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# PREPARATION AND *IN-VITRO* CHARACTERIZATION OF NEBIVOLOL TRANSDERMAL PATCHES USING SOLVENT CASTING TECHNIQUE

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## ABSTRACT

The aim of the present work was investigatedto develop and evaluate transdermal patches of nebivolol. The transdermal patches of nebivolol were prepared by solvent casting technique. The twelve formulations of nebivolol patches were prepared ( 1:1,1:2,1:3,1:4,) different composition of HPMC K100M, HPMC $K_4M$,Metalose SR,Glycerin, Tween 80as 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 solubility determination, melting point determination, partition coefficient, permeability coefficient, Thickness, Folding Endurance, Swelling Index, Moisture Content, Moisture Uptake, Water Vapor Transmission (WVT) Study, Tensile Strength Test, In-vitroPermeation Study, Gel Strength, drug release kinetics studies, Stability Studies. The physicochemical interactions between nebivolol and different polymers were studied by Fourier Transform Infrared (FTIR). The maximum drug release in 12 h was 98.08% ($F_{10}$, HPMC $K_4M$: HPMC K100 is 1:4), which is significant (P < 0.05). Furthermore, the formulation $F_{10}$ showed maximum skin permeation (13.93 mg/cm²/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.

## 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 cardio selective $\beta_1$ -receptor blocker with nitric oxide -potentiating vasodilator effect and used in 50 mg dose for the treatment of the 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 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 Tablets IndiaPvt Ltd, Chennai, India. Hydroxy propyl methyl cellulose (HPMC K100), (HPMC-K4M), propylene glycol, Metalose SR, Glycerin, Tween 80 and dibutyl phthalate dimethyl formamide, were procured from S.D. Fine Chem. Ltd., Mumbai, India. The 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. 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 3polymers in 2 combinations ( HPMC K 100 with HPMC K4M and HPMC K100 with Metalose SR) and in different proportions (1:2, 1:4, 1:6, 2:1, 4:1, and 6:1 w/w) by usingsolvent casting technique[5].The polymers like HPMC K4M, HPMC K100, selected as rate controlling polymers as they are biodegradable, easily available, economic, and nontoxic. The purpose of taking mixture of two polymers shows different grades, 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 of nebivolol and stored between sheets of wax paper in a dessicator.

**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],given in table no-1

**Mass variation**

The patches were subjected to mass variation by individually weighing 10 randomly selected patches[7]. Such determinations were carried out for each formulation,given in table no-1

**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)[7]. 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-$\mu$ m 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, given in table no-1.

**5. Percentage of moisture uptake**

A weighed membrane of size 2 cm2 stored in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the membrane was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight, given in table no-1

**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[8]. 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). The cells were verified regarding weight periodically over a period of 24 h. Calculations are made by using the following formula: given in table no-1

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

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[9]. 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. Given intable no-`1.

**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, given in table no-1

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

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

**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[16]. The IR spectrum was recorded using IR Spectrophotometer (Perkin-Elmer FT-IR, Perkin Elmer Inst., USA) by KBr pellet method. Figure no-1.

***In vitro* skin permeation study**

The in-vitro permeation study of fabricated transdermal patches of Nebivolol hydrochloride was carried out by using franzdiffusionn cell The patch was sandwiched between donor and receptor compartments of the diffusion cell. The patch of 2.64 cm was placed in the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 0.5°C was maintained throughout the experiment. Samples of 2ml were withdrawn through the sampling port at different time intervals for a period of 48 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. The samples were analyzed spectrophotometrically at 282 nm, given in table no-2, figure no-2

**Drug release kinetic study**

order to study the exact mechanism of drug release from the nebivolol transdermal patches, drug release data were analyzed according to zero order[11,12], first order[13], and Korsmeyer-Peppas[14,15]. The criterion for selecting the most appropriate model was chosen on the basis of goodness-of-fit test. Figure no-3.

**Stability studies**

Stability studies were performed according to standard stability protocol. 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[18]. 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.

**Formulation of transdermal patches flow chart**

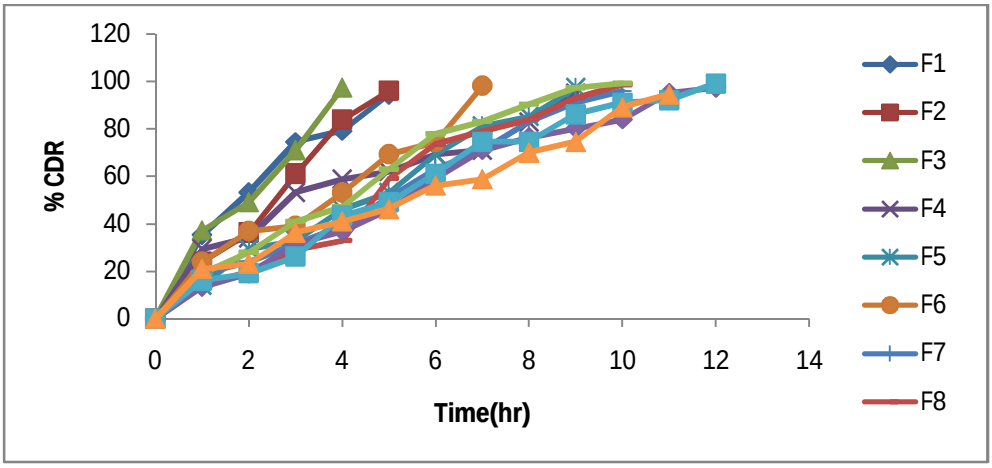
| **Ingredient** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nebivolol (mg) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | |
| HPMC K100M | 250 | 250 | _ | 250 | 250 | _ | 250 | 250 | | 250 | 250 | _ |
| HPMC K4M | 250 | | 250 | _ | 500 | 250 | 750 | | 250 | 1000 | _ | 250 |
| Metolose SR | _ | 250 | 250 | 500 | _ | 500 | | 750 | 750 | | 1000 | 1000 |
| Polyvinyl alcohol (PVA) | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml | 4ml |
| Propylene glycol | | | | | | | | | | | | |
| Dimethyl formamide(DMF) | | | | | | | | | | | | |
| Glycerine | | 2ml | 2ml | 2ml | 2ml | 2ml | 2ml | 2ml | 2ml | 2ml | 2m | 2ml |
| Tween 80 | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml |
| TOTAL | | | | | | | | | | | | |

**Evaluation of Transdermal Patches table no-1**

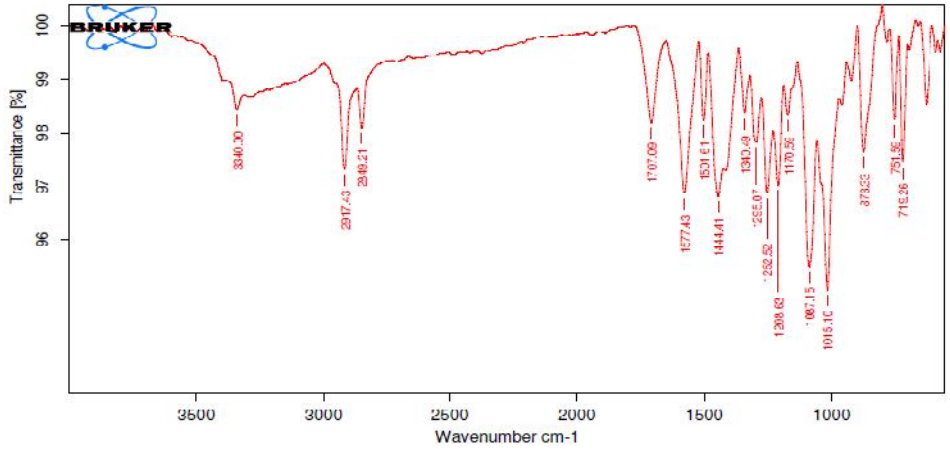
| Formula code | Thickness (mm) | Weight (g) | Drug content (mg) | % Moisture Absorption | % Moisture loss | Folding endurance | Tensile Strength(kg/mm2) |
|---|---|---|---|---|---|---|---|
| F1 | 0.201±0.021 | 0.860±0.017 | 0.272±0.04 | 6.973±2.32 | 12.5±2.50 | 111.0±4.58 | 3.84±0.124 |
| F2 | 0.201±0.022 | 0.860±0.018 | 0.272±0.04 | 6.874±2.37 | 12.62.40 | 108.1±4.57 | 3.84±0.125 |
| F3 | 0.202±0.021 | 0.861±0.017 | 0.262±0.07 | 6.873±2.32 | 12.4±2.12 | 106.13±4.6 | 2.96±0.114 |
| F4 | 0.201±0.023 | 0.862±0.019 | 0.231±0.01 | 6.863±2.12 | 10.5±2.22 | 105.10±5.7 | 2.97±0.145 |
| F5 | 0.201±0.021 | 0.863±0.017 | 0.111±0.04 | 6.888±2.12 | 10.7±2.13 | 107.1±4.02 | 3.41±0.079 |
| F6 | 0.202±0.022 | 08.63±0.019 | 0.222±0.02 | 6.989±2.13 | 9.62.±29 | 109.10±4.0 | 2.42±0.078 |
| F7 | 0.203±0.021 | 0.862±0.081 | 0.242±0.01 | 6.744±2.14 | 9.5±2.28 | 106.1±4.11 | 3.46±0.077 |
| F8 | 0.201±0.023 | 0.860±0.017 | 0.253±0.03 | 6.633±2.22 | 11.6±2.23 | 104.7±5.11 | 2.33±0.066 |
| F9 | 0.204±0.022 | 0.861±0.019 | 0.263±0.04 | 6.534±2.23 | 118±2.27. | 102.13±6.12 | 3.44±0.078 |
| F10 | 0.202±0.021 | 0.862±0.018 | 0.173±0.07 | 6.434±2.14 | 12.8±2.13 | 95.14±6.22 | 2.16±0.076 |
| F11 | 0.202±0.024 | 0.862±0.020 | 0.164±0.06 | 6.343±2.17 | 10.6±2.23 | 111.14±4.21 | 3.46±0.047 |
| F12 | 0.202±0.022 | 0.863±0.017 | 0.154±0.04 | 6.444±2.17 | 10.5±2.14 | 109.12±4.20 | 2.45±0.053 |

**% 0f *in-vitro* drug release studies table no-2**

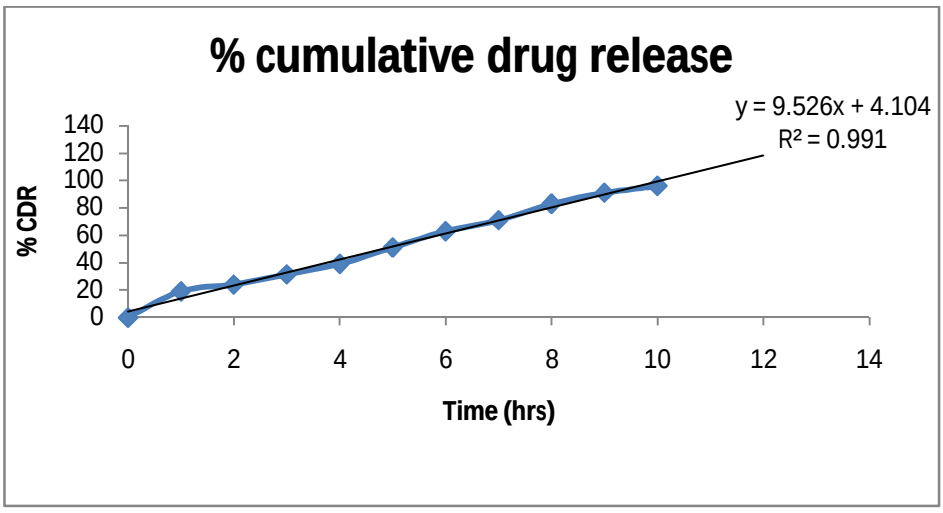
| Time (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 35.31 | 24.05 | 37.22 | 29.4 | 14.12 | 24.05 | 19.09 | 14.12 | 19.09 | 13.36 | 16.03 | 21.01 |
| 2 | 53.26 | 36.27 | 49.06 | 34.17 | 29.4 | 37.03 | 24.05 | 20.04 | 28.06 | 19.09 | 19.09 | 23.10 |
| 3 | 74.45 | 61.09 | 71.01 | 53.26 | 33.02 | 39.13 | 31.5 | 29.01 | 41.04 | 31.5 | 26.15 | 36.27 |
| 4 | 79.22 | 84.00 | 97.36 | 58.8 | 46.2 | 53.07 | 39.13 | 33.02 | 47.15 | 37.03 | 43.33 | 41.04 |
| 5 | 94.5 | 96.02 | | 62.04 | 53.07 | 69.31 | 51.16 | 59.18 | 63.09 | 46.21 | 49.06 | 46.20 |
| 6 | | | | 69.30 | 69.3 | 74.45 | 63.00 | 73.5 | 77.71 | 59.18 | 61.09 | 56.12 |
| 7 | | | | 71.01 | 81.13 | 91.12 | 71.01 | 79.03 | 83.04 | 71.01 | 74.45 | 58.80 |
| 8 | | | | 83.04 | 85.14 | | 83.04 | 84.00 | 90.30 | 76.36 | 74.45 | 70.06 |
| 9 | | | | 95.07 | 97.36 | | 91.06 | 93.16 | 97.17 | 80.18 | 86.10 | 74.45 |
| 10 | | | | | | | 96.02 | 98.7 | 99.08 | 84.01 | 91.06 | 89.15 |
| 11 | | | | | | | | | | 95.07 | 92.01 | 94.50 |
| 12 | | | | | | | | | | 98.36 | 97.08 | |




**% Of*In-Vitro* Cumulative Drug Release Of Formulations Figure No-2**




**IR Spectra Of Nebivolol figure no-1**




**Zero order kinetic release figure no-3**

## RESULTS AND DISCUSSION

The transdermal patches were prepared by using nebivolol and the rate controlling polymers in different proportions as represented in Table no-1. The generalized transdermal patches protocol depends on the nature of ingredients, successful solvent casting and optimization at every preparative step. The nebivolol transdermal patches could be prepared successfully using solvent evaporation technique. The physical appearance of all transdermal patches was translucent and non sticky. The physicochemical properties of the nebivolol transdermal patches are presented in table no-2. The thickness of patches varied from **330±0.76 to 410±1.09 µ m (n=5);** casting of the rate-controlling membrane increased the thickness and 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 13.36 %±0.99% to 98.36%±0.84% per patch. The F6 (HPMC$K_4$M:METALOSE 1:2) 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 F10 showed maximum drug content (98.36 %±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 no-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 F4. 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 (F2) 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 with the hydrophobic rate-controlling membrane of EC decreased the values of the moisture vapor transmission rate accordingly (F6). 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 F9 has the highest folding endurance while F5 has the least table no-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 F2 and F3 exhibited greater values of tensile strength (2.39±0.208 and 2.41±0.311 kg/mm $^2$).

## DISCUSSION

Nebivolol in combination with HPMC $K_4$M, HPMC K100 and Metolose with incorporation of Tween-80 (4%) produced smooth, flexible and transparent films. FT-IR spectral studies indicated there was no interaction between Nebivolol and polymers used. Nebivolol patches were prepared with combination of these polymers and evaluated.From the results, it was observed that thickness (0.201-0.204 mm), weight variation (0.860-0.863 g), Folding endurance (95.14-111.14), low moisture loss (9.5-12.62), low moisture absorption (6.343-6.989 %), tensile strength (2.45-3.84) were suitable for maximum stability of the prepared formulations.

The membranes were evaluated for different parameters like thickness, folding endurance, swelling index, moisture content and moisture uptake, water vapour transmission test, tensile strength and percentage elongation, invitroand exvivo permeation, gel strength and stability studies. Observations of all the formulations form physical characterization have shown that the formulations show optimum results. The drug content of TDDS patches ranged from 0.249-0.279 mg.

## CONCLUSION

Matrix type transdermal therapeutic systems of Nebivolol could be prepared with suitable mechanical properties, demonstrated sustained and controlled release of the drug 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 will continue in further research work.

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