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Research Article

Formulation And Evaluation Of Nebivolol Trasdermal Drug Delivery System

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ABSTRACT

The Aim of the present research work are to formulate and evaluate matrix type transdermal drug delivery system which consists of Nebivolol to make a sustained Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β1 – and β2 –adrenergic receptors. The drug release rate increased when the concentration of hydrophilic polymer was increased. The cumulative percentage drug release for all formulations was found. The formulation, F11 [HPMC K4M: Metolose] is considered as a best formulation,since it shows maximum in vitro drug release as 99.08182 12h since it shows maximum in vitro drug release as 99.08182 12h. The best formulation (F11) follows Zero order kinetics and follows Higuchi mechanism in the drug release. Nebivolol in combination with HPMC K4M, K100M and Metolose with incorporation of Tween- 80 (4%) produced smooth, flexible and transparent films. From the results, it was observed that thickness, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug content of TDDS patches ranged from 0.249-0.279 mg.

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INTRODUCTION

Transdermal dosage forms, though a costly alternative to the conventional formulations, are becoming popular because of some unique advantages. Controlled zero-order absorption, simple administration mode and the option of easy removal incase of adverse manifestations make them particularly desirable in cardiovascular therapy. Transdermal delivery systems are those systems designed to deliver the drugs by passage from the dosage form through the skin to be available for distribution via the systemic circulation. The age-old theory that imparted the status of "dead, impermeable barrier devoid of biological activity" to skin had already been challenged by the development of pioneering transdermal products. But a less than impressive commercial growth in this sector had raised some doubts about the feasibility of this route as an efficient device of drug delivery. The journey of transdermal research had commenced with a lot of enthusiasm, as it heralded the promise of noninvasive cutaneous application. The projected advantages were publicized so much that the target consumers were prepared to accept the products even if they were costlier alternatives to the conventional therapy. This acceptability factor had encouraged researchers and industries alike to take up challenging projects in this particular arena. For the last two decades, it remained an area of vital research interest and data was generated for almost every available drug. Transdermal systems are ideally suited for diseases that demand chronic treatment. Hypertension, a disease equally prevalent in the developed and the underdeveloped countries, demands chronic treatment. An analysis shows that cardiovascular disease (CVD) was responsible for the highest mortality rate and mild hypertension may be the humble beginning for the fatal cardiovascular ailments. Hypertensive patients need to be on prolonged medication and sometimes lifelong therapy is advised. Hence noncompliance of the therapy, especially in cases where dosing frequency is high is a major problem. Transdermal delivery is considered to be the ideal method which can bypass the difficulties of first-pass metabolism, enable absolute elimination of GIT toxic effects, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate without the hazards of specialist care as is required in the intravenous infusion. Since transdermal patches offer a better quality of life, they are more popular than the oral dosage forms. Sizeable number of antihypertensive undergo extensive first-pass metabolism, which too can be avoided by transdermal therapy. Hence cardiovascular agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation.

CHITOSAN AND ITS MODIFICATION:

Chitosan, a natural, biodegradable, biocompatible, bio adhesive polymer, is gaining attention in the pharmaceutical field for a wide range of drug delivery. Chitosan is a copolymer of glucosamine and N-acetyl glucosamine linked by β 1–4 glucosidic bonds obtained by N- deacetylation of chitin. It has been reported that chitosan acts as a penetration enhancer by opening epithelial tight-junctions. Due to its positive charges at physiological pH, chitosan is also bioadhesive, which increases retention at the site of application. The main reasons for this increasing attention are certainly its interesting intrinsic properties. Recently, it could be shown that polymers with thiol groups provide much higher adhesive properties. Beyond it, reports of novel developed thiolated polymers, which have been designed for bioadhesive systems, give reasons for their use as matrices for transdermal delivery. Chitosan offers the advantage of easy chemical modifications on account of the primary amino group at the 2-position of each polymer subunit as a result thioglycolic acid was attached covalently to chitosan. This was achieved by the formation of

amide bonds between the primary amino groups of the polymer and the carboxylic acid group of thioglycolic acid to form conjugated chitosan.3,7,8,9

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

It has been recognized that transdermal rate controlled drug delivery offers one or more of the following potential biomedical benefits:

1. Avoid the risks and inconveniences of intravenous therapy.
2. Bypass the variation in the absorption and metabolism associated with oral administration.
3. Permit continuous drug administration and the use of drugs with a short biological halflife.
4. Increase the bioavailability and efficacy of drugs through the bypass of hepatic first-pass elimination.
5. Reduce inter- and intra-patient variability and this is particularly true for those situations in which drug release from the transdermal patch is slower than drug diffusion across the stratum corneum.
6. Drug levels can be maintained in the systemic circulation, within the therapeutic window (i.e., above the minimum effective concentration, but below the level at which side-effects become apparent), for prolonged periods of time.
7. Reduce the chance of overdosing or underdosing through the prolonged, preprogrammed delivery of drug at the required therapeutic rate.
8. Provide a simplified therapeutic regimen leading to better patient compliance.
9. Permit a rapid termination of the medication, if needed, by simply removing the transdermal drug delivery system from the skin surface.1, 4, 18

DISADVANTAGES

The limitations of the transdermal drug delivery system are listed below:

1. A molecular weight less than 500 Dalton is essential to ensure ease of diffusion across the stratum corneum, since solute diffusivity is inversely related to its size.
2. Sufficient aqueous and lipid solubility, a Log P (octanol/water) between 1–3 is required for the permeant to successfully traverse the stratum corneum and its underlying aqueous layers for systemic delivery to occur.
3. Intra and intervariability associated with the permeability of intact and diseased human skin. This implies that there will be fast, slow and normal skin absorptionprofiles resulting in varying biological responses. The barrier nature of intact stratum corneum ensures that this route is only applicable for very potent drugs that require only minute concentrations (e.g. 10–30 ng/ml for nicotine) in the blood for a therapeutic effect.
4. Pre systemic metabolism; the presence of enzymes in the skin such as peptidases and esterases might metabolize the drug into a form that is therapeutically inactive, thereby reducing the efficacy of the drug.
5. Skin irritation and sensitization; referred to as the “Achilles heel” of dermal and transdermal delivery. The skin as an immunological barrier may be provoked by exposure to certain stimuli. This may include drugs, excipients or components of delivery devices resulting in erythema, oedema, etc. The limitations of transdermal drug delivery system due to ionic drugs, large molecular weight drugs and delivery in a pulsatile fashion can be overcome to some extent by novel approaches such as iontophoresis, electroporation and ultrasound.

MATERIAL AND METHODOLOGY:

MATERIALS:

Sr. No	Ingredients	Company Name
1	**Nebivolol**	Spectrum Pharma Research Solutions
2	Ethanol	S.D. Fine Chem. Ltd. India.
3	Acetic acid	S.D. Fine Chem. Ltd. India.
4	Glycerin	S.D. Fine Chem. Ltd. India.
5	Sodium chloride	Rankem
6	Disodium hydrogen phosphate	Rankem
7	Potassium Dihydrogen Phosphate	Merck
8	Methanol	S.D. Fine Chem. Ltd. India.

INSTRUMENTS:

Sr. No	Instruments	Source
1	Electronic Balance	Citizen
2	Digital pH Meter	Consolidated Electric Industries, Bangalore
3	Magnetic Stirrer	Remi equipment's 1MLH
4	UV-Visible Spectrophotometer	Shimadzu UV 1601. Japan
5	Hot Air Oven	Consolidated Electric Industries, Bangalore
6	Modified Franz Diffusion Cell	Locally fabricated

PRE-FORMULATION STUDY

Physical Appearance: Examine the authenticity of the received Nebivolol gift sample.

Melting point determination :

Melting point of Nebivolol was determined by the means of Thiels tube method. Three hundred ml of paraffin was Poured to Thiels tube, and sealed with the flame. Melting temperature of Nebivolol was recognized using thermometer.

FTIR Analysis

Fourier Transform Infra Red analysis (FTIR) was used to consider drug-excipient interaction by detecting the samples in the range of 400-4000 cm-1.The pure drug was combined with surfactant, co-surfactant and oil and the mixture was analyzed. Spectral comparison was done with FTIR of pure drug to eliminate the possibility of important functional groups of the drug that interacts with the excipients.

Determination of λmax :

10 mg of Nebivololwas placed in 2 volumetric flasks of 100ml. Buffer of pH 7.4 is used as the diluents to make stock solution A. Exact ten ml was removed from it and transferred to 100ml volumetric flask (mention stock solution B). Sample from stock solution B was used and detected under UV Spectrophotometer. 250 nm was the point where λmaxwasobtained

METHODOLOGY:

The total 12 batches (F1-F12) of matrix type transdermal patches were fabricated using different ratios of HPMC and Metalose as mentioned in table. Nebivolol (50 mg) was added slowly to the polymeric solutions of individual batch and stirred on a magnetic stirrer until a uniform mixture was obtained. The mixture was then poured on the glass mold, which was covered with a glass funnel of appropriate size to govern evaporation rate of the solvent. The casting solvent was subsequently permitted to evaporate overnight at 40°C for attaining the dried patches.21 After drying, the patches were cut from the glass mold. Backing membrane was affixed with suitable adhesive and dried at the room temperature. The patches were then kept between sheets of wax

paper and stored in desiccators for their evaluation followed by optimization.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Nebivolol	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
HPMC K100M	500mg	_	_	750mg	_	_	1gm	_	_	375mg	375mg	_
HPMC K4M	_	500mg	_	_	750mg	_	_	1gm	_	375mg	_	375mg
Metolose SR	_	_	500mg	_	_	750mg	_	_	1gm	_	375mg	375mg
Glycerin	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
Tween 80	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml

ANALYTICAL METHOD USED IN THE DETERMINATION NEBIVOLOL

The UV spectrophotometrically method was developed for the analysis of the drug using double beam Shimadzu 1601 spectrophotometer.

Determination of λmax

Nebivolol was dissolved in pH 7.4 phosphate buffer solution (PBS): Ethanol in1:1 ratio and further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1601) in the range from 190 to 380 nm, using PBS pH 7.4: Ethanol mixture as blank. The λmax of the drug was found to be 281 nm.

Preparation of phosphate buffer pH 7.4

0.2 M potassium Dihydrogen phosphate was prepared and 250 ml of this solution was mixed with 195.5 ml of 0.2 M NaOH and volume was made up to 1000 ml with distilled water. The pH of the buffer was adjusted to 7.4.

Standard curve for Nebivolol

100 mg of Nebivolol was accurately weighed and dissolved in 100 ml of PBS pH 7.4: ethanol in 1:1 ratio to prepare stock solution I. 1 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare stock solution II, further 2ml, 4 ml, 6ml, 8ml, 10ml and 12ml of II stock was again diluted to 10 ml with the same solvent to get solution containing 2 Cg/ml, 4 Cg/ml, 6 Cg/ml, 8 Cg/ml, 10 Cg/ml, 12 Cg/ml, as the final solutions. Then the absorbance was measured in a UV spectrophotometer at 243 nm against PBS pH 7.4: ethanol as blank. The absorbances so obtained were tabulated as in

EVALUATION OF TRANSDERMAL PATCHES

The transdermal membranes prepared were evaluated for the following parameters:

1. Thickness
2. Folding Endurance
3. Swelling Index
4. Moisture Content
5. Moisture Uptake
6. Water Vapor Transmission (WVT) Study
7. Tensile Strength Test
8. In-vitro Permeation Study
9. Ex-vivo Permeation Study
10. Gel Strength
11. Stability Studies

Thickness

Thickness of all the membranes were measured at five different points on each membrane and average of five readings was taken.

Folding endurance

A modified USP tablet disintegrating tester was used to determinine the folding endurance of the membrane. It consisted of fixed and movable jaws that could be moved up and down at the rate of 30

strokes per minute. The distance between the 2 jaws at their farthest and closest were 6 centimeter and 0.5 centimeter respectively. The membrane (6cm length) was clamped between the jaws in such a way that the jaws were at their closest, the membrane beat across its middle and when at their farthest, the membrane was in a stretched condition. Thus for every stroke of the movable jaw the membrane went through one cycle of bending and stretching. The folding endurance is expressed as the number of strokes required to either break or develop visible cracks on the membrane. The test was conducted for 20 min equating 600 strokes. The locally fabricated folding endurance tester is shown in Figure A.

Swelling index

The polymeric membrane cut into 3 cm2 were weighed accurately and allowed to swell on a agar gel plate contain 2% w/v. Individual membranes were weighed periodically until they showed a constant weight.

$$\text{Swelling Index} = \frac{\text{Wet weight - Initial weight}}{\text{Wet weight}} \text{X } 100$$

Percentage of moisture content

The membrane of size 3 cm2 were weighed individually and stored in desiccator consists of fused calcium chloride at room temperature for 24 h. Individual membranes were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

$$\%\text{Moisture Content} = \frac{\text{Initial weight - final weight}}{\text{final weight}} \text{X } 100$$

Percentage of moisture uptake

A weighed membrane of size 3 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.

Water vapor transmission (WVT) study

The membrane 3.142 cm2 was fixed over the brim of a glass vial, consists of 2 g of fused calcium chloride as desiccant. The vial was weighed and kept in desiccator contain saturated solution of potassium chloride to provide 84% relative humidity. The vial was taken out and weighed at every 24 h intervals for a period of 7 days. The flux i.e. the amount of water vapour transmitted through 1 centimeter2 per 24 h and permeability coefficient were calculated using the formula.

$$P = \frac{\text{Slope}}{\text{'P'}} \text{X } 24$$

Where, P = permeability coefficient.

'P' = Vapour pressure of saturated solution of potassium chloride.

Tensile strength and extension

Tensile strength of the films was determined by using housefield universal testing machine. The sensitivity of the machine was 1 mg – 500 mg. It consists of two load cell jaws. The upper one is movable and lower one was fixed. The films of specific size (4x1 cms) was fixed between these grips and upper jaw was moved at a speed of 100 mm/min. (ISI STD speed) applying force gradually till the films break. The tensile strength of the films was taken directly from the dialed reading in kilogram and extension of film in mm.

In vitro skin permeation study

The in vitro skin permeation experiments were conducted in a modified Franz diffusion cell (receptor compartment capacity: 16 ml; surface area: 1.5 cm2). The diffusion cell consists of two compartments; the upper compartment i.e. the donor compartment which contains the transdermal system with rate controlling membrane in contact with the dialysis membrane; the bottom part contains the receptor solution, the water jacket for temperature control and the

sampling port. The permeation study was carried out across the dialysis membrane-110. The receiver compartment was filled with 16 ml of ethanol: phosphate buffer pH 7.4 (1:1). The donor compartment was then placed in position such that the surface of the membrane just touches the receptor fluid surface. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred at 50 rpm; the temperature of whole assembly was maintained at 370c 0R.5oC by circulating hot water inside the water jacket. The samples were withdrawn at different time intervals up to 24 h and replenished with an equal volume of ethanol: buffer solution at each time interval. The absorbance of withdrawn samples was measured at 281 nm using U.V spectrophotometer.

Ex-vivo permeation studies

Ex-vivo skin permeation studies were performed [Institutional animal ethics committee. National college of pharmacy. Shimoga. IAEC/IW/1013/9-10] by using a modified Franz diffusion cell with a receptor compartment capacity of 16 ml. The Wistar albino rat's skin containing epidermis and stratum corneum excised from the dorsal surface was mounted between the donor and receptor compartment of the diffusion cell. The transdermal device was placed over the skin. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4: ethanol mixture in ratio 1:1. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred at 50 rpm; the temperature of whole assembly was maintained at 370c +/- 0.5°C by circulating hot water inside the water jacket. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of water: phosphate buffer pH 7.4 at each sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time. The locally fabricated modified Franz diffusion cell

Gel strength

Gel strength of the chitosan and conjugated chitosan was determined using locally fabricated instrument, having free moving piston with pointed conical tip (tip length-10 mm; tip angle-60°) along with the provision to apply the load over the piston. The 10 % w/v gels of both the polymers were prepared individually using 4 % v/v hydrochloric acid as a solvent. The homogenized gel was filled in sample holder and stored below 10°C in a refrigerator for 24 h. The gel strength of the polymer was determined by placing the piston tip over gel surface and the load was applied over the piston at a constant rate by adding the water using i.v. infusion set at a constant flow rate (100 ml/min). The load required to pierce the piston tip upto 4 mm in the gel was taken as the gel strength of that polymer. The temperature of the gel was maintained below 10°C throughout the study.

Stability studies

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life. ICH specifies the length of study and storage conditions.

Long term testing:

25oC +/- 25oC / 75% RH • +/-5% for 12 months

Accelerated testing:

40oC +/- 250C / 75% RH +/-• 5% for 6 months

Method

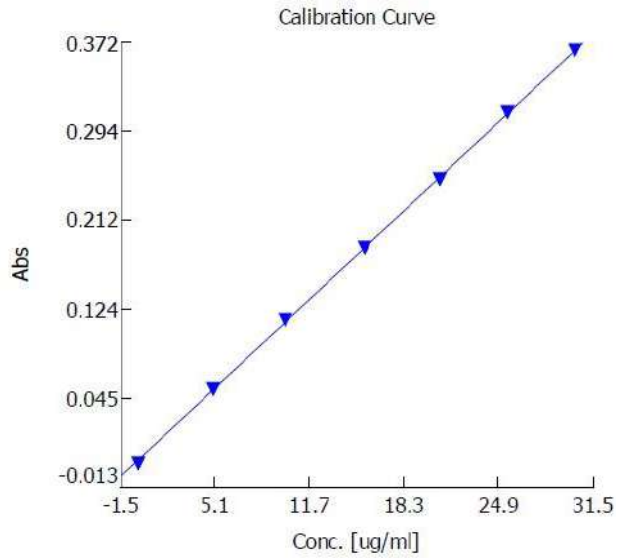
The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were then stored at 40oC /

75% RH for 2 months and evaluated for their permeation study

EXPERIMENTAL RESULTS

CONSTRUCTION OF STANDARD GRAPH OF NEBOVOLOL

Concentration (µg/ml)	Absorbance at 238 nm
0	0
5	0.065
10	0.128
15	0.188
20	0.241
25	0.301
30	0.355



EVALUATION OF TRANSDERMALPATCHES

Formula code	Thickness(mm)	Weight (g)	Folding endurance	% moisture absorption
F1	0.201±0.021	0.860±0.017	111.0±4.582	6.973±2.324
F2	0.201±0.022	0.860±0.018	108.1±4.573	6.874±2.374
F3	0.202±0.021	0.861±0.017	106.13±4.664	6.873±2.324
F4	0.201±0.023	0.862±0.019	105.10±5.72	6.863±2.121
F5	0.201±0.021	0.863±0.017	107.1±4.021	6.888±2.122
F6	0.202±0.022	08.63±0.019	109.10±4.001	6.989±2.133
F7	0.203±0.021	0.862±0.081	106.1±4.111	6.744±2.144
F8	0.201±0.023	0.860±0.017	104.7±5.11	6.633±2.223
F9	0.204±0.022	0.861±0.019	102.13±6.12	6.534±2.234
F10	0.202±0.021	0.862±0.018	95.14±6.222	6.434±2.143
F11	0.202±0.024	0.862±0.020	111.14±4.223	6.343±2.174
F12	0.202±0.022	0.863±0.017	109.12±4.233	6.444±2.174

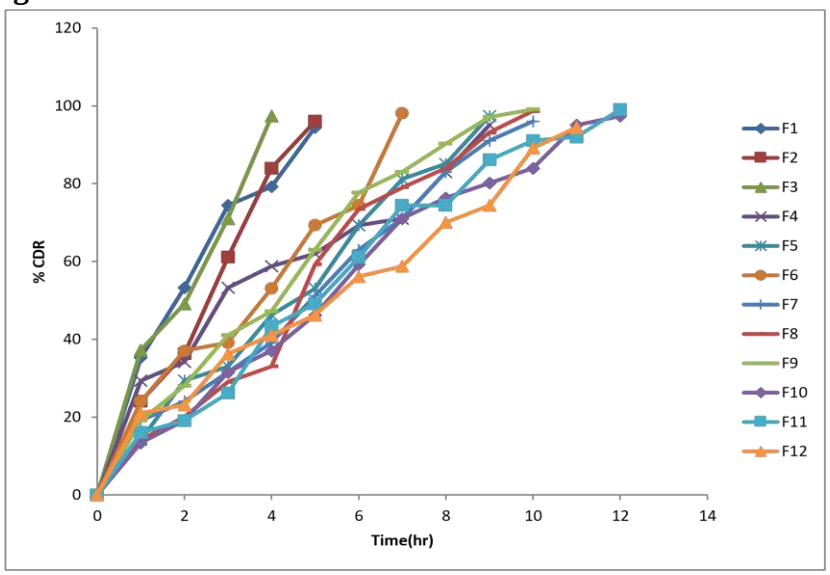
IN VITRO DISSOLUTION RESULTS OF FORMULATIONS

Time (hrs.)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	35.31818	24.05455	37.22727	29.4	14.12727	24.05455
2	53.26364	36.27273	49.06364	34.17273	29.4	37.03636

3	74.45455	61.09091	71.01818	53.26364	33.02727	39.13636
4	79.22727	84	97.36364	58.8	46.2	53.07273
5	94.5	96.02727		62.04545	53.07273	69.3
6				69.3	69.3	74.45455
7				71.01818	81.13636	98.12727
8				83.04545	85.14545	
9				95.07273	97.36364	
10						
11						
12						

Time (hrs.)	F7	F8	F9	F10	F11
0	0	0	0	0	0
1	19.09091	14.12727	19.09091	13.36364	16.03636
2	24.05455	20.04545	28.06364	19.09091	19.09091
3	31.5	29.01818	41.04545	31.5	26.15455
4	39.13636	33.02727	47.15455	37.03636	43.33636
5	51.16364	59.18182	63	46.2	49.06364
6	63	73.5	77.7	59.18182	61.09091
7	71.01818	79.03636	83.04545	71.01818	74.45455
8	83.04545	84	90.3	76.36364	74.45455
9	91.06364	93.16364	97.17273	80.18182	86.1
10	96.02727	98.7	99.08182	84	91.06364
11				95.07273	92.01818

% Cumulative Drug release of Formulations



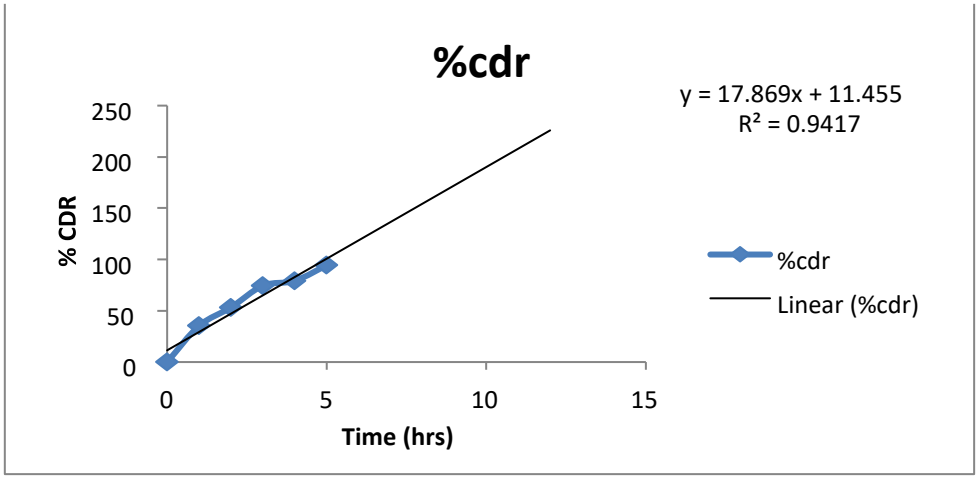
% CDR

RATE ORDER KINETICS

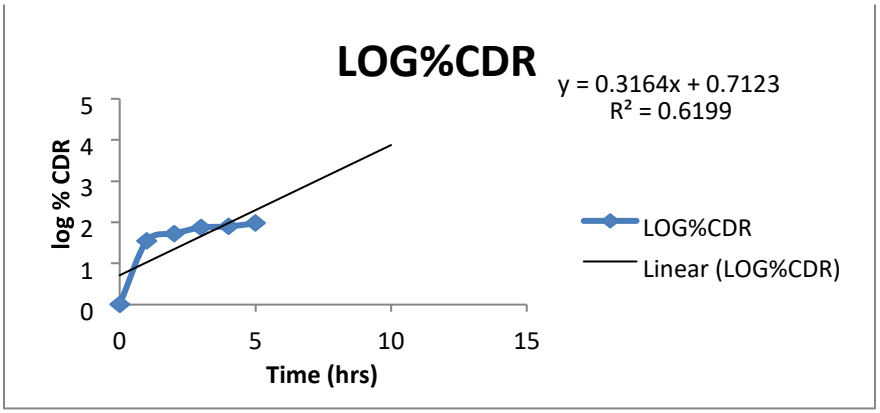
The best formulation (F11) follows Zero order kinetics and follows Higuchi mechanism in the drug release.

RATE ORDER KINETICS

F1 Zero order



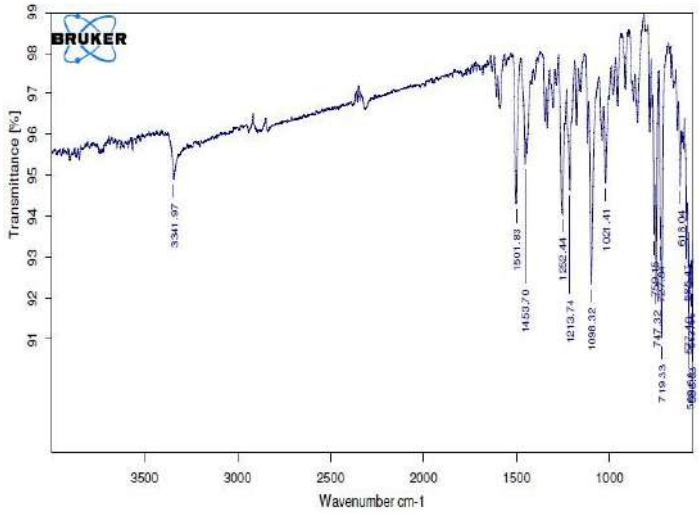
1st order



FT-IR SPECTROPHOTOMETRICALLY ANALYSIS

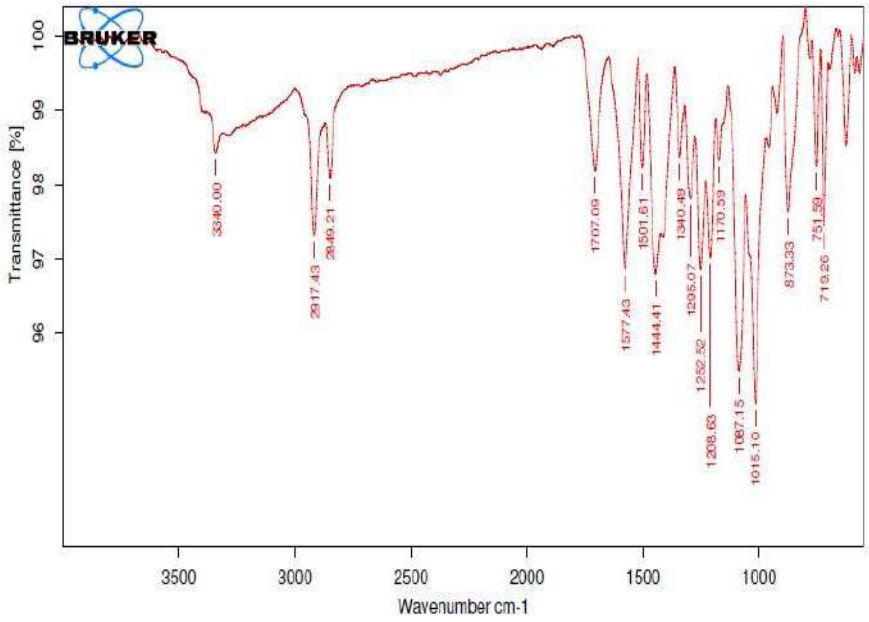
The samples of chitosan and conjugated chitosan were prepared in the form of KBr pellets and subjected for scanning from 4000 cm-1 to 600 cm-1 using FT-IR spectrophotometer (SHIMADZU FT-IR 8400)

IR SPECTRA OF NEBIVOLOL



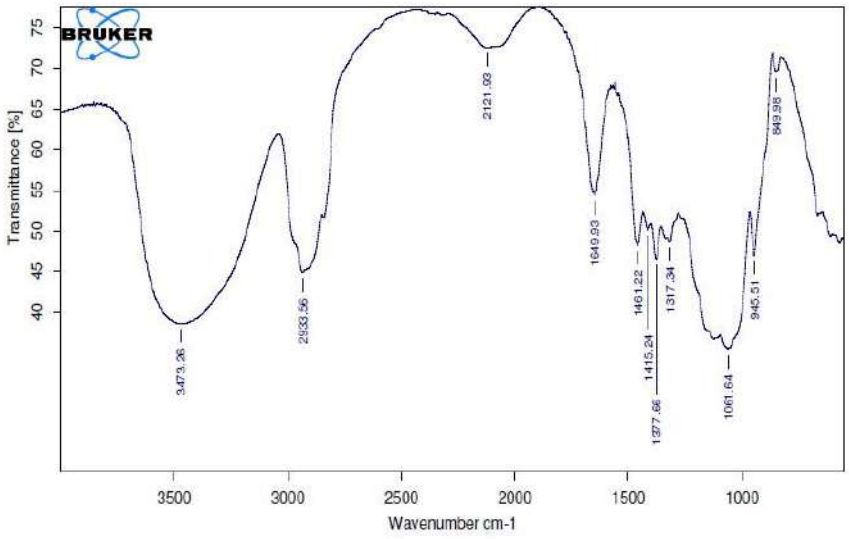
IR SPECTRA OF NEBIVOLOL

BEST FORMULATION IR SPECTRA OF NEBIVOLOL



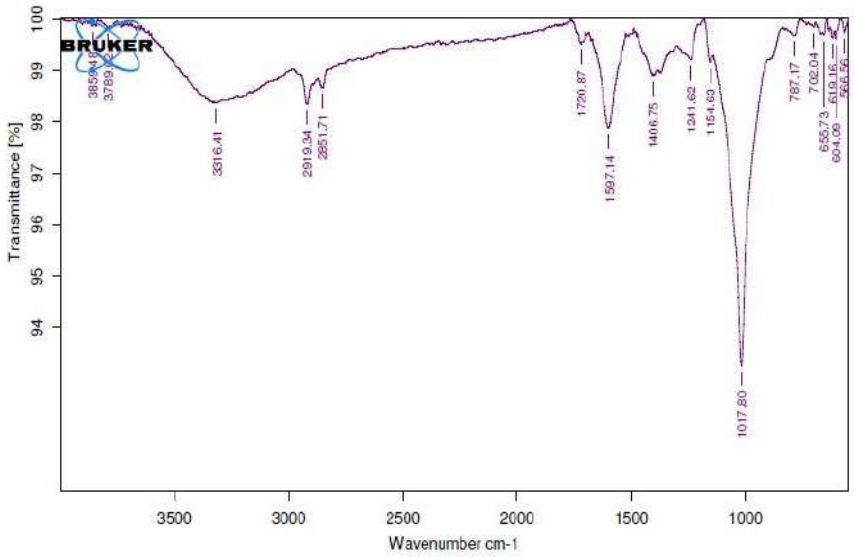
BEST FORMULATION IR SPECTRA OF NEBIVOLOL

IR SPECTRA OF HPMC K4M



IR SPECTRA OF HPMC K4M

IR SPECTRA OF METOLOSE



IR SPECTRA OF METOLOS

DISCUSSION

Nebivolol in combination with HPMC K4M, K100M and Metolose with incorporation of Tween80 (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, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug content of TDDS patches ranged from 0.249-0.279 mg. 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, invitro and exvivo permeation, gel strength and stability studies. Observations of all the formulations form physical characterization have shown that the formulations show optimum results.

SUMMARY & CONCLUSION

SUMMARY

The transdermal route of drug delivery is becoming increasingly popular with the demonstration of the percutaneous absorption of large number of drugs. The transdermal drug delivery system approaches zero order drug input and performs as a constant intravenous infusion. For this purpose, the fabrication of TDDS requires suitable matrix systems, rate controlling membranes and drug reservoirs. Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β1 - and β2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. In the present study different polymers like HPMC K4M, K100M and Metolose were used to prepare matrix type transdermal system of Nebivolol. Drug and polymers were subjected for compatibility study using differential scanning calorimetry, which suggested that there was no interaction between drug and polymers. The results of permeation study indicated that the drug permeation was in controlled fashion. To analyze the mechanism of drug release from the membranes, the invitro permeation data were fitted to zero order, first order, Higuchi release

model and Korsmeyer and Peppas model. It was observed that the drug permeation followed anamolous (Non Fickian) diffusion in S0, S1, S2, S4, S5 membranes and S3 membrane follows anamolous (Non Fickian) case 2 profile.

CONCLUSION

Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β1 - and β2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, BYSTOLIC does not demonstrate α1adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity. The drug and polymers were subjected for the compatibility study using DSC, which suggested that there was no significant interaction between the drug and polymers. The drug release rate increased when the concentration of hydrophilic polymer was increased. The cumulative percentage drug release for all formulations was found. The formulation, F11 [HPMC K4M: Metolose] is considered as a best formulation, since it shows maximum in vitro drug release as 99.08182 12h. The best formulation (F11) follows Zero order kinetics and follows Higuchi mechanism in the drug release.

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