Zainab Ahmed Sadeq et al /J. Pharm. Sci. & Res. Vol. 11(3), 2019, 1052-1055

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Preparation, *in-vitro* Evaluation,Mechanical Characterization,and Release Of Nebivelol Hydrochloride as A Transdermal Film using combined Eudragite-Polyvinyl Alcohol as Adhesive Film Forming Polymer

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Abstract

Objective: The main objective of this study was to prepare Nebivelol Hydrochloride (NEB) as transdermal film using combined Eudragit E and PVA as adhesive film forming polymer .

Methods: The transdermal films were prepared by solvent casting evaporation technique using different concentration of both Eudragit E and polyvinyl alcohol (PVA) polymers with glycerin at concentration 30% of polymer weight as plasticizer. The all prepare films were evaluated for weight variation, surface pH, folding endurance, content uniformity, swelling index and in-vitro- drug release study.Skin adhesive was studied to evaluate the effect of glycerin on the skin adhesive strength. Both FTIR and DSC analysis were investigated to exclude any interaction between drug and the used polymers .

Results: The obtained results indicated that all the prepared films were clear, smooth and transparent in appearance, the measured surface pH of all prepared films were close to the skin pH in range (5.7-5.9), the folding endurance were found more than 300, drug content between 89.81-100.2 % which indicate nebivelol HCl uniformly distribute throughout prepared film and lye within the range of British Pharmacopoeia. Also as Eudragit E concentration increase lead to significant increase in tensile strength and decrease percentage of elongations, while significant decrease in drug release from the film .

Conclusions It can be concluded that Nebivelol hydrochloride can be formulated as transdermal film using Eudragit E100 as Bioadhesive film forming polymer with PVA and glycerin as plasticizer with extended drug release for 24h.

Keywords: Nebivelol hydrochloride, Eudragit E100, PVA, solvent casting method.

INTRODUCTION:

A transdermal film was developed in 1970s and FDA approved it in 1979s for motion sickness treatments, a transdermal film which is also called a skin film is a medicated adhesive dosage form placed on skin and act as delivery for a specific dose of drug to be provided through the skin and into blood body circulation [1]. Anew efforts for drug delivery is by using the skin as an application site to deliver the drug into body blood stream at predetermined rate and maintains the drug blood concentration within therapeutic range. Transdermal drug delivery have many benefit over oral and/or intravenous dosage form such as prevent hepatic first-pass metabolism, minimized systemic toxicity incidence and patient compliance improvement. For typical transdermal administration, the drug should have many physiochemical properties such as short half-life, small dose and low molecular weight [2]. Nebivelol HCL is a cardio selective B-blocker used for hypertension management, its nebivoioum2, 2-iminobisethanol derivative with chemical formula $C_{22}H_{25}F_2NO_4HCL$, M.wt = 441.90 g/mole, M.P 219-222c and PKa 8.22, it undergo extensive first pass metabolism in the liver after oral administration with bioavailability 12%, also it causes abdominal pain and GIT disturbance, so that to minimize the side effect and increase the bioavailability, we prepare transdermal film of nebivelol [3].

MATERIALS AND METHODS:

Materials:

Nebivelol HCl was purchased from Provizer Pharma, India .Polyvinylalchol [PVA] was obtained from fine Indian chemicals. Eudragit E100 obtained from Rohm, GmbH, weiterstd, Germany, England. Glycerin was purchased from [panreac, Espana]. All other reagents and chemicals used were of analytical grade.

Methods:

The calculated amount of PVA was dissolved in purified water and heated by using hot plate at 80 C° with stirring, after that the polymer solution was left to cool [4]. While Eudragit was prepared by dissolving the calculated amount of polymer in the ethanol 95% v/v with stirring on magnetic stirrer ,[5] after that glycerin (plasticizer) was added at concentration 30% of polymer weight and added to polymer solution, finally the calculated amount of nebivelol HCl added (after dissolving in 5ml of methanol) into polymers solution with stirring. The prepared solution left overnight to remove air bubbles and produce clear solution, then these solution were poured in to a petridish of diameter 9cm and left to dry in hot air oven adjusted at 50 C° until flexible film obtained then the resulted film removed from the petridish , divided into 2x2 cm^2 (table1) and used for evaluation [6].

Table 1: formulas composition of Nebivelol HCl transdermal films

Ingredient(mg)	Formula code					
	F1	F2	F3	F4	F5	F6
Nebivelol	10	10	20	10	10	10
PVA	50	37.5	37.5	25	12.5	37.5
Eudragit E100	12.5	25	25	37.5	50	25
Glycerin	18.75	18.75	18.75	18.75	18.75	----

Evaluation of Nebivelol HCl film

Weight variation:

Three randomly film from each formulation were weighted by using electronic digital balance then the average weight was measured [7].

Thickness:

Three randomly film were chosen from each formulation and thickness measure by electronic vernia at five different points, then take the average value [8].

Content uniformity:

This test was done by dissolving the prepared film containing 10mg of nebivelol HCl in 100ml of phosphate buffer pH 7.4 for one hour under magnetic stirrer, after that the resulted solution filtered, diluted with buffer solution pH 7.4 and finally determine nebivelol content at ƛ max 281nm by UV spectrophotometer and this test done in triplicate [9]

Folding Endurance:

Folding endurance done by reparative folding three randomly film at same point until break, the number of time of film folded at same point without rupture gave the number of folding endurance value [10].

Surface pH:

The film was put in glass tube containing 10ml DW, after one hour, the pH of film surface measured by using digital pH meter, this method done in triplicate [11].

Swelling Index:

The film capacity to uptake the water was measured by swelling index, the film was weighted on a apreweight slide (Wo) and dipping in petridish containing 50ml phosphate buffer pH 7.4, after that the slide was removed from petridish at regular time interval for one hour and reweight again (wt), the swelling index was measured according to following equation and done in triplicate [12]:

SI= Wt – Wo /Wo x 100

Mechanical properties measurement:

Mechanical properties involve both tensile Strength (TS) and percentage elongation (%EB) which can be testing by tensometer 10 Monsanto, USA, in which the prepared film cut as dumbbell shape fig (1) and hold between two clamps, then the film was pulled by the top of clamp at 100mm/min, so that TS and %EB can be measured when the film was broken using the equation [13]:

$$TS = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of sample (mm}^2\text{)}}$$

$$\%EB = \frac{\text{Increase in length}}{\text{Original length}}$$

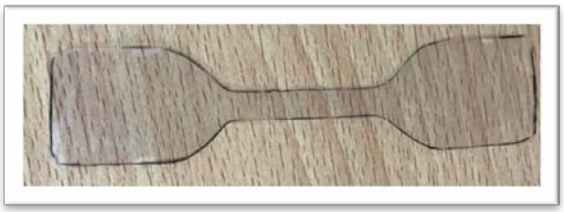

Fig (1) Sample Cut into Dumbbell Shape for Mechanical Properties.

In-Vitro drug release study:

USP dissolution apparatus type II (paddle type) used in which a film of diameter 2x2 cm^2 place in the bottom of 500ml phosphate buffer pH 7.4 jar (dissolution media) at 32± o.5 C° and rotate at 50 rpm, sample of 5ml was withdrawal from the jar at regular period(0.5,1,2,4,6,8,10,14,18,24h) and replace with same volume of phosphate buffer pH 7.4 then the sample filter and analyze at 281 nm by UV spectrophotometer ,all the operations were carried out in triplicate[11] [14].

Skin adhesive study

To demonstrate the effect of glycerin (plasticizer) on the skin adhesive strength of the prepared transdermal films, modified balance figure (2) was used in which a section of goat skin [6] fitting on bottle glass vial by (rubber piece) with height –adjustable hook, the vial attached to one of the balance pan and aplastic cap (used to collect water), was put on the other side. Drop by drop water was added to the plastic cap until detachment the glass slide from goat skin, the minimum weight which is required to detach two surface is represented by adhesive force $F= 980m/\pi r^2$, when F adhesive force ($dyne/cm^2$) of the film per unit area of goat skin (cm^2), r is the radius of the vial which is equal 1.2cm, M balance weigh, this test done in triplicate [15].

Fig (2): Photograph of Adhesive Test Device.

FTIR study

The Nebivelol HCl and polymer interaction was determined by analyze the Nebivelol HCl pure powder ,selected formula F2 of Nebivelol HCl by using KBr disc and scan from 400-4000cm-1 using FTIR spectroscopy [16].

Differential Scanning Calorimetric DSC

For determine the compability between the Nebivelol HCl and excipient, we use DSC test. Therefore DSC of pure Nebivelol HCl, selected formula F2 of Nebivelol HCl were carried out by using DSC -60 plus shimdzu, Japan [4].

Table 2: Physical Evaluation Parameters for Nebivelol HCL Transdermal Films. Data represented as mean ±SD, n=3

Formula code	Surface pH	Weight variation(mg)	Thickness(mm)	Folding endurance	Drug Content %
F1	5.74 ± 0.22	137.25 ± 4.74	0.182±0.006	> 300	93.05±0.14
F2	5.7±0.12	140.83 ± 3.54	0.177±0.015	> 300	92.19±0.03
F3	5.85 ±0.08	157.05 ±2.93	0.187±0.063	> 300	100.2±0.43
F4	5.76± 0.91	124.89 ± 6.11	0.173±0.018	> 300	89.81±0.19
F5	5.9 ±0.54	138.11 ±3.2	0.179±0.091	> 300	98.88±0.74

RESULT AND DISCUSSION:

From the obtained results (table 2), it was seen all the prepared film have weight uniformity which range from (124.89-140.83 mg), all the formulas showed acceptable thickness (0.173-0.187nm) with folding endurance more than 300, which mean the prepared films flexible enough when handling and transport without broken. The surface pH range from (5.7-5.9) gave indication there is no side effect or irritation to the skin. For swelling index values fig(3), it was seen as concentration of Eudragit increase F4,F5 leads to decrease in swelling index this may due low water solubility of Eudragit which limit the swelling ability of the polymer.

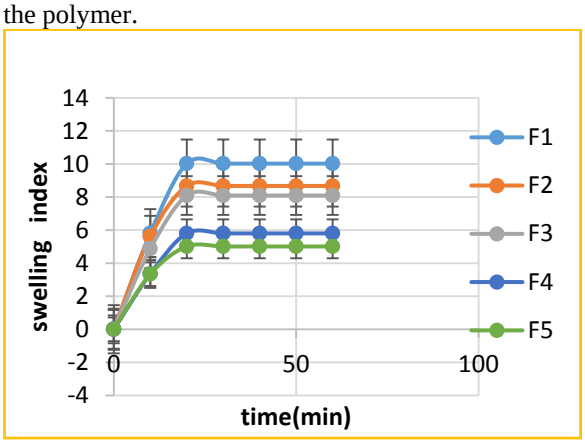

Fig 3: Swelling Index of the Prepared Nebivelol Transdermal Film. Data represented as mean ±SD, n=3

For mechanical properties fig(4), it was found as Eudragit E100 concentration increase(F4,F5) lead to increase in TS and decrease %EB, this may due to Eudragit nature which lead to breakdown the bonds found between PVA chains make the polymer easily rupture, same observation seen in preparation and evaluation of transdermal patch of papaverine HCL [2].

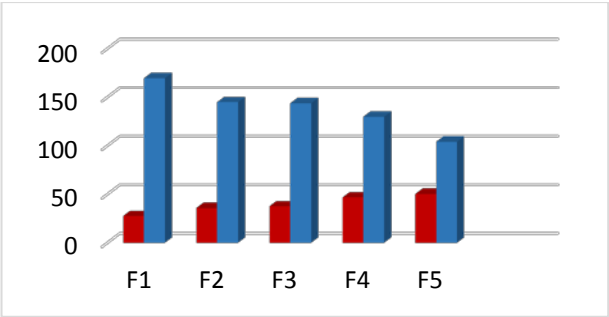

Fig4: Mechanical Properties of Prepared Nebivelol Transdermal Films.

for drug release study fig (4), it was found that as Eudragit concentration increase, there is decrease in drug release because of low affinity of Eudragit to water lead to reduce thermodynamic activity and subsequent reduce nebivelol HCL release from the film [11].also it was found the loading amount nebivelol HCL transdermal films (F3) lead to increase drug release this may due to higher amount of nebivelol HCL dissolve within the polymer.

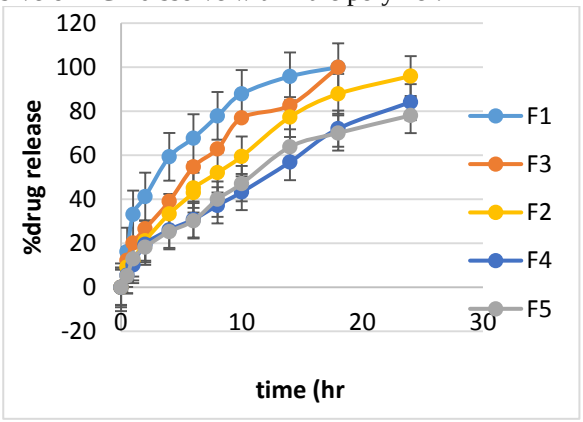

Fig5: Dissolution Behavior of Nebivelol Transdermal Film in Phosphate Buffer pH 7.4 .Data represented as mean ±SD, n=3

for Skin adhesive study fig (6), it was found the presence of glycerin (plasticizer) F2, increase the bio adhesive force when compared to F6 (plasticizer free) this may due to the presence of glycerin lead to formation of secondary bond with the polymer chains, making two adjacent polymer chain linked to each other which leading to improvement adhesive ability to the surface of the skin by formation strong adhesive bond [17].

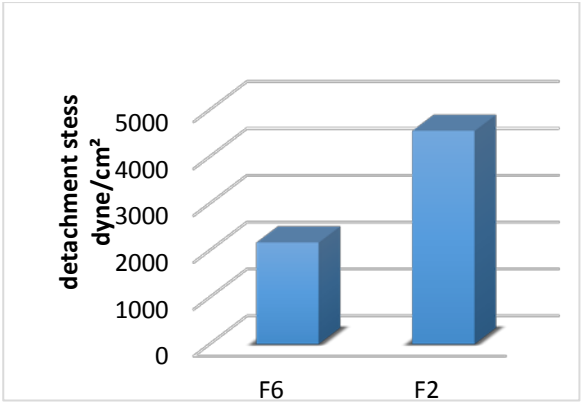

Fig 6: Comparison of Detachment Stress of Nebivelol Transdermal Film of F2 and F6.

for DSC study , nebivelol HCL produce sharp endothermic peak around its melting point which is equal to 221 C give indication the drug use in its pure state [16].while endothermic peak of of nebivelol HCL, Eudragit E100 and PVA in selected formula F2 was observed at 221C indicate that no interaction between them . While for FTIR study for selected formula F2, the presence of characteristic peaks of drug and polymer in the film indicate that no interaction between drug and polymer use in formulation [18] as shown in the table (3).

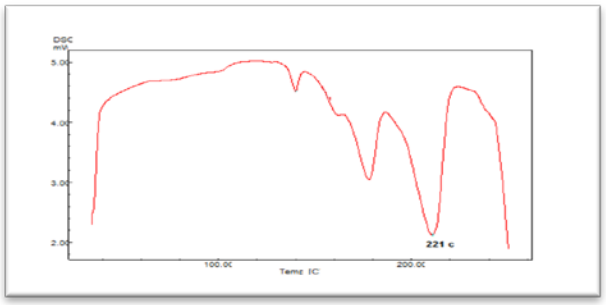

Fig7: DSC thermo gram of pure Nebivelol

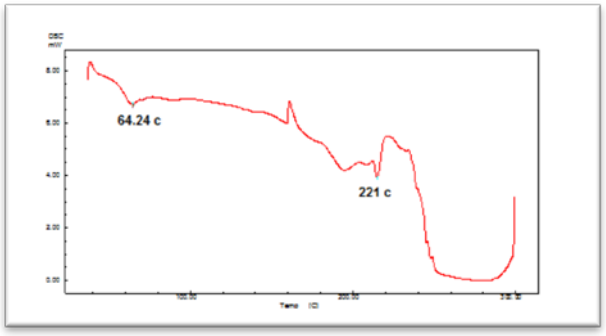

Fig8: DSC thermo gram oof selected formula F2

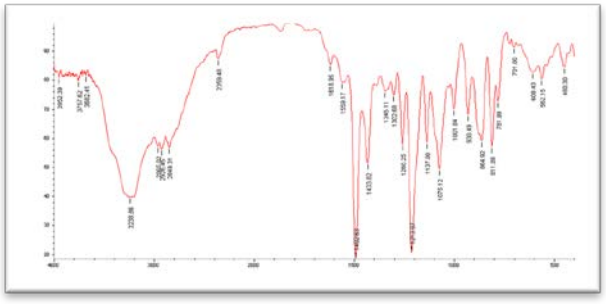

Fig 9: FT-IR spectrum of pure captopril

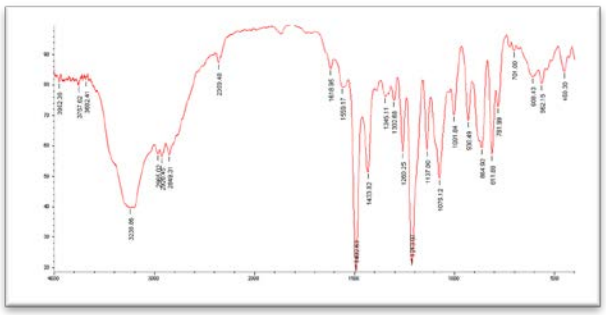

Fig 10: FT-IR spectrum of selected formula F2.

Table 3: FT-IR absorption bands of Nebivelol and selected formula F2

Characteristic groups	Pure drug[18]	selected formula F2
OH	3238.86	3198.36
Cyclic ether C-O stretch	1260.25	1260.25
Aryl substituted C=C	1618.95	1618.95
C-N stretch	1302.68	1300.75
C-H stretch	2926.45	2924.2

CONCLUSION

It can be concluded that Nebivelol hydrochloride can be formulated as transdermal film using Eudragit E100 as Bioadhesive film forming polymer with PVA and glycerin as plasticizer with extended drug release for 24h, therefore F2 was chosen as selected formula with Surface pH 5.7±0.12, weight variation (mg) 140.83 ± 3.54, thickness (mm) 0.177±0.015, folding endurance > 300, drug content % 98.88±0.74 with extended drug release 96.24% over 24h.

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