nebivolol Loaded Transdermal Patches

The prepared transdermal patches of Nebivolol were evaluated for their

physicochemical characteristics such as appearance, weight variation, thickness, folding endurance, drug content, and invitro drug permeation through albino rat skin. The physical appearance of the various formulations in terms of their transparency, smoothness, flexibility, stickiness, homogeneity, and opaque properties were recorded. All the prepared transdermal patches are shown below in figure no.7.

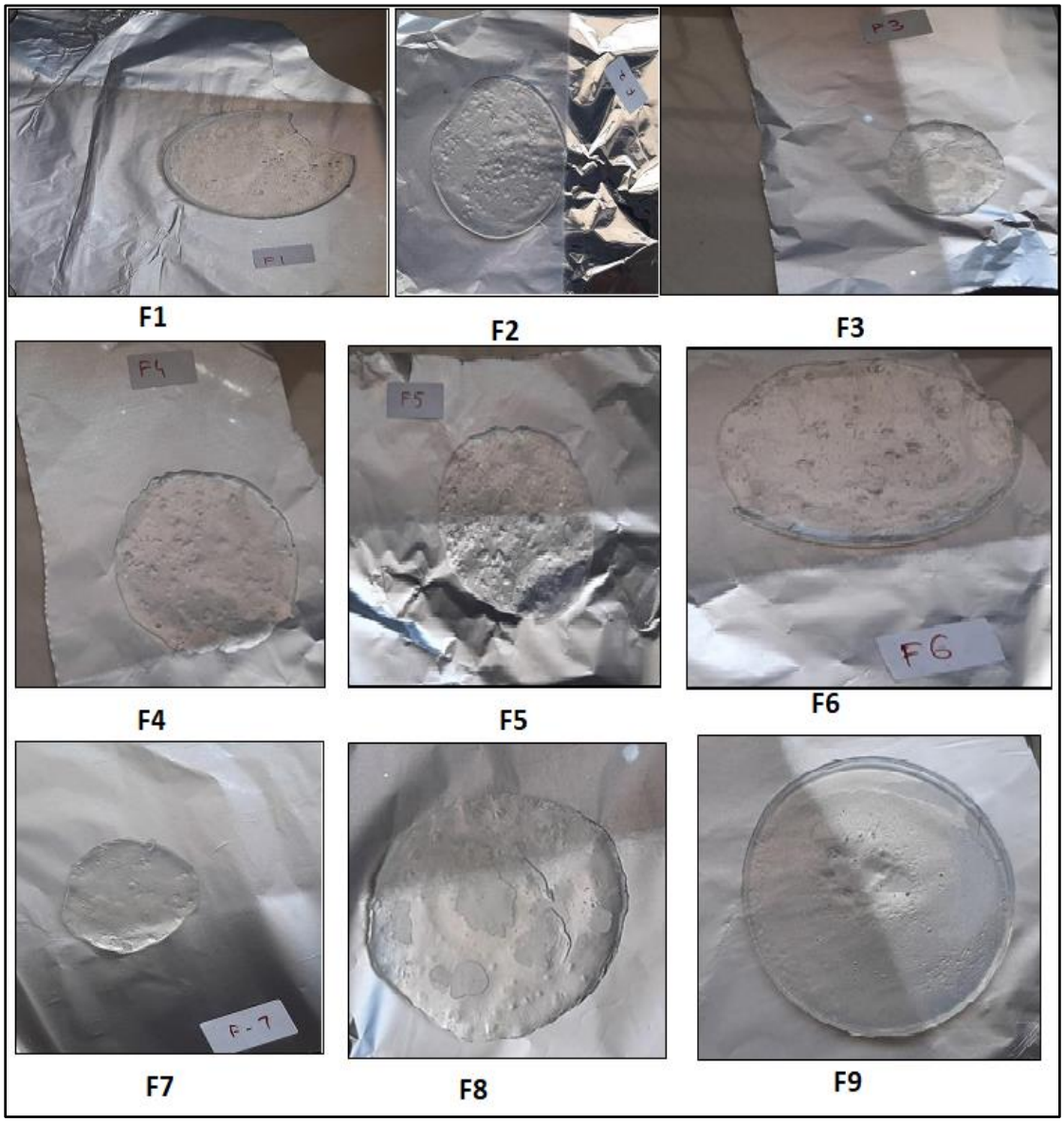

Figure No.7: Transdermal formulations of Nebivolol F1 to F9.

Table No.9: Physical characteristics of transdermal patches

Formulation code	Thickness (mm)	Folding endurance	Drug Content (%)	Surface pH
F1	0.200 ±0.88	278 ±4.72	97.9 ±1.24	5.99
F2	0.216 ±0.72	259 ±2.51	98.00 ±1.41	6.23
F3	0.310 ±0.55	265 ±3.46	98.00 ±1.73	6.14
F4	0.190 ±0.99	270 ±3.18	98.21 ±1.87	6.14
F5	0.169 ±0.39	290 ±4.72	98.31 ±1.15	6.50
F6	0.232 ±0.92	242 ±3.05	97.72 ±1.45	6.59
F7	0.198 ±0.67	256 ±3.13	98.10 ±1.51	6.01
F8	0.321 ±0.25	280 ±4.16	97.96 ±1.42	5.88
F9	0.334 ±0.18	278 ±4.32	98.23 ±1.36	5.01

Weight Uniformity

The weights ranged between 50.5 ± 0.75 mg and 52.15 ± 2.15 mg, which indicates that different batches patch weights, were relatively similar .

Table No.10: Weight uniformity of transdermal patch formulations

Formulation code	W1 (gm)	W2 (gm)	W3 (gm)	Average weight (gm)
F1	5.40	5.39	5.40	5.396 ± 0.67
F2	5.08	5.13	5.13	5.113 ± 0.58
F3	5.20	5.22	5.24	5.22 ± 0.12
F4	5.04	5.03	5.03	5.03 ± 0.50
F5	5.24	5.21	5.21	5.22 ± 0.12
F6	5.41	5.42	5.45	5.42 ± 0.31
F7	5.02	4.98	5.06	5.02 ± 0.10
F8	5.05	5.04	5.04	5.043± 0,10
F9	5.21	5.23	5.23	5.22 ± 0.12

Percentage Moisture Absorption

The percentage moisture uptake for HPMC-EC was found to be in the range of 1.2 % to 4.8 %, which might be attributable to the polymer's hydrophilic and hydrophobic properties.

Percentage Moisture Loss

The patches remained stable and became a totally free from becoming completely dry and brittle due to the decreased moisture content in the formulations, which also protects the material against microbial contamination and bulkiness as represented in Table11.

Swellability

The percentage of Nebivolol loaded HPMC E50 and EC patches that swelled was about 35%, indicating significant swelling as depicted in Table 11.

TableNo.11: Physicochemical characteristics of transdermal patches

Formulation code	Swellability(%)	Moisture uptake(%)	Moisture loss (%)
F1	25.52 ±1.9	2.72 ±0.67	1.93 ±0.54
F2	26.14 ±1.03	3.09 ±0.76	2.31 ±0.97
F3	29.98 ±0.98	3.66 ±0.73	2.23 ±0.91
F4	43.46 ±1.16	2.58 ±1.65	3.68 ±1.06
F5	23.30 ±0.86	2.51 ±0.98	2.16 ±0.80
F6	36.60 ±0.99	2.69 ±0.70	3.00 ±0.99
F7	36.83 ±1.10	2.96 ±0.96	3.13 ±1.20
F8	31.60 ±1.16	2.83 ±1.19	2.68 ±0.79
F9	26.10 ±0.98	2.33 ±1.20	2.99 ±1.01

In-Vitro Drug Release Study

For a low dose of Nebivolol, the cumulative percent drug release was higher in the case of Ethyl cellulose containing polymer matrix, which released 4.67 mg /cm^2/12 h. The cumulative % drug release for all formulation ranges from 38.97 ±1.10 to 45.98 ±2.12 in 12h as shown in Table 12.

Table No.12: Cumulative percentage drug released of Nebivolol transdermal patches [F1-F9]

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	% Cumulative Drug Release								
1	0.22 ±0.87	0.94 ±0.44	1.24 ±0.27	1.01 ±0.19	0.82 ±0.13	0.62 ±0.67	0.54 ±0.23	1.51 ±0.05	0.43 ±0.13
2	3.37 ±1.26	4.09 ±1.33	4.99 ±1.33	5 ±1.8	2 ±1.4	3.03 ±1.0	3.79 ±0.87	4 ±0.76	2.73 ±0.20
3	8.01 ±1.33	8.23 ±1.45	8.01 ±1.45	9.23 ±1.22	4.69 ±2.4	7.87 ±1.05	8.54 ±1.0	9.54 ±1	6.35 ±0.76
4	12 ±1.89	11.98 ±1.72	12.23 ±1.72	13.95 ±1.38	9.3 ±1.49	13.76 ±1.23	13.2 ±0.83	14.53 ±0.79	11.31 ±0.99
5	17.1 ±2.0	15.76 ±1.63	16 ±1.63	17.66 ±1.59	15.01 ±2.48	18.06 ±2.4	17.42 ±1.02	19.99 ±1.01	15 ±1.0
6	22.13 ±2.3	20.98 ±1.82	22.1 ±1.82	21.74 ±1.66	21.9 ±2.02	23.43 ±1.29	22 ±2.03	24.01 ±1.23	19.8 ±1.07

7	28.9 ±1.67	26.77 ±1.25	25.97 ±1.25	25.23 ±1.91	27.63 ±1.30	28.01 ±2.30	26.76 ±1.99	28.88 ±0.45	23.05 ±1.15
8	34.02 ±1.31	31.23 ±1.19	29.76 ±1.19	29.45 ±1.83	33.86 ±2.10	33 ±2.54	31.32 ±1.65	35 ±0.99	27.76 ±1.11
9	37.67 ±1.63	35.88 ±1.31	34.39 ±1.32	34.34 ±1.77	39.15 ±2.56	36.09 ±2.0	36.17 ±1.90	37.23 ±1.45	30.09 ±0.54
10	40.03 ±1.26	41 ±1.67	38.74 ±1.83	38 ±1.45	42.02 ±1.99	41.99 ±1,14	39 ±2.0	39 ±2.05	34.98 ±1.45
11	41.89 ±2.3	42.42 ±1.33	39 ±1.95	39.11 ±1.21	45.29 ±2.54	42.01 ±2.6	40.9 ±1.52	40.12 ±2.12	37.8 ±1.47
12	43 ±1.72	40 ±1.72	39.85 ±1.18	40.24 ±1.07	45.98 ±2.12	42.50 ±2.03	41.01 ±1.34	43.99 ±2.03	38.97 ±1.10

Figure No. 8: Diffusion cell apparatus along with egg shell membrane

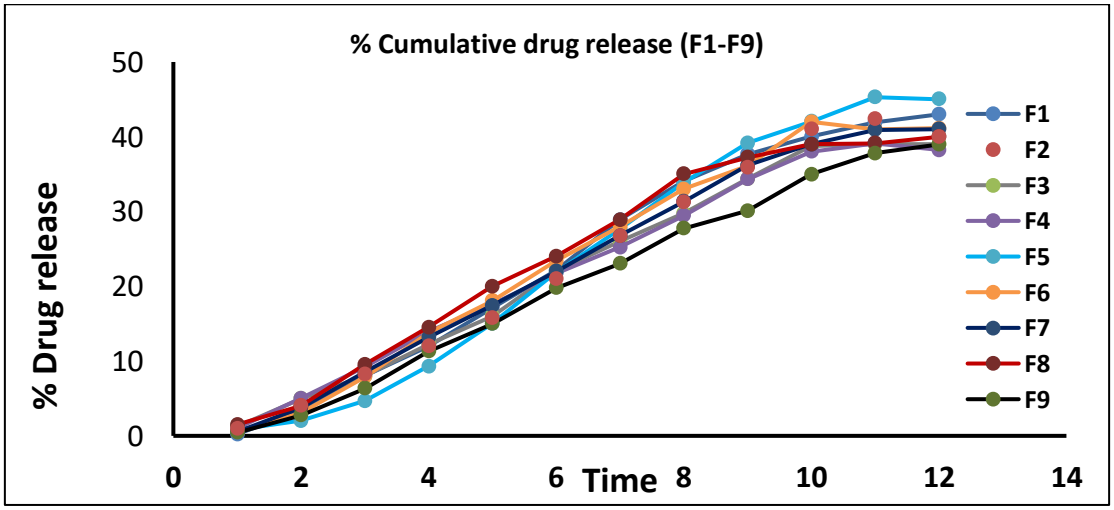

Figure No.9: Cumulative drug release of Nebivolol through transdermal patches [F1-F9]

In-Vitro **Flux Calculation**

Among all the formulation, F5 batch showed maximum of flux of 64.37 ±1.06 µg cm^{-2} h^{-1} through egg membrane.

Table No.13: Flux Permeability study

Formulation code	$Flux^b$ (µg cm^{-2} h^{-1})
F1	60.2 ±0.27
F2	56.07±0.88
F3	55.85 ±0.88
F4	56.41 ±1.26
F5	64.37 ±1.06
F6	59.55 ±0.60
F7	58.99 ±0.60
F8	61.62 ±0.69
F9	54.61 ±1.73

Stability Studies

The stability study for optimized formulation F5 was conducted at 40^0 C, 75% RH as per ICH guideline. The formulation F5 were evaluated for the drug content and *in-vitro* % drug release after 1, 2 and 3 months is shown in Table 14 Therefore, it was ascertained that, the transdermal patches of Nebivolol could be stored for a period of at least 2 years.

It was also observed that there was no significant variation in the physical appearance, average weight, and moisture uptake after placing the patches at various temperature and humidity conditions for a period of 3 months.[54]

Table No.14: Stability study for optimized formulation F5 at 40±2ºC+75% RH

		Accelerated term: (40°C ± 2°C/75 ± 5% RH)		
Sr.no.	**Parameters**	**30 days**	**60 days**	**90 days**
1	**% Total drug content**	98.31 ±1.15	98.25 ±1.00	97.99 ±0.15
2	***In-vitro* drug release**	45.98 ±2.12	45.0 ±1.23	45.0 ±0.98

Conclusion

Transdermal patch of Nebivolol utilizing different polymers such as HPMC E50, PVP, Eudragit RS100, and ethyl cellulose and plasticizers such as PEG-400 and Dibutyl

phthalate and DMSO as a penetration enhancer via solvent casting method for a low dose of the drug. The FTIR spectrophotometer was used to obtain the spectra of the drug and physical mixtures of drug-polymers, which demonstrated the lack of incompatibility between the drug (Nebivolol) and the physical mixture of polymers. On the developed transdermal patches, physicochemical properties, in-vitro permeation investigations, content uniformity, percent Swellability, percent Moisture absorption, percent Moisture loss, Folding endurance trials were all conducted. After all of the assessments, it was discovered that the F5 formulation is the best of the nine formulations. Kinetic study was done analyzing zero order model, first order model, Higuchi model and Korsmeyer Peppas model and it was observed that the optimized batch followed zero order and non-fickian diffusion model. The best batch was then subjected to flux calculations and stability tests and was confirmed to be stable according to ICH Q1C norms.

References

1. *Mycek MJ, Harvey RA, Champe RC. Lippincott's Illustrated Reviews Pharmacology. Philadelphia: Lippincott-Raven 2009.*
2. *Breitkreutz D, Mirancea N, Nischt R. Basement membranes in skin: Unique matrix structures with diverse functions? Histochemistry and Cell Biology 2009; 132(1):1–10.*
3. *McGrath JA, Eady RA, Pope FM. Rook's Textbook of Dermatology (7th ed.). Blackwell Publishing 2004:3.1–3.6.*
4. *Tortora, G. J. and Derrickson, B. Principles of anatomy and physiology. 11th Edition. John Wiley and Sons, 2007; 145-170.*
5. *Menon, G. K., Cleary, G. W. and Lane, M. E. The structure and function of the stratum corneum. International Journal of Pharmaceutics. 2012, 435(1), 3-9.*
6. *Jepps, O. G., Dancik, Y., Anissimov, Y. G. and Roberts, M. S. Modeling the human skin barrier: Towards a better understanding of dermal absorption. Advanced Drug Delivery Reviews 2013; 65(2), 152-168.*
7. *Indian pharmacopoeia, 8th edition volume I.2018, 888-889.*
8. *Elgindy N, Samy W. Evaluation of the mechanical properties and drug release of cross- linked Eudragit films containing metronidazole. International journal of pharmaceutics. 2009 Jul 6;376(1-2):1-6.*
9. *Snook KA, Robert Van Ess II, Werner JR, Clement RS, Ocon-Grove OM, Dodds JW, Ryan KJ, Acosta EP, Zurlo JJ, Mulvihill ML. Transdermal delivery of enfuvirtide in a porcine model using a low-frequency, low-power ultrasound transducer patch. Ultrasound in medicine & biology. 2019 Feb 1;45(2):513-25.*
10. *Zhao D, Chen Z, Hu S, Lin J, Shao Z, Wang G, Xiao W, Zheng Y, Zhang Z, Shi Y, Li Z. Efficacy and safety of loxoprofen hydrogel transdermal patch versus loxoprofen tablet in Chinese patients with myalgia: a double-blind, double-dummy, parallel-group, randomized, controlled, non-inferiority trial. Clinical drug investigation. 2019 Apr;39(4):369-77.*
11. *Bukala BR, Browning M, Cowen PJ, Harmer CJ, Murphy SE. Overnight transdermal scopolamine patch administration has no clear effect on cognition and emotional processing in healthy volunteers. Journal of Psychopharmacology. 2019 Feb;33(2):255- 7.*
12. *Li Z, Fang X, Yu D. Transdermal drug delivery systems and their use in obesity treatment. International Journal of Molecular Sciences. 2021 Nov 25;22(23):12754.*

13. *Stanekzai A, Sudhakar CK, Zhakfar AM, Karan VS. Recent approaches in transdermal drug delivery system. Research Journal of Pharmacy and Technology. 2019 Sep 1;12(9):4550-8.*
14. *Saleem MN, Idris M. Formulation design and development of a unani transdermal patch for antiemetic therapy and its pharmaceutical evaluation. Scientifica. 2016 Jun 15;2016.*
15. *Park H, Otte A, Park K. Evolution of drug delivery systems: From 1950 to 2020 and beyond. Journal of Controlled Release. 2022 Feb 1;342:53-65..*
16. *Kaur G, Grewal J, Jyoti K, Jain UK, Chandra R, Madan J. Oral controlled and sustained drug delivery systems: Concepts, advances, preclinical, and clinical status. InDrug targeting and stimuli sensitive drug delivery systems 2018 Jan 1 (pp. 567-626). William Andrew Publishing.*
17. *Wiedersberg S, Guy RH. Transdermal drug delivery: 30+ years of war and still fighting!. Journal of controlled Release. 2014 Sep 28;190:150-6.*
18. *Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum. Pharmaceutics. 2015 Oct 22;7(4):438-70.*
19. *Wong, W.F.; Ang, K.P.; Sethi, G.; Looi, C.Y. Recent Advancement of Medical Patch for Transdermal Drug Delivery. Medicina 2023, 59, 778..*
20. *Messerli FH, Schmieder RE, Nunez BD. Heterogeneous pathophysiology of essential hypertension: implications for therapy. American Heart Journal. 1986 Oct 1;112(4):886-93.*
21. *Babu AS, Padmakumar R, Nayak K, Shetty R, Mohapatra AK, Maiya AG. Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: A randomized clinical trial. Indian heart journal. 2019 Mar 1;71(2):161-5.*
22. *Chaturvedi S, Garg A. An insight of techniques for the assessment of permeation flux across the skin for optimization of topical and transdermal drug delivery systems. Journal of Drug Delivery Science and Technology. 2021 Apr 1;62:102355.*