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RESEARCH ARTICLE

NEW ERA IN THE TREATMENT OF HYPERTENSION: A DRUG METOPROLOL SUCCINATE USED AS A TRANSDERMAL DRUG DELIVARY SYSTEM

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ABSTRACT

The objective of the present investigation was to formulate (Controlled) and evaluate transdermal Drug delivery system of Metoprolol Succinate. The primary object is to overcome hepatic first pass metabolism and delivery of drug at controlled rate to achieve therapeutically effective drug level for a prolonged period of time of Metoprolol Succinate. On the basis of relatively better performance of various polymers, combination was selected for the fabrication of drug-reservoir. Propylene glycol as a plasticizer and PEG 400 as surfactant, Tween 80 and DMSO as a penetration enhancer were employed in fabrication of drug reservoir. Acetone and Ethanol is used as a solvent for dissolving the HPMC and ERS100 respectively. Medicated films were evaluated for physical & mechanical properties like Drug content, Folding endurance, Weight variation, % moisture content, %moisture uptake, and Thickness.

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INTRODUCTION

Transdermal Drug Delivery System (TDDS) is a polymeric drug delivery system which contains drug either in a reservoir with a rate-controlling membrane or dispersed in a polymer matrix. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Transdermal therapeutic system is essentially a multilaminate structure that is composed of Basic Component are Drug, Polymer matrix /Drug reserviour, Release liner, Adhesives, Backing layer, Peel Strip, Permeation enhancers. Transdermal route of administration can not be employed for all types of drugs. It depends upon optimal physicochemical properties of the drug, its biological properties, type of drug delivery system and the requirement of penetration enhancers etc. In addition consideration of the pharmacokinetic and pharmacodynamic properties of drug is necessary. The most important requirement of drug to be delivered transdermally is demonstrated by need for controlled delivery, such as short half-life, adverse effect associated with other route or a complex oral or I.V. dose regimen. Polymer is the backbone of Transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or drug polymer matrix is sandwich between two polymeric layers. An outer impervious baking layer that

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prevent the loss of drug through the baking surface and inner polymeric layer that function as an adhesive and rate controlling membrane. The transdermal system requires proper selection of polymeric material or a series of polymers whose diffusive characteristics will be such that a desired permeation rate of a specific drug or other bioactive agent can be obtained. In addition, the solute size and polymer structure control the solute diffusion coefficient. Depending upon the nature of polymer water interaction polymer can be broadly classified into

- Hydrophobic polymers.
- Hydrophilic polymers.
- Water-soluble polymers. (Hydrogels.)

Release liner: It protects the patch during storage. The liner is removed prior to use.

Adhesives: The fasting of all transdermal devices to the skin can be achieved by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. The adhesive must posses' sufficient property so as to firmly secure the system to the skin surface and to maintain it in position for as long as desired even in the presence of water. After removal of patch any traces of adhesive left behind must be capable of being washed with water & soap. Adhesion is understood to be the net effect of three phenomenons.

Peel: The resistance against the breakage of the adhesive bond.
Track: **-** The ability of a polymer to adhere to a substrate with little contact pressure.

Creep: The viscous relaxation of the adhesive bond upon shear.
Backing layer: It protects the patch from the outer environment. The backing layer should be impermeable to drug and penetration enhancers. It serves as a function of holding the entire system and protects drug reservoir from atmosphere. The commonly used backing materials are polyesters aluminized polyethylene terapthalate and siliconized polyethylene terapthalate and aluminum foil of metalized polyester laminated with polyethylene. Peel Strip: The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage & protects the finished device against contamination. Polyesters foils, aluminium foil and other metalized laminates are typical materials which are commonly used. Penetation Enhancers: Majority of drugs do not penetrate the skin at a rate sufficiently high for therapeutic efficacy. The stratum corneum is generally recognized as a principle skin barrier for entry of foreign substances. To achieve and to maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin must be overcome. Skin penetration enhancers have been used to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. Eg: DMSO, Alkyl methyl suphoxide, Pyrolidones, Urea, SLS.

Design of Transdermal Delivery System: The basic components of any transdermal delivery system include the drug dissolved or dispersed in an inert polymer matrix that provides support and platform for drug release. There are two basic designs of the patch system that dictate drug release characteristics and patch behavior.

Matrix or Monolithic: The inert polymer matrix binds with the drug and controls its release from the device.

Reservoir or Membrane: The polymer matrix does not control drug release. Instead, a rate controlling membrane present between the drug matrix and the adhesive layer provides the rate limiting barrier for drug release from the device. Technologies for Developing Transdermal Drug Delivery Systems: Several technologies have been successfully developed to provide a mechanism of rate control over the release and the transdermal permeation of drugs

- Polymer membrane partition-controlled TDD systems- or Membrane - Moderated Transdermal
- Drug Delivery System (Reservoir type):
- Adhesive Dispersion - TDDS (Mixed Monolithic Reservoir type):
- Matrix diffusion- controlled TDDS (Monolithic Device)
- Micro reservoir diffusion- controlled TDDS

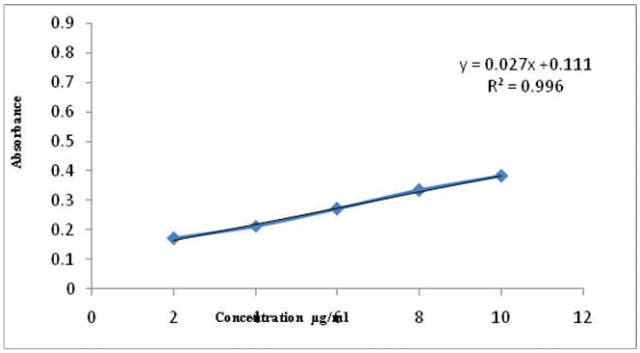
MATERIAL AND METHOD

The drug Metoprolol Succinate & Polymers was procured/gifted by pharmaceutical companies and are listed in Table 1

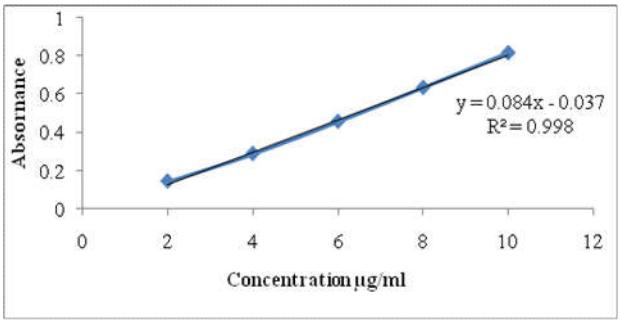
Preparation of Transdermal Patch (Patel, 2012; Sanjoy, 2011; Jain, 1997; Patel, 2009; Dinesh kumar, 2011**):** Transdermal patch containing Metoprolol Succinate was prepared by the solvent evaporation technique for the formulation shown in Table 7. Solution of HPMC and Eudragit RS100 were prepared separately in Ethanol and Acetone, respectively. Two polymeric solutions were mixed to which weight amount of Metoprolol Succinate was added slowly. The appropriate amount of propylene glycol as plasticizer, surfactant ((PEG400) and Permeation enhancer (TWEEN 80/DMSO) were added and mixed. The drug–polymer homogeneous dispersion was formed by slow stirring with a mechanical stirrer then the solution was poured in a Petridish of 23.74cm^2. The Petridish was kept aside for drying at room temperature for 24hr .Inverted plastic funnel was placed over the petridish to prevent the current of air. After drying, the patches were peeled from Petridish. The patches were cut with a circular of 2 cm internal diameter then wrapped in aluminum foil; aluminum foil was used as backing membrane and preserved in desicator for further studies. Following are the optimized formula by which patch are prepared.

Characterization of Drug

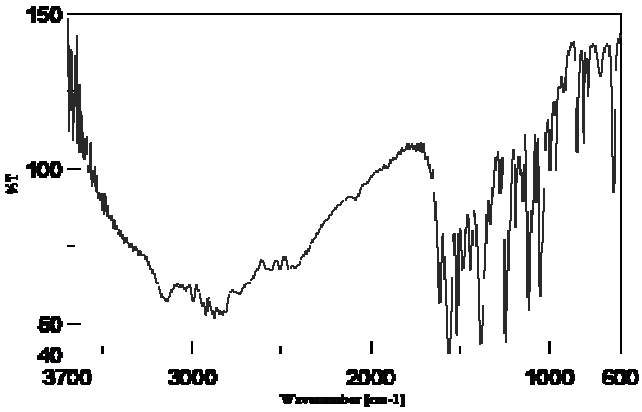
Transdermal patch after drying



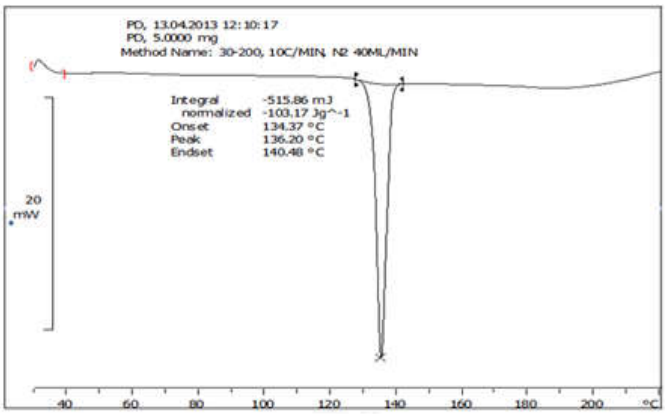
Graph 1. Calibration curve of Metoprolol Succinate: pH 7.4 phosphate buffer



Graph No.2. Calibration curve of Metoprolol Succinate: Methanol



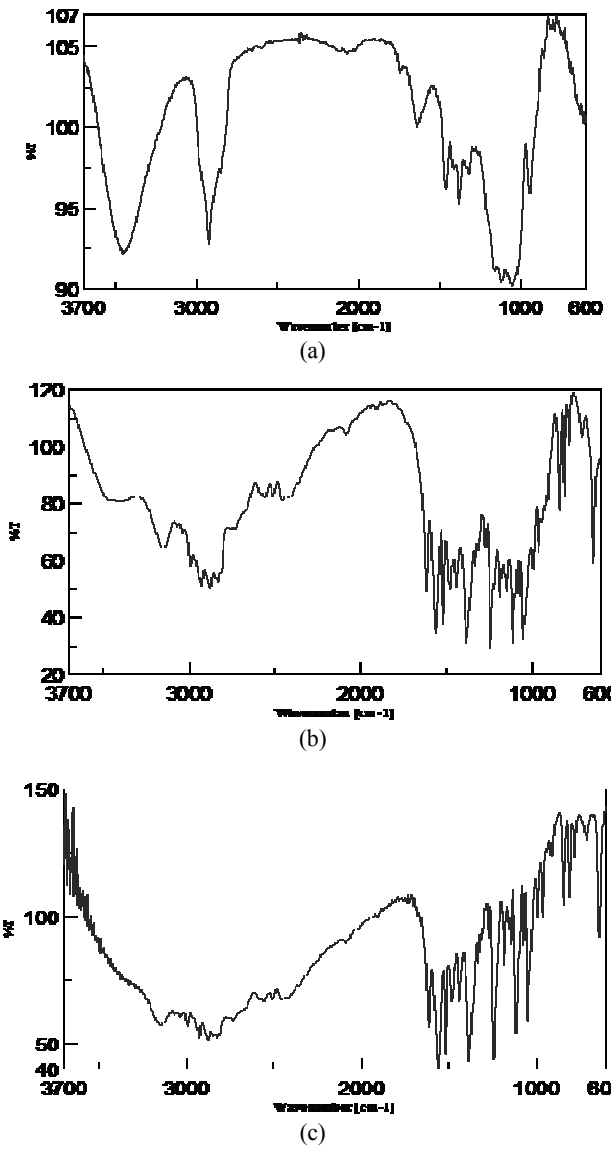
Graph No. 3. FT-IR of Drug (Metoprolol Succinate)



Graph No. 4. DSC of Drug (Metoprolol Succinate)

Organoleptic characteristics of drug: The physical characteristic of drug including Description, colour, odour, taste.

Melting Point: The drug was filled into a glass capillary tube, which was sealed at one end. The temperature was noted when it completely melted.

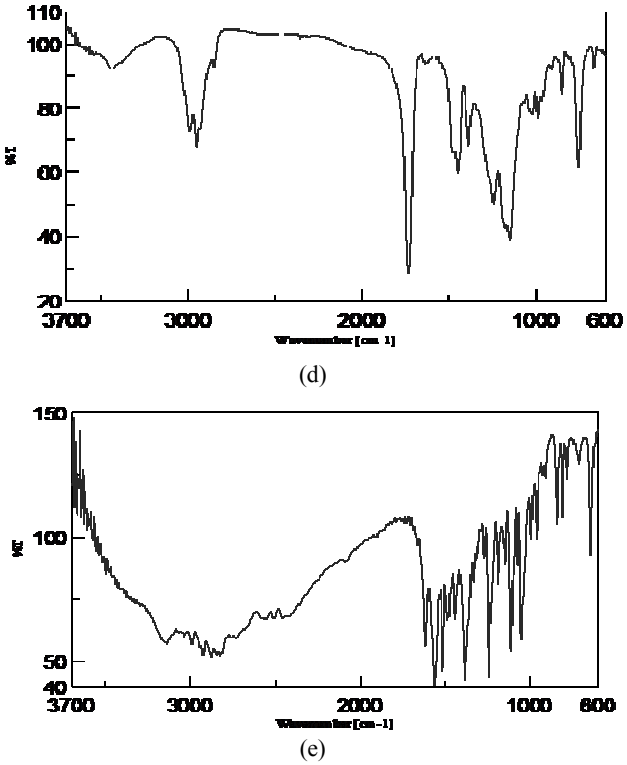


(a)

(b)

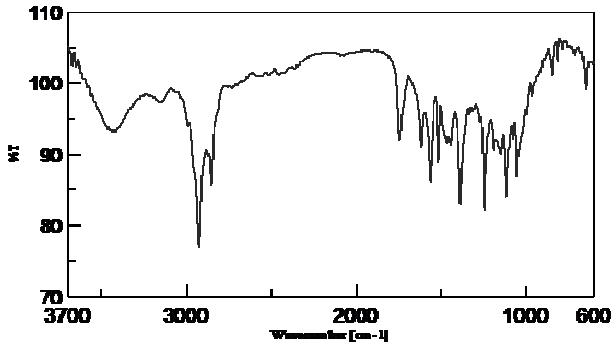
(c)

Graph No. 5. FT-IR spectra of a) HPMC b) Drug c) Drug + HPMC



(d)

(e)



(f)

Graph No. 6. FT-IR spectra of d) ERS100 e) Drug f) Drug + ERS100

Preparation of standard calibration curve of Metoprolol Succinate in Phosphate Buffer pH7.4 (Indian Pharmacopoeia, 2010). A standard solution of 100 µg / ml was prepared by dissolving 10 mg of Drug in 100 ml phosphate buffer pH 7.4, from this solution aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 were pipette out in to 10ml volumetric flask and volume was made up to the mark with buffer. The solution thus will have the concentrations between 2, 4, 6, 8, and10 µg respectively. The content was mixed properly and the absorbance was measured at 221.5 nm against blank by UV- visible double beam spectrophotometer (UV- 2600, Thermo-Fischer Scientific Ltd, India). A standard curve of Absorbance Vs concentration was plotted.

Preparation of standard calibration curve of Metoprolol Succinate in Methanol: A standard solution of 100 µg / ml was prepared by dissolving 10 mg of Drug in 100 ml Methanol, from this solution aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 were pipette out into 10ml volumetric flask and volume was made up to the mark with buffer. The solution thus will have the concentrations between 2, 4, 6, 8, and10 µg respectively. The content was mixed properly and the absorbance was measured at 223.0 nm against blank by UV- visible double beam spectrophotometer (UV- 2600, Thermo-Fischer Scientific Ltd, India).A standard curve of Absorbance Vs concentration was plotted.

Infrared spectra of Metoprolol Succinate: The pure drug was mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over a wave range of 3700 - 600cm.$^{-1}$

Differential Scanning Calorimetry of Drug: DSC of Drug i.e. Metoprolol Succinate is taken by using instrument Mettler Toeedo USA.

Drug – Excipients compatibility study (Sanjoy, 2011; Chathoth Suja, 2012**):**

Drug – Excipients Compatibility study is done by three methods.

Physical compatibility study: In this study Drug was mixed with different excipients combined with each other and place it for some period (4 Weeks) at R.T. and observed the physical changes such as color change.

Infrared spectra of Metoprolol Succinate and different polymer (Biswajit Mukherjee, 2005; Aqil, 2002)**.** In this study Drug +different Excipients combined with each other and place it for some period (4 Weeks) at R.T. The combinations of drug – polymer I.R. taken at 3700 - 600 cm-1 range the spectra were recorded with the FTIR Jasco Model-4100, Japan.

Differential Scanning Calorimetry of Drug Mixture (Drug+HPMC+ERS100) (Chathoth Suja, 2012**):** DSC are taken containing Drug (Metoprolol Succinate), HPMC, and ERS100 at Govt. College of pharmacy Aurangabad by using instrument Shimadzu DW 60 Japan.

RESULTS AND DISCUSSION

Organoleptic characteristics of drug

Melting Point

Preparation of standard calibration curve of Metoprolol Succinate in pH 7.4 Phosphate Buffer (λmax = 251.5 nm): A standard curve of Absorbance VS concentration was plotted.

Preparation of standard calibration curve of Metoprolol Succinate in Methanol (λmax = 223.0 nm) A standard curve of Absorbance Vs concentration was plotted.

FT- IR. Of Metoprolol Succinate: The major absorption bands are given in Table 7.

Differential scanning calorimetry of Drug: The DSC thermo gram of Drug (Metoprolol Succinate) displayed the characteristic onset at 134.37 ^{0}C corresponding to its melting point.

Drug – Excipients compatibility study (Sanjoy, 2011; Chathoth Suja, 2012**):**

Drug – Excipients Compatibility studies result by three methods

Physical compatibility study: In this study it is observed that there is no physical changes such as color changes not occur with drug was mixed with different excipients for period of 4 Weeks at R.T.

Infrared spectra of Metoprolol Succinate and different polymer (Biswajit Mukherjee, 2005; Aqil, 2002**):** The FT-IR spectra of all the sample were taken .The FT-IR spectra of Drug+ HPMC, Drug + ERS100, Drug + HPMC+ERS100, shows the characteristic peak of Metoprolol Succinate 3040-3010 , 3320-3140, 1350-1260, 2960-2850, 1650-1550.

The result shows that there is no significant change in characteristic peak of Metoprolol Succinate .The FT-IR study reveals that the drug (Metoprolol Succinate) not show any interaction with polymer this indicate drug (Metoprolol Succinate) is compatible with the polymer which are selected for the formulation.

Differential Scanning Calorimetry Drug Mixture (Chathoth Suja, 2012**):** The DSC thermo gram Containing Drug (Metoprolol Succinate), HPMC, and ERS100, Shown that there was no change in the melting point of Drug. This starts at 129.26^{o} C and end at 160.64^{o}C, so we conclude that the formulations was stable and ideal for transdermal drug delivery system. Reported Melting point 136 ^{o}C Observed Melting point 135.99^{o}C.

Table No.1. List of active ingredient and polymers used in the work.

Sr.No.	Name of Chemical	Product Information	Procured./Gifted By
1	Metoprolol Succinate	Standard: IP Grade	Wockhardt Pharmaceutical, Aurangabad.
2	Eudragit RS100	AR Grade	Evonik Pharma, Mumbai.
3	HPMC	AR Grade	Modern Scientific Chemical Labs, Nashik.
4	Propylene glycol	AR Grade	Modern Scientific Chemical Labs, Nashik.
5	Polyethylene glycol	AR Grade	Modern Scientific Chemical Labs, Nashik.
6	Tween 80	AR Grade	Modern Scientific Chemical Labs, Nashik.
7	DMSO	AR Grade	Modern Scientific Chemical Labs, Nashik.
8	Calcium chloride	AR Grade	Modern Scientific Chemical Labs, Nashik.
9	Sodium chloride	AR Grade	Modern Scientific Chemical Labs, Nashik.
10.	Acetone	AR Grade	Modern Scientific Chemical Labs, Nashik.
11	Ethanol	AR Grade	Modern Scientific Chemical Labs, Nashik.

Table 2. List of Instruments used in the work

Sr. No.	Instrument Name	Make and Model
1	Magnetic Stirrer	REMI Electrotechnik Ltd, Vasai, India.
2	UV-Visible double beam pectrophotometer	UV- 2600, Thermo-Fischer Scientific Ltd, India.
3	FTIR	Jasco Model-4100, Japan.
4	Analytical weighing balance	Phoenix, 300-P, India.
5	DSC	i) Shimadzu DW 60 Japan. ii) Mettler Toeedo USA.
6	Stability chamber	(Microtronics).
7	Hot air oven	Remi

Table No. 3. Optimized Formulation (2:1 & 1:1 Polymer Ratio)

Composition (mg/ml)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	60	60	60	60	60	60	60	60	60	60	60	60
HPMC	334	334	334	334	334	334	250	250	250	250	250	250
ERS100	166	166	166	166	166	166	250	250	250	250	250	250
PG	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
PEG400	0.2	0.3	-	-	-	-	0.2	0.3	-	-	-	-
Tween 80	-	-	0.2	0.3	-	-	-	-	0.2	0.3	-	-
DMSO	-	-	-	-	0.2	0.3	-	-	-	-	0.2	0.3
Acetone	5	5	5	5	5	5	5	5	5	5	5	5
Ethanol (q.s)	20	20	20	20	20	20	20	20	20	20	20	20

Table No.4. Organoleptic characteristic of Metoprolol Succinate

Properties	Reported	Observed
Description	Crystalline powder	Crystalline powder
Taste	Tasteless	Tasteless
Colour	White	White
Odour	Odourless	Odourless

Table No. 5. Melting Point

Drug	Reported	Observed
Metoprolol Succinate	136^0 C	134-136^0 C

Table No. 6. Standard calibration curve of Metoprolol Succinate in pH 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance
2	0.171±0.016
4	0.214±0.031
6	0.271±0.024
8	0.334±0.057
10	0.383±0.023

Table No.7. Standard calibration curve of Metoprolol Succinate in methanol

Concentration (µg/ml)	Absorbance
2	0.145± 0.057
4	0.289±0.034
6	0.457±0.017
8	0.634±0.064
10	0.815±0.043

Table No.8. Absorption bands.

Aromatic CH Stretch	3040-3010 cm^{-1}
2^0 Amine NH	3320-3140 cm^{-1}
CH-OH Alcohol (2^0)	1350-1260 cm^{-1}
Alkyl CH- Stretch (CH_2-CH_2)	2960-2850 cm^{-1}
Aromatic & Aliphatic Ether	1650-1550cm^{-1}

Table No. 9. Drug – Excipients compatibility study

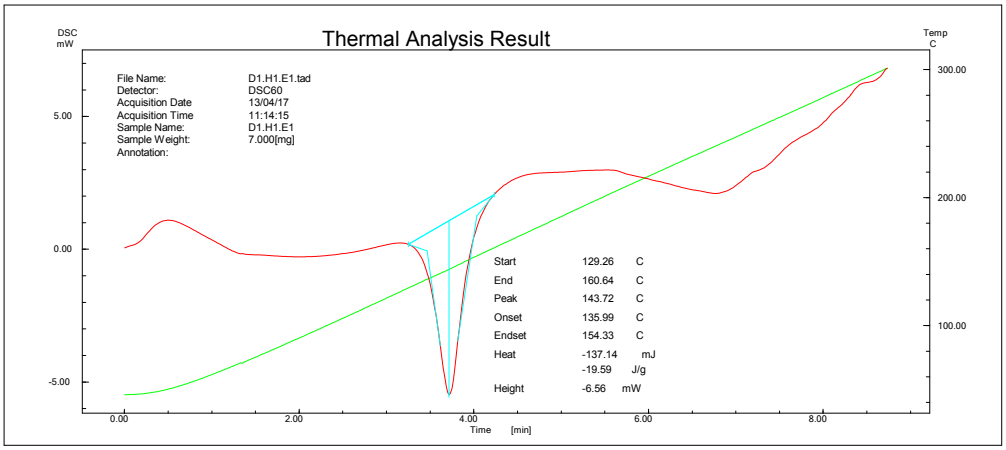
Physical mixture	Initial Observation	After 1weeks	After 2weeks	After 3weeks	After 4weeks
HPMC+DRUG	White color	No change	No change	No change	No change
ERS100+DRUG	White color	No change	No change	No change	No change
HPMC+DRUG+ ERS100	White color	No change	No change	No change	No change

Table No.10. Evaluation of Transdermal Patches

Sr. no.	Formulation	% Drug content	Folding endurance (No. of time)	%Moisture Content	Weight variation(mg)	Thickness(mm)
1	F1	97.31±0.036	207±5.011	2.23	21.39±0.034	0.185±0.005
2	F2	97.55±0.055	218±4.028	2.14	20.71±0.018	0.189±0.011
3	F3	96.44±0.025	226±2.013	1.83	22.67±0.025	0.260±0.014
4	F4	97.59±0.036	237±6.018	1.70	21.33±0.008	0.263±0.012
5	F5	98.20±0.004	249±4.028	1.28	20.74±0.032	0.205±0.066
6	F6	98.12±0.032	258±5.241	1.20	22.08±0.021	0.208±0.011
7	F7	97.92±0.026	271±6.550	1.17	21.61±0.019	0.184±0.002
8	F8	97.48±0.015	269±5.081	1.11	20.54±0.032	0.187±0.008
9	F9	96.33±0.036	276±2.016	1.02	21.77±0.015	0.261±0.005
10	F10	98.07±0.027	285±5.113	0.98	20.79±0.023	0.264±0.010
11	F11	97.66±0.065	292±4.019	0.87	20.52±0.026	0.201±0.013
12	F12	98.77±0.034	300±6.115	0.72	22.27±0.015	0.203± 0.004

Table No.11. Cumulative % Drug released

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F12 (Skin)
0hr	0	0	0	0	0	0	0	0	0	0	0	0	0
1	13.85	13.77	13.55	13.03	12.88	12.81	12.66	12.07	11.4	11.18	11.33	10.44	10.37
2	18.96	18.37	17.85	17.5	16.88	16.96	15.92	15.03	15.62	14.44	14.22	13.77	13.70
4	29.55	28.07	27.77	27.03	25.4	26.07	25.33	24.55	23.25	23.85	23.25	22.59	21.11
8	65.7	64.22	59.33	59.62	56.22	55.03	53.11	47.4	45.62	44.22	42.22	39.18	37.48
12	94.14	92.88	87.03	86.88	84.81	83.03	81.25	68.07	65.11	63.03	60.74	58.29	55.40
13	96.37	95.18	91.4	90.07	89.85	88.66	86.88	78.59	76.29	75.11	72.59	60.66	57.70
14		97.11	94.88	94.07	92.29	93.77	91.25	80.37	78.88	76.07	74.88	65.85	63.55
15			95.18	95.48	94.22	95.18	95.4	87.48	85.4	84.22	83.33	78.37	72.59
16					96.44	97.25	96.44	95.33	92.22	90.29	88.74	81.25	76.66
20							97.70	97.11	95.18	94.37	93.18	88.59	86.44
21								98.07	97.92	96.44	95.03	90.44	89.33
22									98.22	97.92	96.37	92.37	91.25
23											97.85	93.18	94.14
24												94.14	96.66



Reported Melting point 136 ^oC **Observed Melting point 135.99^oC**

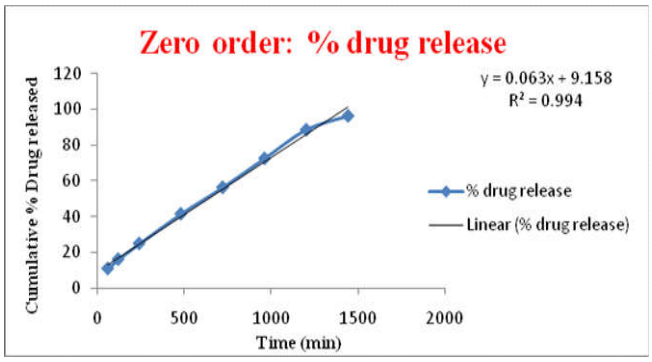
Graph No.7. DSC of Drug+ HPMC+ERS100

Table No.12. Kinetic for Best fit model F1-F6 formulation (Indian Pharmacopoeia, 2010)

Formulation	Model	R^2 value	Slope
F1	Higuchi	0.956	-13.84
F2	Higuchi	0.916	-11.75
F3	Higuchi	0.946	-12.73
F4	Higuchi	0.946	-12.91
F5	Higuchi	0.956	-13.58
F6	Higuchi	0.955	-13.65

Table No.13. Kinetic for Best fit model F7-F12 formulation

Formulation	Model	R^2 value	Slope
F1	Higuchi	0.956	-13.84
F2	Higuchi	0.916	-11.75
F3	Higuchi	0.946	-12.73
F4	Higuchi	0.946	-12.91
F5	Higuchi	0.956	-13.58
F6	Higuchi	0.955	-13.65



Graph No.7. Kinetic of Optimized Formulation F12

Summary and Conclusion: The selected drug sample was authenticated by FT- IR (Jasco Model-4100, Japan) & UV spectroscopy (UV- 2600, Thermo-Fischer Scientific Ltd, India). UV calibration curve of drug showed correlation coefficient between 0.996 to 1.000, and 0.998to 1.000. This indicates linearity. The peaks obtained in the recorded IR spectra established the chemical identity of drug. Results are shown in Table No.8 and Graph No. 3. Melting point was determined; results are shown in Table No.4 Before proceeding for formulation drug-excipients interaction studies were performed, results indicated no interaction between drug and excipients (Table No.9 and Graph No.6 and 7). Due to continuous lipid region in the stratum corneum, it is believed that passive transdermal diffusion occurs predominantly through the lipid phase of the skin for this reason, hydrophobic drugs generally have better transport through skin while water soluble ionic drug have very limited permeability. It consisting of the bioadhesive polymer HPMC and rate -controlling polymer of Eudragit RS100 with DMSO as permeation enhancer demonstrated sustained and controlled release polymer. Effect of various chemicals applied as penetration enhancers on the permeation of Metoprolol Succinate across cellophane membrane and human cadaver skin were investigated using Franz diffusion cell. Remarkable enhancement was noted, whereas no significant influence was observed with PEG400 as a surfactant. Maximum permeation of Drug was seen with formulation F7-F11 as a controlled release at 20to 23 hr. and F12 formulation shows maximum skin permeation observed as compare to other formulations i.e.96.66% ±0.046 at required in 24 hr. respectively.

By using 1: 1 polymer ratio it can be considered as effective skin permeation of Drug, with potential application in transdermal drug delivery of the drug. In view of low permeability of drug, it was considered appropriate to develop monolithic device of drug. The properties of hydrophilic, lipophilic and combination of hydrophilic and lipophilic polymers namely HPMC : Eudragit RS 100 were used in various combinations to evaluate their potential in the development of drug reservoir for drug. On the basis of relatively better performance of various polymers, combination was selected for the fabrication of drug-reservoir. Propylene glycol as a plasticizer and PEG 400 as surfactant, Tween 80 and DMSO as a penetration enhancer were employed in fabrication of drug reservoir.Acetone and Ethanol is used as a solvent for dissolving the HPMC and ERS100 respectively. Medicated films were evaluated for physical & mechanical properties like Drug content, Folding endurance, Weight variation, % moisture content, %moisture uptake, and Thickness.

Formulations were prepared and subjected to *in-vitro* drug release evaluation using Franz diffusion cell, by using cellophane and human cadaver skin as a membrane. Formulation F12 showing highest cumulative % drug release by using human cadaver skin as a permeation membrane and they were selected for further study. Formulation F12 was having maximum rate of permeation and it was selected as optimized formulation for further study. In order to understand mechanism of drug release, *in vitro* release data were treated to kinetic models and linearity was observed with respect to Higuchi equation. The correlation coefficient obtained from Higuchi plot and zero order was found to be in the range of R^2 value 0 .916 to 0.956 and 0.982-0.995 respectively. This indicates that the mechanism of drug release was diffusion type. Developed formulation has the best effective combination of polymer, and lastly the drug remained stable in TDDS during storage observed in stability study for three month at R.T. and Humidity chamber. From above studies it can be concluded that the polymeric matrix-type transdermal films of Metoprolol Succinate prepared with different grades and ratios of polymers gives the ideal transdermal drug delivery system of Metoprolol Succinate.

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