



FABRICATION DEVELOPMENT AND PERMEATION STUDIES OF ANTIHYPERTENSIVE DRUG NEBIVOLOL HYDROCHLORIDE TRANSDERMAL PATCHES

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ABSTRACT:

Nebivolol Hydrochloride is selective Beta blocker having a unique character which distinguishes it from other beta blockers. It increases the release of nitric oxide which causes vasodilation which in turn improves the arterial compliance and decreases the peripheral vascular resistance. The objective of present investigation is to design, evaluate the physical parameters and to carry out the permeation studies of Nebivolol Hydrochloride antihypertensive Transdermal patch by employing suitable polymers such as Eudragit RL100, and Eudragit RS100. The drug and polymer compatibility study has been studied by FTIR and DSC studies. The prepared Nebivolol transdermal patches were subjected various evaluation parameters like weight variation, drug content, moisture content, moisture uptake, thickness uniformity, *invitro* diffusion study, after performing all evaluation tests, it is confirmed that formulation F2 is the optimized formulation and it shows better *invitro* diffusion compared to other formulations.

Key words: Nebivolol Hydrochloride; TDDS; Eudragit RS100; Eudragit RL 100; Zero order model; Higuchi model; Korsmeyer's model

INTRODUCTION

Transdermal drug delivery is type of drug delivery which comes under the category of controlled drug delivery system. In which the main aim is to deliver the drug through the skin in to the systemic circulation at a predetermined rate². This type of drug delivery helps to overcome from many problems like plasma drug fluctuations, multidose therapy, hepatic first pass metabolism etc.³ Drugs which are administered through conventional dosage form produces more fluctuations in plasma drug concentration and leads to undesirable toxicity and poor effectiveness.⁴

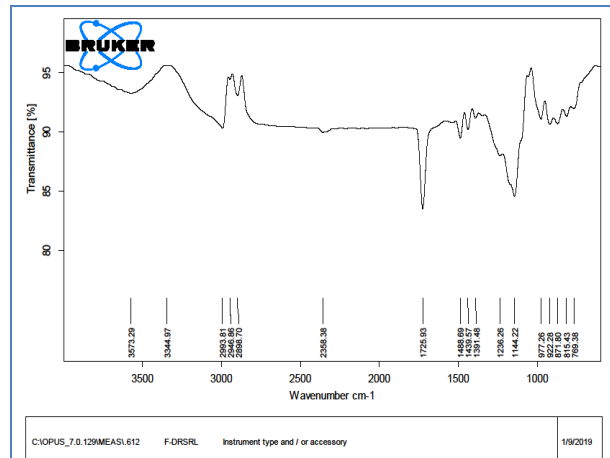
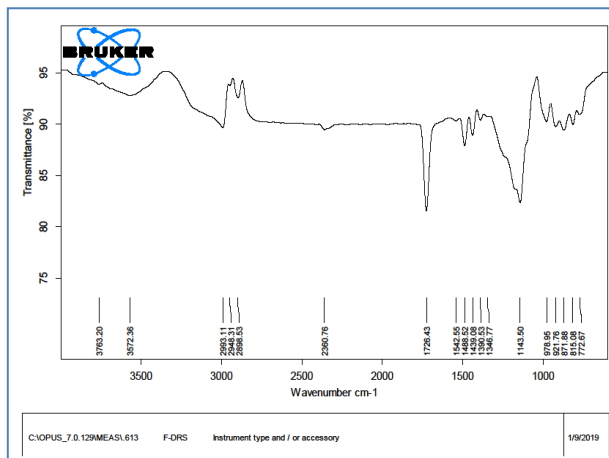
In the olden days humans have applied various agents like cosmetics and therapeutic agents to the skin for long term drug delivery. However nowadays the skin becomes one of the important routes for the drug delivery.⁵ Nebivolol Hydrochloride is a beta blocker Antihypertensive drug. Beta blockers produce their action by acting

selectively or non-selectively on beta receptors. Nebivolol may be considered both depending on its concentration in the body. Nebivolol at 10mg or below is selective beta₁ blocker whereas at higher concentration it loses its selectivity and acts on both beta₁ and beta₂. Nebivolol also possess vasoactive factors. It produces vasodilation by releasing endothelial nitric oxide.

Materials and Methods

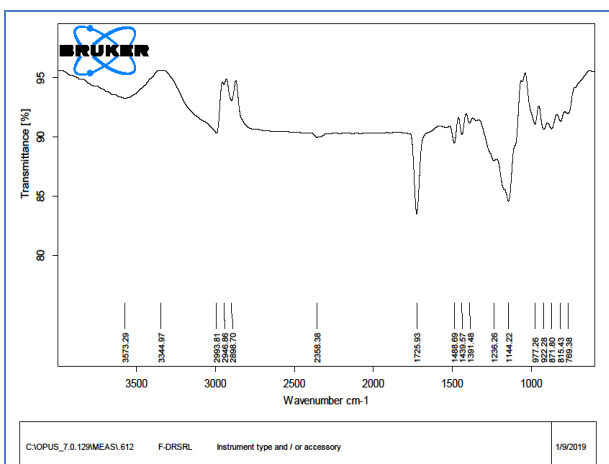
Nebivolol Hydrochloride from Aarti Pharma BTM compound, behind SBI West, Mumbai, Eudragit RS 100 and Eudragit RL 100 from S.D.Fine chemicals Ltd, Dichloromethane from Qualigens fine Chemicals, Chloroform from S.D.Fine chemicals Ltd, Tween 60 from Evonikpharmar Pvt. Ltd, Dibutyl phthalate from Qualigens fine Chemicals,

IR spectrum of Nebivolol HCl



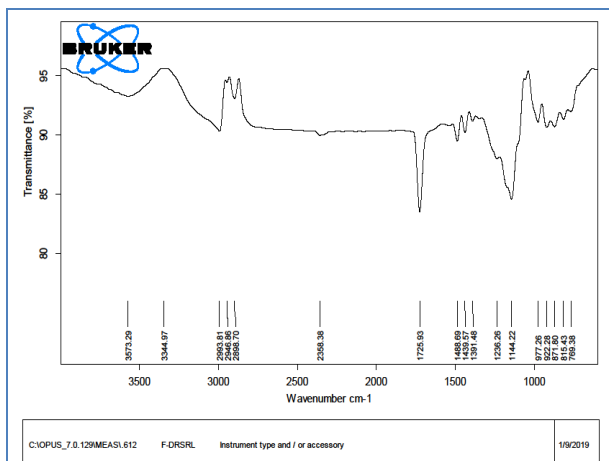
IR spectra of Nebivolol and Eudragit RS

The FTIR characteristic peaks of the Nebivolol Hydrochloride



Reference peaks (cm-1)	Observed peaks (cm-1)	Inference
3650.00	3608.99	O-H- stretching for alcohol & Phenol
3400.00	3492.35	N-H- stretching for amide
2872.00	2902.91	C-H- (aliphatic) stretching
2380.00	2359.02	N-H-stretching for Hydrochloride salts of amino acids
1575.00	1542.27	-N-H-bending
1220.00	1258.21	-C=O- stretching
1020.00	1002.62	-C-O- (ester) stretching

IR spectra of Nebivolol and Eudragit RL

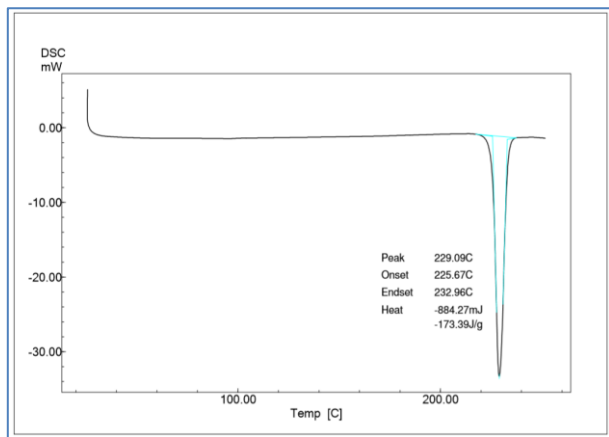


The FTIR characteristic peaks of the polymers

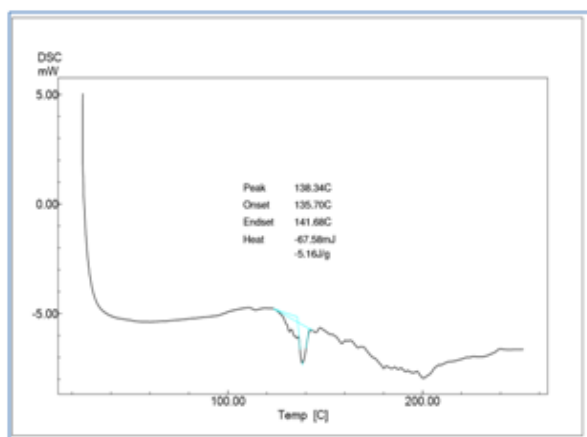
Reference peaks (cm-1)	Observed peaks (cm-1)	Inference
3650.00	3573.29	O-H- stretching for alcohol & Phenol
2840.00	2898.70	(C-H-stretching) Alkanes
1754.00	1725.93	(-C=C- stretching)
900.00	977.26	C-H- bending

IR spectra of Nebivolol HCL, Eudragit RS and Eudragit RL

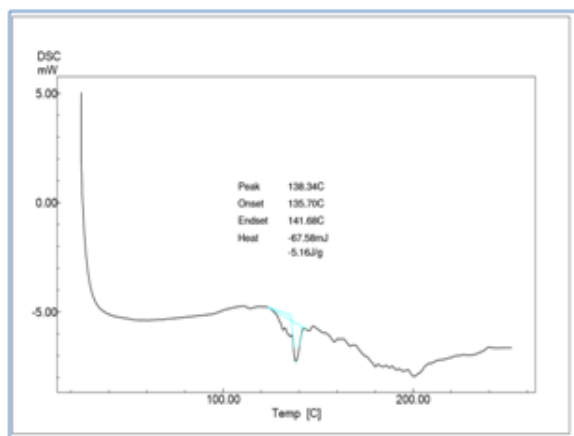
DSC of Nebivolol Hydrochloride (DRUG)



DSC of Nebivolol HCL and Eudragit RS 100 and Eudragit RL 100



DSC of Eudragit RS 100 and Eudragit RL 100



DSC characteristic peaks of drug and polymers

Sr. No.	Sample combination	Characteristic peaks
1	Nebivolol hydrochloride	229.09
2	Eudragit RL and Eudragit RS	138.34
3	Nebivolol hydrochloride, Eudragit RS and RL	138.34 and 191.58

METHOD FOR THE ESTIMATION OF NEBIVOLOL HYDROCHLORIDE⁶

A spectroscopic method based on the measurement of absorbance at 282 nm

Materials:

Nebivolol Hydrochloride is a gift sample from Aarti Pharma.

Standard Solution:^{7, 8}

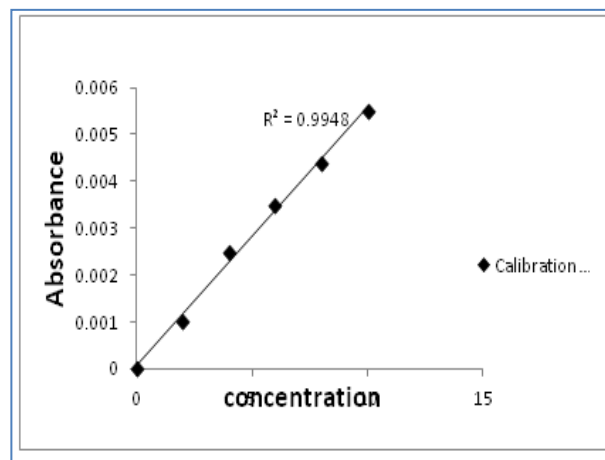
10 mg of nebivolol was dissolved in 10ml methanol in 100 ml of volumetric flask.

Procedure:

The Standard solution of Nebivolol was subsequently diluted with 7.4 ph. buffer series of dilutions containing 2, 4, 6, 8, & 10µg in 1 ml solution. The absorbance of these solution was measured in UV- Spectrophotometer at 282 nm using 7.4 ph. buffer as blank. The concentration of Nebivolol and the corresponding are given in table. The absorbance was plotted against concentration of Nebivolol Hydrochloride.

Estimation of Nebivolol HCl

Nebivolol Hydrochloride Concentration (µg/ml)	Absorbance
2	0.0038
4	0.0054
6	0.0068
8	0.0087
10	0.0097



Preparation of transdermal patches^{9, 10}

The transdermal patches are prepared by solvent evaporation method. The polymers (Eudragit RS100 and Eudragit RL 100) are accurately weighed

and dissolved in 10 ml of solvent and known volume of plasticizer and permeation enhancer were added and mixed thoroughly to get the homogenous dispersion. Then 100mg of drug was dissolved in the solution and mixed for 10 min. The

resultant solution was poured in to Petri dish. And kept evaporation for 24hrs and dried films were removed and cut in to suitable sizes and stored in the desiccators.

Table 1:

FORMULATION CODE						
INGREDIENTS	F1	F2	F3	F4	F5	F6
Nebivolol HCl (Mg)	100	100	100	100	100	100
EUDRAGIT RS 100	200	400	-	300	100	150
EUDRAGIT RL 100	200	-	400	100	300	250
DCM (ml)	5	5	5	5	5	5
CHLOROFORM (ml)	5	5	5	5	5	5
DIBUTYPTHALATE (ml)	20%	20%	20%	20%	20%	20%
TWEEN 60	15%	15%	15%	15%	15%	15%

Evaluation of Transdermal Patches

Film thickness¹¹:

The thickness of the film can be determined by using micrometre, electronic Vernier callipers, dial gauge, or screw gauge. Thickness is measured at five different points of on the film. And average of five readings is considered.

Folding endurance^{12, 13}:

Folding endurance of the patches can be determined by continuous and repeatedly folding of the film at the same place till it will break. The number of times that it will take to break gives the folding endurance value of the patch.

Percentage moisture uptake^{14, 15}

A weighed film is kept in desiccator at room temperature for 24 hrs then it is taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a dessicator until a constant weight for the film is obtained. The percentage moisture uptake is calculated by using the following formula.

Weight uniformity^{16, 17}

Weight uniformity of the patches can be determined by randomly selecting about ten patches. A specified area of the patch is cut at

different parts of the patch and weighed by using digital balance. Then calculate the overage weight and standard deviation value from the individual weights. These determinations are performed for each formulation.

Tensile strength^{18, 19}

Tensile strength of the patch is determined by using a modified pully system. In this method weight of the pulley is gradually increased in order to increase the pulling force until the patch breaks. The force required to break the patch gives the tensile strength value. Tensile strength of the patch is calculated as kg/cm².

Drug content:^{20, 21}

In determination of drug content, a small portion of the film (1x1 or 2x2) is cut and then put this in 100ml of buffer (pH 7.4 or 6.8 or as prescribed) and shaken continuously for 24 hrs then the whole solution is ultrasonicated for 15min. After filtration the drug is estimated spectrophotometrically and drug content is determined.

Percentage of moisture content²²,

The patches are weighed individually and transferred in a dessicator having anhydrous calcium chloride or activated silica at room temperature for 24 hrs. Then films are individually

weighed until they show constant weight. Calculation of percentage moisture content is done by using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Invitro drug release studies:

a) Invitro Drug Release

The fabricated film was placed on the semi permeable membrane and attached to the modified diffusion cell such that the cell’s drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37 ± 1° C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time

intervals and replaced. with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 282 nm.

b) Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (Q v/s t), first order (Log(Q₀-Q) v/s t) , Higuchi’s square root of time (Q v/s √t) and KorsemyerPeppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q₀-Q) is the cumulative percentage of drug remaining after time t.

Table 2: Physicochemical Evaluation of Nebivolol Transdermal Patches

Formulat ion code	Thickness	Folding Endurance	Tensile Strength	Weight Variation	Moisture content	Moisture Uptake	Drug content
F1	0.23 ±0.008	88 ±5.35	1.90 ±0.049	323 ± 2.160	2.36 ±0.20	2.87 ± 0.49	87.86 ±0.65
F2	0.24 ±0.016	92 ±2.94	1.83 ±0.093	418 ± 0.471	2.4 ± 0.16	4.68 ± 0.13	89.63 ±0.96
F3	0.24 ±0.012	91 ±4.98	2.04 ±0.067	311 ±3.399	2.47 ±0.27	4.39 ± 0.35	80.83 ±0.62
F4	0.24 ±0.021	91 ±2.86	1.85 ±0.079	309 ±2.054	2.6 ±0.22	5.6 ± 0.26	65.00 ±0.81
F5	0.25 ±0.016	95 ±1.63	2.12 ±0.060	436 ±2.624	2.16 ±0.02	2.23 ± 0.03	53.86 ±0.65
F6	0.26 ±0.016	92 ±1.63	1.94 ±0.021	366 ±2.494	3.26 ±0.12	5.65 ± 0.22	75.7 ±0.49

Table 2: Invitro drug release profile of Nebivolol hydrochloride Transdermal patch

Time	F1	F2	F3	F4	F5	F6
1	13.5	12.6	11.1	11.3	11.6	12.7
2	26.7	27.5	18.1	21.3	15.3	18.5
3	39.6	40.8	23.1	26.3	19.5	24.7
4	42.5	45.8	28.1	36.4	22.3	28.5
5	46.8	49.5	33.5	42.2	26.5	35.6
6	51.5	54.7	39.2	46.2	31.2	39.6
7	55.8	58.2	46.2	51.2	36.8	44.5
8	62.5	62.2	49.2	55.6	41.2	48.5
9	64.8	68.1	54	58.3	45.6	52.4
10	68.2	71.6	58.5	62.8	51.3	56.2
11	73.6	75.1	64.5	65.3	54.6	59.6
12	78.6	84.2	71.5	72.3	58.7	62.3

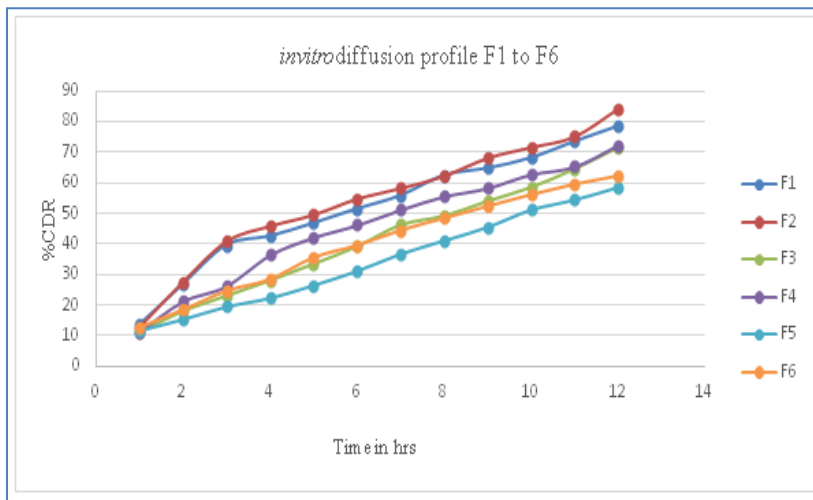


Table 3: Regression co-efficient (R²) values of Nebivolol Transdermal patches according to different kinetic models

Formulation	Zero order		Higuchi R ²	First order		Peppas	
	R ²	n		R ²	n	R ²	n
F1	0.9101	4.8801	0.9864	0.9792	0.047	0.9662	0.6151
F2	0.9189	5.2469	0.9855	0.9754	0.056	0.9576	0.6469
F3	0.9698	4.8646	0.9684	0.9804	0.040	0.9945	0.7292
F4	0.9333	4.7037	0.9840	0.9825	0.0407	0.9838	0.6847
F5	0.9649	4.0010	0.9608	0.9771	0.064	0.9772	0.6802
F6	0.9323	4.0626	0.9822	0.9716	0.069	0.9905	0.6318

DISCUSSION

In order to investigate the possible interaction between drug and selected polymers. FT-IR spectra and DSC studies were carried out. IR- spectrum for pure drug and physical mixture of drug and polymer were obtained and characterised. It indicates that pure drug functional group peaks were present in all formulations with small changes in peak position, after incorporated with polymers. So that the results clearly indicate both drug and polymer are compatible. DSC indicates that Drug and polymers are compatible with each other at different temperature. The results are given in. The patches from F1 to F6 exhibited uniform weight ranging from 307 mg to 440 mg and thickness F1 to F6 are ranging from 0.23 to 0.24 mm. Based on the weight variation study it is observed that formulation F4 exhibits least weight of 307mg But it is observed that formulation F5 exhibits about

440mg which is the highest weight when compared to other formulations. When developed patches are evaluated for moisture content it is observed that F1 exhibits least moisture content 2.1 and F6 exhibits highest moisture content 3.4 compared to other formulations. Hence it is observed that polymer ratio Eudragit RS100 and Eudragit RL100 in the equal ratio that is 200:200 shows low moisture content whereas same polymers in a ratio of 150: 250 shows high moisture content. In case of moisture uptake, it is observed that F1 shows low moisture uptake 2.18 where as F4 and F6 show high moisture uptake 5.89. When the developed patches are subjected to Tensile strength evaluation it is observed that F2 shows low strength 1.72Kg and F5 shows high tensile strength 2.15Kg. Folding endurance evaluation has been carried out on formulations F1 to F6 the result obtained shows F1 has low folding endurance 81 and F3, F5 has more folding endurance value. On

the basis of results obtained by doing tensile strength and folding endurance it is observed that the formulations which shows more tensile strength and folding endurance has good elasticity and mechanical strength. Among the various batches, the uniformity weight and thickness indicate that the polymeric solution of the drug is well dispersed in the patches. All the formulations (F1 to F6) exhibited fairly uniform drug content ranging from 54 % to 88 % respectively. The *in vitro* permeation studies of patches using cellophane membrane barrier was carried out using modified diffusion cell. The cumulative percentage of drug permeated from F1 to F6 formulation was given in the following order F2 > F1 > F4 > F3 > F6 > F5. In *in vitro* permeation studies it was observed that the drug permeation from the patches F2 has greater diffusion of drug when compared to other formulations. This is due to F2 has low tensile strength value which indicates that it has less elasticity and mechanical strength based on this it is observed that as the elasticity and mechanical strength of the patches increases the diffusion of drug from the formulation decreases and as the elasticity and mechanical strength decreases the diffusion of drug from the formulation increases. From the graph it is evident that drug release is more in formulation F2 which is formulated by using single polymer Eudragit RS 100 as compared to other formulations. The release kinetics was evaluated by making use of zero order, First order, Higuchi's diffusion and Korsmeyer – Peppas's equation. The drug release through the transdermal patches of Nebivolol HCl follows Korsmeyer – Peppas's model. By fitting in Korsmeyer – Peppas's equation the release kinetics follows non Fickian kinetics. The range of n values of Korsmeyer – Peppas's equation is below 0.5, which indicates Fickian kinetics. If the n value of Korsmeyer- peppas's equation is between 0.5 to 1, this indicates non Fickian kinetics. Here the patches of Nebivolol HCl release kinetics fitted in 'n' values are in between 0.5 to 1, so the release is following non Fickian, diffusion-controlled kinetics. Based on all the above preformulation studies the drug was suitable for making the transdermal formulation.

Conclusion

Based on all these factors the transdermal drug delivery system F2- is having greater % drug

release. Formulation F5- having less drug release capacity than other formulations. The formulation F2- shows better extended release up to 12 hrs when compared to other formulations. So it was concluded that the formulation F2- prepared by using Eudragit RS 100 is better formulation for control release of drug up to 12 hrs of time. However, the *in vitro* drug release of the best formulation F2 follows Korsmeyer's peppas model and the mechanism of diffusion. Results of the present study encouraged that the Nebivolol HCl with Eudragit transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

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