RESEARCH ARTICLE

Formulation design preparation and *in vitro* characterization of nebivolol transdermal patches

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The aim of the present investigation is to develop and evaluate transdermal patches of nebivolol. The transdermal patches of nebivolol were prepared by solvent evaporation technique. Twelve formulations of nebivolol patches were prepared that composed of ethyl cellulose (EC) with hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose with polyvinyl pyrrolidine (PVP) in different ratios of 1:2, 1:4, 1:6, 2:1, 4:1, and 6:1 w/w, as film former. Polyvinyl alcohol (4% w/v) was used to prepare the backing membrane. All formulations contained Tween 80 (4% v/w) as penetration enhancer and propylene glycol (40% v/w) as plasticizer in dimethyl formamide as solvent system. The prepared transdermal patches of nebivolol were evaluated for thickness, mass variation, drug content, moisture content, moisture vapor transmission, folding endurance, tensile strength, *ex vivo* drug permeation study, drug release kinetics, scanning electron microscopy, primary skin irritancy study, and stability study. The physicochemical interactions between nebivolol and different polymers were studied by Fourier Transform Infrared (FTIR). The maximum drug release in 24 h was 95.185% (T2, HPMC:EC is 1:4), which is significant ($P < 0.05$). Furthermore, the formulation T2 showed maximum skin permeation (13.93 mg/cm^2/h) in comparison with other formulations. The mechanical properties and tensile strength revealed that the formulations were found to be strong enough but not brittle. FTIR studies did not show any evidence of interaction between the drug and the polymers. Nebivolol matrix-type transdermal therapeutic systems could be prepared with the required flux having suitable mechanical properties.

Keywords: *Folding endurance, in vitro drug release, nebivolol, permeation enhancer, transdermal patches*

INTRODUCTION

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. Transdermal route has advantages over conventional modes of drug administration as it avoids hepatic first pass metabolism and improves patient compliance.[1] However, the highly organized structure of stratum cornea forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery.[2]

Nebivolol is a highly cardioselective β_1-receptor blocker with nitric oxide-potentiating vasodilatory effect and used in 10 mg dose for the treatment of hypertension. It is a white to almost white powder that is soluble in methanol, dimethylsulfoxide (DMS), and *NN*-dimethylformamide (DMF), sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene. The active isomer (D-nebivolol) has an effective half-life of about 12 h. Mean peak plasma nebivolol concentrations occur approximately 1.5–4 h postdosing. The *in vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin.[3] There are no reports on transdermal patches

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of nebivolol. The objective of the present work is to develop the nebivolol monolithic transdermal patches and evaluate their *in vitro* drug release pattern and mechanical properties.

MATERIALS AND METHODS

Nebivolol was obtained as gift sample from Glenmark Pvt. Ltd, Mumbai, India. Ethyl cellulose (EC-20 cps), polyvinyl pyrrolidone (PVP-K30), hydroxyl propyl methyl cellulose (HPMC-K4M), polyvinyl alcohol (PVA) and dibutyl phthalate were procured from S.D. Fine Chem. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade and procured from an authorized dealer.

Drug partition coefficient

The partition coefficient study was performed using *n*-octanol as the oil phase and phosphate buffer (pH 7.4) as the aqueous phase. The two phases were mixed in equal quantities and were saturated with each other on a mechanical water bath shaker (100 rpm) at 37°C for 24 h. The saturated phases were separated by centrifugation at 2000 rpm. Standard plots of the drug were prepared from both phosphate buffer pH 7.4 and *n*-octanol. Equal volumes (10 mL) of the two phases were placed in hexaplicate in conical flasks and 100 mg of drug was added to each flask. The flasks were shaken (100 rpm) at 37°C for 6 h to achieve complete partitioning. The two phases were separated by centrifugation at 1000 rpm for 5 min and were then analyzed for respective drug contents.[4]

Preparation of the transdermal patches

Matrix-type transdermal patches containing nebivolol were prepared using 3 polymers in 2 combinations (EC with HPMC K4M and EC with PVP K30) and in different proportions (1:2, 1:4, 1:6, 2:1, 4:1, and 6:1 w/w) by solvent evaporation technique using cylindrical glass molds with both sides open.[5] The polymers like HPMC, EC, and PVP were selected as rate controlling polymers as they are biodegradable, easily available, economic, and nontoxic. The purpose of taking mixture of two polymers, one polymer is hydrophobic (EC) and another is hydrophilic, which may release the drug in a controlled manner with a definite rate. The bottom of the mold was wrapped with aluminum foil. The backing membrane was cast by pouring 4% w/v PVA solution in distilled water followed by drying at 60°C for 6 h in a hot air oven. The polymers of each combination were dissolved in dimethyl formamide. Propylene glycol (40% v/w of polymer weight) was added as plasticizer and Tween 80 (4% v/w of polymer weight) was used as permeation enhancer. Nebivolol (11 mg) was added and stirred with a mechanical stirrer to get a homogeneous dispersion. The dispersion (2 mL) was cast on the prepared PVA backing membrane in each mold. The rate of evaporation was controlled by inverting a funnel over the mold and dried at 40°C for 6 h in hot air oven and the films were cut into small patches (3.24 cm^2) containing 3.25 mg of nebivolol and stored between sheets of wax paper in a desiccator.

Characterization of transdermal patches

Thickness of the films

The thickness of the patches was assessed at 6 different points of the patches with a micrometer (Mitutoyo Co., Japan) and mean values were calculated. For each formulation 3 randomly selected patches were used.[6]

Mass variation

The patches were subjected to mass variation by individually weighing 10 randomly selected patches. Such determinations were carried out for each formulation.[7]

Drug content

Each patch was dissolved in 5 mL of dimethyl formamide and the volume was made up to 10 mL with phosphate buffer (pH 7.4). The dimethyl formamide was evaporated using a rotary vacuum evaporator at 45°C. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45-μm membrane, diluted suitably and the drug content of test solutions (against blank solution) were measured at 281 nm by using double beam UV–Vis spectrophotometer (Thermospectronic-1, UK).[7]

Moisture content study

The prepared patches were weighed and kept in desiccator containing activated silica at room temperature for 24 h. The individual films were weighed on every alternate day until a constant weight was achieved. The percentage of moisture content was calculated by determining the difference between initial and final weight with respect to final weight.[8]

Moisture vapor transmission

This study involves glass vials of equal diameter (1.4 mm) as transmission cells. The transdermal patch of known thickness was fixed over the edge of the glass vial containing 3 g of fused calcium chloride as a desiccant by using an adhesive. The initial weight of cells were measured and kept in a humidity chamber 80%±5% RH at 27°C±2°C for 24 h (containing saturated solution of potassium chloride, 200 mL).[5,8] The cells were verified regarding weight periodically over a period of 24 h. Calculations are made by using the following formula:

$$\text{WVT rate} = W \times L/S \quad (1)$$

Where, W is water vapor transmitted (g), L is thickness of the transdermal patch (cm) and S is exposed surface area (cm^2).

Determination of folding endurance

Folding endurance of the film was determined manually by folding a small strip of the film at the same place till it breaks. The maximum number of folding operations done at the same place of the film without breaking or cracking, gives the value of folding endurance, where the cracking point of the films were considered as the end point.[9]

Elongation and tensile strength measurement

The tensile strength measurement was made using an instrument assembled in the laboratory and following the method of Sadhana *et al*.[10] The films were fixed individually to the assembly; the required weights to break the films were noted. The percentage of elongation of the films was measured by attaching a pointer mounted on the assembly. Tensile strength was calculated by using the following formula:

$$\text{Tensile strength} = (\text{break force}/a \times b) \times (1 + L/l) \quad (2)$$

Where a is width, b is thickness, L is length, and l is elongation of the films.

In vitro skin permeation study

Films measuring 3.14 cm^2 were subjected to an *in vitro* permeation study using a modified Keshary–Chien diffusion cell (cell capacity, 100 mL). Male guinea pigs (Hartley strain, $n=5$ for each formulation), each weighing 250–300 g and 6 months of age were used in the present study. They were housed in cages in the animal house under controlled temperature 27°C±2°C and light conditions. They were fed with a standard laboratory diet; water was provided ad libitum. Guinea pigs were killed by cervical dislocation and dorsal skin was removed. After removing the epidermal hairs and subcutaneous fat, the skin was treated with 0.32 M ammonia solution for 35 min. The skin, so obtained, was examined microscopically for any possible damage. The skin thus obtained was kept in normal saline solution and stored at 4°C±1°C. The treated skin was placed overnight in contact with the receptor phase, phosphate buffer pH 7.4. Guinea pig dorsal skin was clamped between the donor and recipient compartments.[11,12]

The film was placed in the donor compartment over the skin and covered with Para film. The temperature of receptor phase was maintained at 37°C±1°C throughout the experiment. The compartment was in contact with the ambient environment. The amount of drug permeated through guinea pig skin was determined by withdrawing samples of 1 mL at predetermined time intervals (1 h) and replacing them with an equal volume of prewarmed phosphate buffer pH 7.4 at 37°C±1°C. The samples were then analyzed for drug content spectrophotometrically at λ_{max} 281 nm using double beam UV–Vis spectrophotometer.

Drug release kinetic study

In order to study the exact mechanism of drug release from the nebivolol transdermal patches, drug release data were analyzed according to zero order,[13] first order,[14] and Korsmeyer–Peppas.[15,16] The criterion for selecting the most appropriate model was chosen on the basis of goodness-of-fit test.

Drug–polymer interaction study

To study the possible interaction between nebivolol and polymeric materials of the patches, infrared (IR) spectroscopy was carried out on pure substances and their physical mixtures. The IR spectrum was recorded using IR Spectrophotometer (Perkin–Elmer FT-IR, Perkin Elmer Inst., USA) by KBr pellet method.[17]

Scanning electron microscopy

The scanning electron microscopy (SEM) analysis was carried out using a scanning electron microscope (LEO, 435 VP, U.K., RRL, Bhubaneswar, Orissa). Prior to examination, samples were mounted on an aluminum stub using a double-sided adhesive tape and making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.[18]

Primary skin irritancy studies

Albino rabbits of both sexes, each weighing 1.5–2.0 kg and 24 months of age were used in this study ($n=5$ in each group). They were housed in cages in the animal house under controlled temperature (27°C±2°C) and light conditions. They were fed a standard laboratory diet; water was provided ad libitum. The dorsal surface of the rabbits was cleared and the hairs were removed by shaving. The skin was cleared with rectified spirit. The patches were applied to the shaved skin of rabbits and secured using adhesive tape USP (Leucoplast TM). On one side of the back, a control patch (without any drug, group I) and on the other side an experimental patch (group II) were secured. A 0.8% (V/V) aqueous solution of formaldehyde was applied as a standard irritant (group III) and its effect was compared with test. The animals were observed for any sign of erythema or edema for a period of 7 days.[19] Ethical clearance for the handling of experimental animals was obtained from the institutional animal ethical committee (IAEC - Regd. No. JCP/ 09/ 72/ IAEC/ 0010)) formed for this purpose.

Stability study

Stability studies were performed according to standard stability protocol.[20] The effect of aging on physical appearance, drug content, and on other properties were studied by packing the best selected transdermal polymeric films in properly sealed aluminum foils and then the film was stored in a dessicator at ambient conditions for a study period of 60 days. The samples were analyzed for drug content every 2 weeks by UV–Vis spectrophotometer at 281 nm. Stability study was also carried out by measuring the change in thickness, folding endurance, and moisture content.

Statistical analysis

All the data were statistically verified with standard deviation, standard error mean, and one-way ANOVA at 5% level of significance.[21]

RESULTS AND DISCUSSION

n-Octanol and phosphate buffer (pH 7.4) are considered to be the standard system for determining the drug partition coefficient between guinea pig skin and *in vitro* fluid. The logarithmic value of the partition coefficient was found to be 0.81. The results obtained indicated that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch. The transdermal patches were prepared by using nebivolol and the rate controlling polymers in different proportions as represented in Table 1. The generalized transdermal patches protocol depends on the nature of ingredients, successful casting and optimization at every preparative step. Nebivolol transdermal patches could be prepared successfully using solvent evaporation technique. The physical appearance of all transdermal patches was translucent and nonsticky. The physicochemical properties of the nebivolol transdermal patches are presented in Tables 2 and 3. The thickness of patches varied from 330±0.76 to 410±1.09 μm (n=5); casting of the rate-controlling membrane increased the thickness [Table 2]. The mass was found to be uniform in the prepared batches and varied from 16.60±0.60 to 29.87±0.27 mg per patch (n=5). For various formulations, the drug content varied from 54.75%±0.99% to 102.28%±0.59% per patch. The T6 (EC:HPMC, 1:6) showed lowest drug content, which may be either due to improper solubility of drug in polymeric solution or uneven distribution of drug in transdermal patch. The formulation T3 showed maximum drug content (105.80%±0.84%). The drug content analysis of the prepared formulations has shown that the process employed to prepare the patches in this study was capable of giving films with a uniform drug content and minimum batch variability. The moisture content of all the formulations is shown in Table 2. The moisture content is increased as hydrophilic polymer concentration increased and vice versa. Among all the formulations, the lowest moisture content was found in formulation T4. The lower moisture content in the formulations helps them to remain stable. Furthermore, completely dried and brittle films limit the bulkiness of the patches. The patch (T2) formulated with EC and HPMC (1:4) showed maximum MVT of 13.93%±0.31%, which can be attributed to the hydrophilic nature of the polymer (HPMC). The casting of the HPMC-drug reservoir

Table 1: Formulation design of nebivolol transdermal patches

Ingredients (mg) Formulations	Nebivolol (mg)	EC: HPMC	EC: PVP	Propyleneglycol (%)*	Tween 80 (%)*
T1	11	1:2	-	40	4
T2	11	1:4	-	40	4
T3	11	1:6	-	40	4
T4	11	2:1	-	40	4
T5	11	4:1	-	40	4
T6	11	6:1	-	40	4
T7	11	-	1:2	40	4
T8	11	-	1:4	40	4
T9	11	-	1:6	40	4
T10	11	-	2:1	40	4
T11	11	-	4:1	40	4
T12	11	-	6:1	40	4

(%), Percentage of polymer weight; EC: ethyl cellulose, HPMC: hydroxy propyl methyl cellulose, PVP: poly vinyl pyrrolidine

Table 2: Physical parameters of nebivolol transdermal patches

Formulation code	Thickness (μm) mean±SD	Mass (mg) mean±SD	Drug content (%) mean±SD	Moisture content (%) mean±SD	MVT (%) mean±SD
T1	380±0.18	21.14±0.40	99.20±0.67	8.36±1.02	11.05±0.11
T2	370±0.87	29.87±0.27	102.28±0.59	8.73±0.43	13.93±0.31
T3	410±1.09	27.01±0.56	105.80±0.84	10.73±0.11	12.43±0.55
T4	390±1.11	16.60±0.60	70.59±0.39	6.06±0.31	8.02±0.26
T5	330±0.85	23.51±0.70	61.79±0.79	11.5±0.25	7.24±0.19
T6	350±0.69	19.57±0.24	54.75±0.99	12.8±0.15	6.82±0.13
T7	350±0.77	22.48±0.26	97.00±1.15	14.22±0.51	10.66±0.58
T8	330±0.76	20.63±0.23	100.08±0.91	16.41±0.69	12.19±0.61
T9	350±1.16	29.83±0.11	98.32±0.64	18.50±0.37	13.61±0.49
T10	340±0.66	17.93±0.32	86.00±0.79	11.73±0.31	9.69±0.81
T11	360±1.12	19.44±0.53	79.84±0.87	8.06±0.33	6.32±0.41
T12	350±0.81	18.83±0.49	81.60±1.07	7.83±0.21	5.93±0.72

All values are represented as mean±standard deviation (n=5). Standard error of mean < 0.669

Table 3: Physical parameters, *ex vivo* skin permeation, and permeation rate study of nebivolol transdermal patches

Formulation code	Folding endurance mean±SD	TS (kg/mm²) mean±SD	Q_{24} permeation[a] mean±SD	Permeation rate (mg/cm²/h) mean±SD
T1	75±1.04	0.31±0.038	84.795±0.81	11.05±0.12
T2	89±1.01	2.39±0.208	95.185±0.29	13.93±0.09
T3	103±1.12	2.41±0.311	69.634±0.69	12.43±0.19
T4	62±0.98	1.58±0.052	65.657±0.83	8.02±0.11
T5	54±0.88	2.15±0.077	88.768±0.77	7.24±0.21
T6	56±1.18	2.35±0.067	60.996±0.81	6.82±0.16
T7	91±0.80	0.13±0.021	60.885±0.90	10.66±0.23
T8	98±1.11	0.56±0.014	93.299±1.02	12.19±0.12
T9	112±1.07	0.83±0.047	91.126±0.66	13.61±0.22
T10	74±0.79	1.47±0.051	77.584±0.72	9.69±0.27
T11	68±0.75	2.20±0.091	80.874±0.61	6.32±0.31
T12	64±0.82	0.66±0.052	82.629±0.81	5.93±0.28

ANOVA

Source of variation	SS	df	MS	*F*	*P* value	*F* crit
Between groups	62858.41	5	13852.9	4.563342	1.1610	3.23887
Within groups	17.4752	16	0.30357			
Total	62875.89	21				

Folding endurance is expressed in terms of no. of folding, TS: tensile strength, [a]Cumulative % of drug permeated in 24 h of study, All values are represented as mean±standard deviation (n=3), Standard error of mean < 0.681

with the hydrophobic rate-controlling membrane of EC decreased the values of the moisture vapor transmission rate accordingly (T6). The folding endurance measures the ability of patch to withstand rupture and its strength. The result indicated that the folding endurance was in the range of 54±0.88 to 112±1.07 (n=3). The patch T9 has the highest folding endurance while T5 has the least [Table 3]. The tensile strength gives an indication of the strength and elasticity of the film. A soft and weak polymer provides low TS; a hard and brittle polymer or a soft and tough polymer offers moderate TS, whereas a hard and tough polymer is characterized by high TS. It is suggested that a good transdermal patch should have a relatively high TS. The result of tensile strength is shown in Table 3. The transdermal formulations T2 and T3 exhibited greater values of tensile strength (2.39±0.208 and 2.41±0.311 kg/mm²).

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and the nature of formulation, as well as physiological and physicochemical properties of the biological membrane. In this study, different formulations exhibited variable amounts of nebivolol release pattern through guinea pig skin in the *in vitro* studies. To examine the drug permeation kinetics and mechanism, the data were fitted to models representing zero order, first order, and Korsmeyer–Peppas. Drug permeation profiles from different formulations are shown in Figures 4 and 5. It was found that 95.185% of the drug was released within 24 h from T2 following zero-order kinetics. It indicates that the patch can be applied once in a day. Therefore, rate-controlling membranes of ethyl cellulose were cast with the aim to achieve controlled release of nebivolol from drug reservoirs of HPMC. There was improvement in the drug permeability across guinea pig skin in the formulations containing a permeation enhancer. The permeation rate for formulations T1–T12 was in the range 5.93–13.93 mg/cm²/h. The highest permeation rate was observed in the patches T2 containing ethyl cellulose and HPMC (1:4), whereas the least permeation rate was observed in the patches T12 containing ethyl cellulose and PVP (6:1). The kinetic parameters of drug permeation for different formulations are presented in Table 4. The zero-order plots of T2 and T8 were found to be fairly linear, as indicated by their high regression values. Therefore, it was ascertained that the drug permeation from these formulations could follow either near-zero or zero-order kinetics. Hence, to confirm the exact mechanism of drug permeation from these patches, the data were fitted according to the Korsmeyer–Peppas model. Korsmeyer *et al.* used a simple empirical equation to describe the general solute release behavior from controlled release polymer matrices: $m_t / m_\infty = kt^n$ where m_t / m_∞ is the fraction of drug released, k is the kinetic constant, t is release time, and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders, and discs, regardless of the release mechanism. The value of n gives an indication of the release mechanism: when n=1, the release rate is independent of time (zero-order) (case II transport), n=0.5 stands for Fickian diffusion and when $0.5 < n < 1.0$, diffusion and non-Fickian transport are implicated. Lastly, when $n > 1.0$, super case II transport is apparent. Among all the formulations, formulation T2 released maximum amount of drug in a more constant manner in comparison to other formulations following zero-order kinetics with case II transport mechanism.

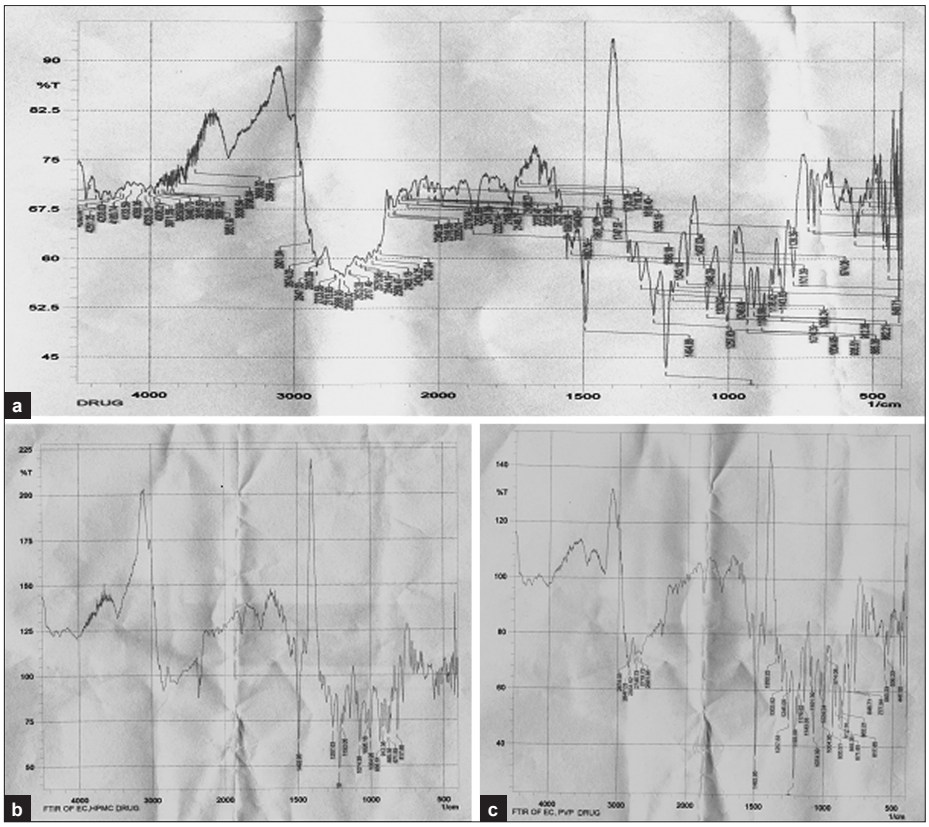

Figure 1: FT-IR spectra and analysis region of nebivolol (a), transdermal patch formulation containing EC and HPMC (b), transdermal patch formulation containing EC and PVP (c)

Table 4. *In vitro* kinetics study of nebivolol permeation across guinea pig skin from transdermal patches

Formulation code	Zero order		First order		Korsmeyer–Peppas	
	k_0 (mg/h)	R^2	k_0 (mg/h)	R^2	R^2	n
T1	0.354	0.895	0.144	0.890	0.900	0.876
T2	0.078	0.965	0.098	0.901	0.879	0.985
T3	0.221	0.876	0.201	0.891	0.873	1.003
T4	0.109	0.938	0.110	0.960	0.963	1.008
T5	0.046	0.781	0.077	0.809	0.803	0.896
T6	0.047	0.778	0.127	0.801	0.823	0.945
T7	0.126	0.789	0.029	0.863	0.816	1.102
T8	0.029	0.937	0.087	0.911	0.805	1.009
T9	0.308	0.935	0.108	0.937	0.881	0.889
T10	0.087	0.912	0.092	0.933	0.891	0.992
T11	0.105	0.863	0.101	0.903	0.861	1.070
T12	0.086	0.812	0.079	0.899	0.789	1.011

R^2, Coefficient of regression, *n*, diffusion exponent related to mechanism of drug release, according to equation, $m_t / m_\infty = kt^n$

The interaction between the drug and the carrier often leads to identifiable changes in the FT-IR profile of solid systems. FT-IR spectra for pure drug, carrier, and transdermal patch formulation T2 (1:4 drug/polymer ratios) have been depicted in Figure 1. The spectrum of transdermal patch formulation was equivalent to the addition spectrum of polymer and drug indicating no interaction occurring in the simple physical mixture of drug and polymer. The scanning electron microscopy study of transdermal patch T2 revealed that the drug is present in the polymer in matrix type as depicted in Figures 2 and 3. No signs of erythema, edema, or ulceration were observed on the skin of albino rabbits after 7 days, indicating that the transdermal patches are nonirritant to skin. The accelerated stability studies were performed according to ICH guidelines for 60 days and the results were found to be stable in varying temperatures as shown in table 5. These were further verified with one-way ANOVA method and found to be significant for *F* (2.71553) at 5% level of significance ($P < 0.05$).

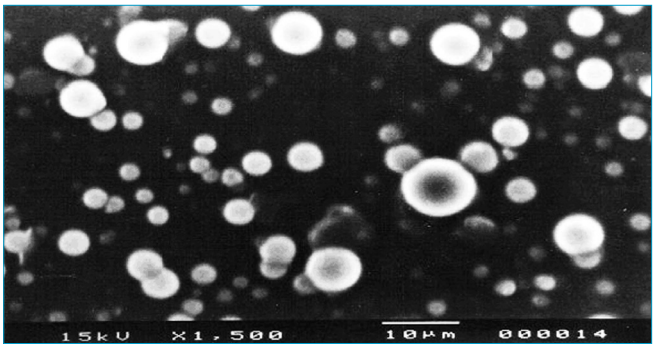

Figure 2: The scanning electron microscopy microphotographs of transdermal patch before skin permeation study at resolution 15 kV × 1500

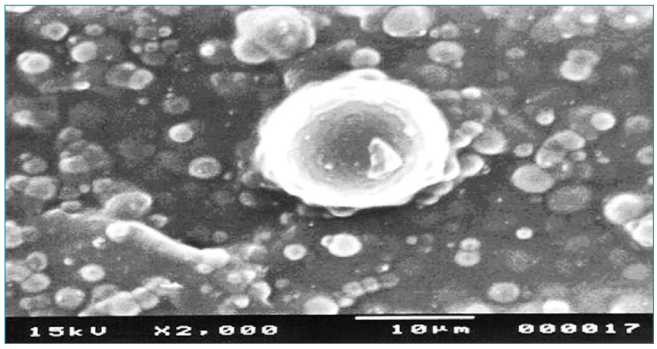

Figure 3: The scanning electron microscopy microphotographs of transdermal patch after skin permeation study at resolution 15 kV × 2000

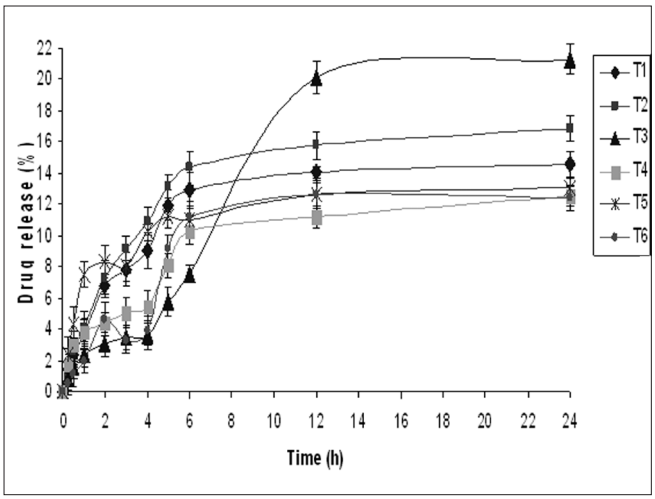

Figure 4: *In vitro* permeation profile of nebivolol transdermal patch formulations through excised hairless guinea pig skin (T1–T6). Each point is represented as mean±standard deviation, *n*=3

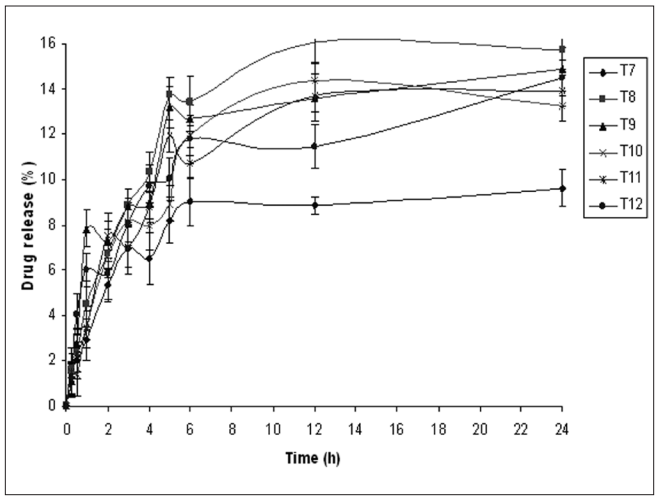

Figure 5: *In vitro* permeation profile of nebivolol transdermal patch formulations through excised hairless guinea pig skin (T7–T12). Each point is represented as mean±standard deviation, *n*=3

Table 5: Stability study of selected transdermal patch formulation as per ICH guidelines

Period (days)	Physical appearance	Thickness (mm) mean±SD	Folding endurance mean±SD	Moisture content (%) mean±SD	Drug content (%) mean±SD
0	Translucent, Non-sticky	0.37±0.18	89±1.01	8.73±0.43	102.28±0.59
15	Translucent, Non-sticky	0.38±0.02	89±0.41	8.76±0.23	102.24±0.91
30	Translucent, Non-sticky	0.38±0.10	87±0.59	8.76±0.18	102.18±0.83
45	Translucent, Non-sticky	0.40±0.11	87±0.72	8.79±0.31	102.15±0.89
60	Translucent, Non-sticky	0.39±0.09	87±1.09	8.80±0.29	101.98±1.03

ANOVA

Source of variation	SS	df	MS	F	*P* value	*F* crit
Between groups	41558.81	3	132272.4	2.71553	0.8392	1.420987
Within groups	4.85712	16	0.412381			
Total	41563.67	19				

Folding endurance is expressed in terms of no. of folding. All values are represented as mean±standard deviation (*n*=3). Standard error of mean < 0.646

CONCLUSION

Matrix type transdermal therapeutic systems of nebivolol could be prepared with the required flux having suitable mechanical properties, demonstrated sustained and controlled release of the drug across guinea pig skin during *in vitro* permeation studies. Further work is recommended in support of its efficacy claims and improved nebivolol bioavailability by long-term pharmacokinetic and pharmacodynamic studies on human beings.

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