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Formulation of Transdermal Drug Delivery System of Metoprolol Tartrate and its Evaluation.

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Abstract -Metoprolol tartrate, a beta adrenoreceptor-blocking agent used in the treatment of cardiovascular disorders. The drug has a short half-life due to extensive first pass metabolism. Modifying the conventional dosage form to transdermal delivery system can successfully rectify this drawback. Different matrix-type transdermal films containing Metoprolol tartrate was formulated with an objective to study the effect of polymers on the release characters. Different blends of polymers such as polyvinyl pyrrolidone (PVP), ethyl cellulose (EC), and hydroxy propyl methyl cellulose (HPMC) were employed for the fabrication of films. The interaction among various components of the matrices was studied by performing fourier transform infrared spectroscopic analysis. The fabricated films were evaluated for various parameters. *Invitro* permeation studies were carried out to identify the ideal film. The formulation having the polymeric combination of Ethyl cellulose and Hydroxy propyl methyl cellulose (1.5: 3.5) met all the evaluation parameters and selected as ideal formulation.
Keywords: Metoprolol tartrate, Transdermal films, *Invitro* permeation studies.

INTRODUCTION

Transdermal drug delivery systems [1] one of the novel approaches to deliver the drug to systemic circulation. Transdermal drug delivery offers controlled release of the active drug to the patient enabling a steady blood level profile. The simplicity of the drug administration is become popular with the demonstration of the percutaneous absorption. In addition, transdermal films are convenient, painless, and it is generally accepted for their improved patient compliance.

Metoprolol tartrate [2] one of the commonly used beta adrenoreceptor blocking agent used in the treatment of cardiovascular disorders. The drug has a poor bioavailability due to its extensive first pass metabolism. The deactivation of drug can be successfully overcome by fabricating the drug in to transdermal therapeutic system. Transdermally delivered drug provides the patients a unique and convenient dosing schedule while providing nearly constant serum levels of medication over a prolonged period.

Drug containing formulations were prepared with different rate controlling polymer matrices[3]. In view of excellent film forming property, Ethyl cellulose, Polyvinylpyrrolidone and hydroxyl propyl methylcellulose has been chosen and studied for its usefulness as polymeric matrix in the development of transdermal films.

MATERIALS AND METHODS

Metoprolol tartrate (M) was obtained as a gift sample from Astra Zeneca Pharma IndiaLtd, Mumbai, Ethylcellulose(EC) and Polyvinylpyrrolidone(PVP) were obtained from Loba Chemicals Mumbai, Hydroxypropylmethylcellulose(HPMC) obtained from High media chemicals, Bangalore, Di butyl phthalate obtained from Ranbaxy Mumbai, Isopropyl myristate obtained from SD Fine Chemicals Mumbai. All other chemicals used were of AR grade. Fabrication of Transdermal Films.

Fabrication of transdermal films of Metoprolol tartrate done by solvent casting method. Fabrication done by combining the polymers in different ratios. EC and PVP films were prepared by dissolving EC in measured volume of chloroform. Then added PVP and mixed thoroughly to get a homogeneous mixture. To this, specified quantities of dibutyl phthalate and isopropyl myristate were added. The polymeric solution of EC and HPMC were prepared by dissolving separately in methanol- chloroform (1:1) mixture.

A weighed amount of drug was dissolved in suitable solvent and dispersed in polymer mixture, poured in to the glass mould placed in a hard rigid and uniformly leveled surface. Solvent evaporation was controlled by covering with a funnel in its inverted position. After 24 hours the films were removed, cut in circular disc with 3.8cm diameter and kept in dessicator for further studies. The composition of various polymeric combinations is given in the Table. 1.

Table 1 Composition of various formulation of Metoprolol Tartrate.

Film Identity	*MT in mg*	*PVP in parts*	*EC in parts*	*HPMC in parts*	*DBP in % W/W*	*IPM in % W/W*
F_1	15	----	4.5	0.5	30	20
F_2	15	-----	4.0	1.0	30	20
F_3	15	----	3.5	1.5	30	20
F_4	15	-----	3.0	2.0	30	20
F_5	15	----	2.5	2.5	30	20
F_6	15	-----	2.0	3.0	30	20
F_7	15	----	1.5	3.5	30	20
F_8	15	4.5	0.5	----	30	20
F_9	15	4.0	1.0	----	30	20
F_{10}	15	3.5	1.5	-----	30	20
F_{11}	15	3.0	2.0	----	30	20
F_{12}	15	2.5	2.5	-----	30	20
F_{13}	15	2.0	3.0	----	30	20
F_{14}	15	1.5	3.5	-----	30	20

EVALUATION OF TRANSDERMAL FILMS [4,6,7]

Folding Endurance

Folding endurance is determined to identify flexibility of the films. Folding endurance was determined by folding the films repeatedly in the same part of the film until it broke.

Film Thickness

Five films from each formulation were selected randomly to study the thickness using thickness gauge and average was determined.

Tensile Strength

Tensile strength as determined by using a modified pulley system. Weight was gradually increased so as to increase the pulley force till the film broke. The percentage elongation before the film get breaks was noted with the help of a magnifying glass on a graph paper and the tensile strength was calculated as kg/mm^2.

Weight Variation Test

The study was carried out by determining weight of randomly selected five films from each batch with the help of high accuracy electronic balance. The average weight of a film and its standard deviation was calculated.

Percentage Of Moisture Content

Randomly selected films were weighed individually and kept in the platform of the dessicator containing anhydrous calcium chloride at room temperature for 24 hours. Films were weighed separately and repeatedly until a constant weight obtained. The percentage of moisture content was calculated by the difference between initial and final weight with respect to the final weight.

Drug Content Determination

Selected film from each batch was put into a 100ml standard flask containing the buffer solution (pH - 7.4) and shaken continuously for 24 hours. Then the solution was filtered and drug content was determined with the help of UV spectrophotometer at wave length 225nm.

***IN VITRO* DRUG PERMEATION STUDIES[5]**

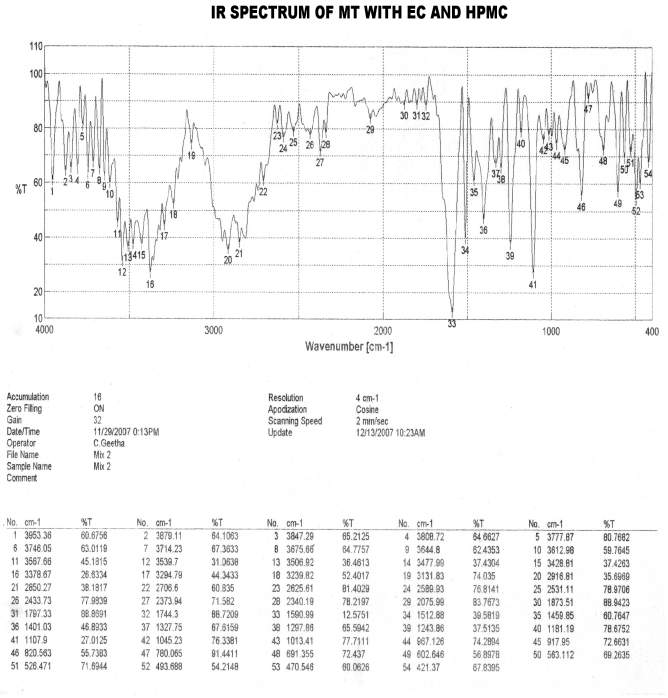
In vitro permeation studies were performed using Franz diffusion cell. The dialysis membrane was mounted between the donor and receptor compartment of the diffusion cell. The dialysis sac was previously soaked for 2 h in PBS. The formulated films were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37 ± 2^{0}C.Samples were withdrawn (2 mL) at predetermined time intervals and replaced with an equal volume of phosphate buffer. The samples were suitably diluted and analyzed to determine drug content using UV spectrophotometer at a wave length of 225nm.

STABILITY STUDIES{4,5,8,9,10]

The prepared films were placed in USP type 1 amber coloured vials. Perfectly closed and sealed vials were placed in a stability chamber at 40^{0}C and an atmosphere of RH 65 % for three months. Each time 3 films were withdrawn and evaluated for physical appearance and drug content.

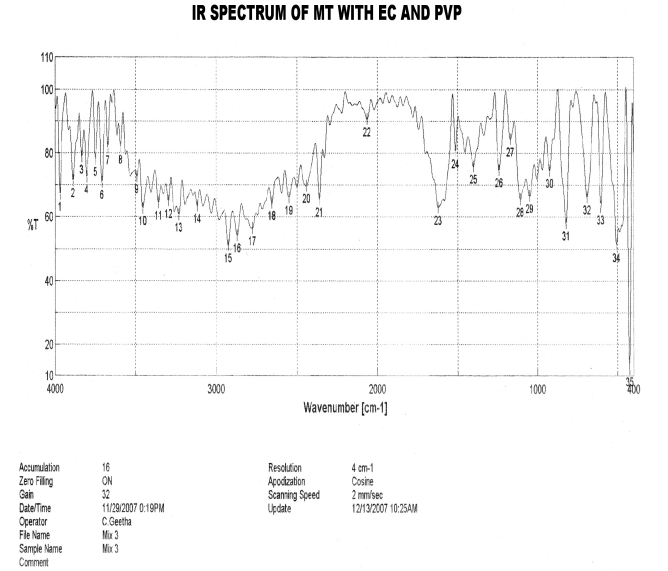
RESULTS AND DISCUSSION

Fabrication of transdermal drug delivery system of Metoprolol tartrate with different combinations of polymers was done by solvent casting method. Fourier transform infrared spectroscopic results confirms the intactness of the drug with the polymers.



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3953.36	60.6756	2	3878.11	64.1063	3	3847.29	65.2125	4	3808.72	64.6827	5	3777.87	60.7682
6	3746.05	63.0119	7	3714.23	67.3633	8	3675.66	64.7757	9	3644.8	62.4353	10	3612.98	59.7645
11	3567.66	45.1915	12	3539.7	31.0638	13	3506.92	36.4613	14	3477.99	37.4304	15	3428.81	37.4263
16	3378.67	26.6334	17	3294.79	44.3433	18	3239.82	52.4017	19	3131.83	74.035	20	2916.81	35.6969
21	2850.27	38.1817	22	2706.6	60.835	23	2625.61	81.4029	24	2589.93	76.8141	25	2531.11	78.9706
26	2433.73	77.9939	27	2373.94	71.582	28	2340.19	78.2197	29	2075.99	83.7673	30	1873.51	88.9423
31	1797.33	88.8991	32	1744.3	88.7209	33	1590.99	12.5751	34	1512.88	39.5819	35	1459.85	60.7647
36	1401.03	46.8933	37	1327.75	67.6159	38	1297.88	65.5942	39	1243.86	37.5135	40	1181.19	78.6752
41	1107.9	27.0125	42	1045.23	76.3381	43	1013.41	77.7111	44	967.126	74.2894	45	917.95	72.6631
46	820.563	56.7383	47	780.065	91.4411	48	691.355	72.437	49	602.646	56.8978	50	563.112	69.2635
51	526.471	71.6944	52	493.688	54.2148	53	470.546	60.0626	54	421.37	67.8395			

Figure 1a



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3868.78	67.0927	2	3888.72	71.4334	3	3836.68	78.7288	4	3805.83	72.4754	5	3750.87	78.0107
6	3711.33	70.7247	7	3673.73	81.7535	8	3591.77	81.9878	9	3491.49	72.8099	10	3455.81	62.7544
11	3361.32	64.4079	12	3299.81	64.9333	13	3235	60.6887	14	3117.37	83.4261	15	2927.41	50.9898
16	2871.49	54.1578	17	2776.99	56.4687	18	2653.57	64.2753	19	2550.4	85.9932	20	2443.37	69.8298
21	2363.34	65.3943	22	2084.42	90.5999	23	1622.8	62.901	24	1513.85	80.8091	25	1398.1	75.8102
26	1240.97	74.6237	27	1171.54	84.3665	28	1108.87	85.3778	29	1050.05	86.527	30	921.807	74.4533
31	820.563	58.0264	32	692.32	66.1888	33	604.574	63.1207	34	506.223	51.1961	35	425.227	12.2001

Figure 1b

Figure 1- IR spectum showing the intactness of drug and polymers.

From the primary evaluation parameters such as folding endurance, Thickness, Tensile strength ,moisture content, meets the ideal properties of the films. As the formulation procedure required fewer processing steps, no major drug loss was observed during the development.

The compatibility studies showed the intactness of drug and polymers. The IR spectra obtained do not have any fluctuations as compared with the combination. Physical appearance studies showed the films are transparent, flexible and translucent. The results of percentage moisture content are directly proportional to the amount of PVP. The formulations containing EC and HPMC showed a gain in weight as compared with PVP-EC combinations. Drug content of all films was found to be adequate with minor variations. The EC-HPMC film met the exact drug content. The formulations containing PVP-EC in varying concentration showed an increase in thickness. The tensile Strength of EC-HPMC films were found to be more as compared to other films. The *in vitro* release of the selected film(EC-HPMC in the ratio 1.5 : 3.5) showed better release characteristics. The cumulative drug release of Metoprolol tartrate from the polymeric films in 24 hours was found to be 95.16 to 98.25 .The results are tabulated in Table No-2 and corresponding figure is represented in Figure No-2. The films F_3, F_7, F_{12} and F_{14} were taken for accelerated stability studies.

Table 2. Table Showing Percentage Drug Release of Ideal films.

Time (Hrs)	*Percentage Cumulative Drug Release*			
	F3	*F7*	*F12*	*F14*
0	0	0	0	0
1	4.35	3.68	5.12	4.25
2	12.88	8.92	8.56	11.58
3	17.64	15.63	10.48	19.93
4	20.97	19.53	19.68	25.86
5	27.63	26.46	21.17	32.564
6	30.82	31.26	32.16	41.56
7	39.67	38.84	48.81	49.35
8	48.92	49.67	63.84	53.54
9	57.24	56.51	89.66	62.54
10	67.98	65.67	95.12	80.82
12	78.52	79.78	97.63	91.86
24	95.16	98.25	97.486	96.025

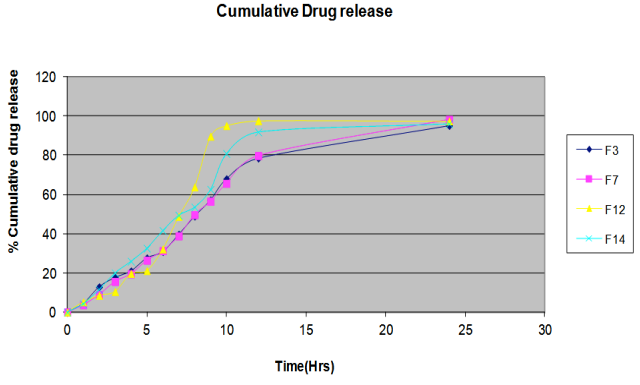


Figure 2- Cumulative Drug Release of selected Films.

Table 3-Percentage drug content for films F_3, F_7, $F_{12}$and F_{19} during accelerated stability studies.

Time in days	*Drug content (37°c)*			
	F_3	*F_7*	*F_{12}*	*F_{14}*
0	100	100	100	100
30	99.70	99.61	99.91	99.25
60	99.51	99.42	99.89	99.08
90	99.22	99.03	99.78	98.76

Accelerated stability studies for the selected films indicated that films having adequate shelf life. From all the above findings and observations the film containing EC- HPMC in the ratio of 1.5: 3.5 showed better physicochemical properties, good release profile, and adequate shelf life. The readings are presented in Table No-3.

From all the evaluation parameters the film denoted by F7 (film containing EC- HPMC in the ratio of 1.5:3.5) exhibits a steady state drug concentration. Thus the formulation selected as ideal film.

CONCLUSION

The purpose of the work was an attempt to develop a transdermal drug delivery system of Metoprolol tartrate using three different polymer combinations i.e. EC- HPMC and EC- PVP in different ratios. Out of 14 formulations, the EC-HPMC films were found to have better characteristics than other batch.

The compatibility studies confirmed the absence of interaction between the drug and polymers. They have been evaluated for physicochemical parameters like physical appearance, average weight, thickness, percent moisture content and drug content. Drug release from the formulations were found out by *in vitro* diffusion studies using Franz diffusion cell.

From the *in vitro* release results, it was found that films prepared by EC-HPMC proved to exhibit better release characteristics. The results for the physicochemical parameters of EC-HPMC films were also better than the other films. Accelerated stability studies indicated that the formulated films have adequate shelf life. The study concluded that the ideal film can employed for the patient to get a steady state drug concentration, which would improve the patient compliance .

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