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RESEARCH ARTICLE

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Formulation and Evaluation of Benazepril Hydrochloride Transdermal Films for Controlled Drug Release

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ABSTRACT

The current research deals with formulation and evaluation of Benazepril hydrochloride transdermal films, by varying ratios of polymers Eudragit RL100, Eudragit RS100 by film casting technique. Preformulation studies were conducted to check the solubility, melting point and partition coefficient. The eleven formulations were analyzed for physicochemical parameters and drug dissolution potential of transdermal films. All the formulations are transparent with minimum weight variation and uniform thickness. The drug content uniformity of all the formulations vary between 96.84 ± 3.7% to 96.98 ± 1.6% indicate uniform drug distribution. The low water vapour transmission values indicate good water vapour permeation. The folding endurance is between 246 ± 4.60 to 315 ± 4.13 indicates that the transdermal films can withstand rupture. *In vitro* drug dissolution study indicates maximum amount of drug 96.8% (F2) released in 24 h when compared with marketed formulation 84.81%. The release order follows Fickian diffusion. The formulation F2 was optimized based on drug flux, permeability coefficient and enhancement ratio.

Keywords: Benazepril Hydrochloride, Transdermal films, Hypertension, Eudragit, Plasticizer, Penetration enhancer, Permeation.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) are systems that deliver the loaded drug across a patient's skin by placing adhesive patch on the skin that induces drug into blood streams directly. [1-2] The TDDS is a transport process through a multi-laminar structure, e.g. from the patch to stratum corneum and finally penetrating into the blood. [3-4] The advantages of TDDS is that the drug is induced directly in the blood stream without entering various defense systems. [5] The TDDS do not undergo drug degradation in GI and first-pass drug metabolism within the liver. Drugs like estradiol (estrogen) [6] or paracetamol [7] causes side-effects like liver damages which can be suppressed by the use of TDDS for effective oral administration. These systems minimize drug side effects, increase patients'

acceptance and require lesser drug dosage. The other advantages of TDDS include increase in therapeutic efficacy and sustained plasma level of drug. The developments of TDDS involves selection of drug, evaluation of drug flux formulation of drug, analysis of physicochemical and stability factors, consideration of patients compliance and economy. The TDDS are multi layered polymeric formulations containing drug sandwiched between polymeric layers, an outer layer to overcome the loss of drug through the backing surface and an inner layer that works as an adhesive. Benazepril is anti hypersensitive drug which is considered as primary treatment for high blood pressure. [8] It is administrated orally in combinations Benazepril/hydrochlorothiazide and Benazepril/ amlodipine. Benazepril inhibits ACE by reducing renin-angiotensin-aldosterone system activity.

MATERIAL AND METHODS

Materials

The drug Benazepril Hydrochloride is kindly sponsored by Aurobindo Pharma Ltd., Hyderabad. HPMC E 15, Eudragit RS 100 and Eudragit RDL were obtained from Dr. Reddy's Laboratories Ltd., Hyderabad. Polyethylene glycol 400, Dimethyl Formamide, Dichloro methane, methanol, Sodium hydroxide and monopotassium phosphate were procured from Finar labs ltd, Mumbai.

Formulation of Benazepril Hydrochloride transdermal films

The Benazepril Hydrochloride transdermal formulations prepared by film casting technique using liquid Paraffin as lubricant. [9] All the polymers (HPMC E15, ERL 100 and ERS100) dissolved in solvent system for homogenous solution followed by ultra sonication. The drug added to the contents with continuous stirring followed by addition of plasticizer and penetration enhancer. The resultant solution lubricated with paraffin, poured into petri dish, solvent allowed to evaporate to obtain Benazepril polymer matrix. Air entrapped in the polymeric solutions created a problem in casting films; swelling of polymers required time (Table 1).

Evaluation of Benazepril Hydrochloride transdermal films

Physical Appearance

All the prepared 11 formulations inspected for physical appearance visually.

Weight uniformity

Weight uniformity is calculated by weighing selected patches in triplets. The average weight and standard deviation is calculated for each formulation. [10]

Thickness uniformity

The thickness of Benazepril Hydrochloride transdermal films is measured at five various points using screw gauge. The average of all the observations tabulated. [11]

Drug content uniformity

The transdermal films were dissolved in suitable solvent for 24 h with constant stirring. The amount of drug was analyzed by UV–Visible Spectrophotometer at 294 nm. [12]

Water vapour transmission (WVT) studies

WVT was measured by fixing the transdermal films over the brim of transmission cells containing fused $CaCl_2$. The initial weight of cells noted, placed in desiccators containing 200 ml of KCl solution. The cells removed from desiccators every consecutive day till seven days and weighed. [13] WVT Rate calculated using the formula

$$\text{Rate of WVT} = W \times L / S$$

Where W stands for the amount of water transmitted in gm, L stands for thickness of the film and S for surface area of exposed film

Folding Endurance

Folding Endurance is the logarithm (to the base of ten) of the number of folds that are required break the test piece under normal conditions. [14]

In-vitro drug permeation study

The formulated transdermal patch membranes are placed in compartment of diffusion cell [15] between receptor and donor. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The samples drawn at regular time intervals, diluted and absorbance is analyzed spectrophotometrically.

Stability studies

The stability of optimized formulations checked at 40°C /75% RH for a period of 90 days. The Transdermal films of 3.14 cm^2 were packed in aluminum foils and placed on petridish and stored at 40°C ± 2°C/ 75% RH ± 5% for three month. After the prescribed time periods the samples evaluated for *in vitro* drug release, drug content, thickness and weight uniformity. [16]

Table 1: Benazepril Hydrochloride TDDS formulations

Code	Amt of Drug (mg/cm^2)	HPMC (mg)	ERL 100 (mg)	ERS 100 (mg)	PEG 400 (%)	DMF (%)	DCM : Methanol 1:1 (ml)
F1	4	800	200	-	15	8	6
F2	4	600	400	-	15	8	6
F3	4	400	600	-	15	8	6
F4	4	200	800	-	15	8	6
F5	4	-	1000	-	15	8	6
F6	4	800	-	200	15	8	6
F7	4	600	-	400	15	8	6
F8	4	400	-	600	15	8	6
F9	4	200	-	800	15	8	6
F10	4	-	-	1000	15	8	6
F11	4	600	200	200	15	8	6

RESULTS

Formulation and evaluation of Benazepril hydrochloride transdermal films

Eleven formulations were prepared with varying compositions of polymers (The polymers HPMC E15, ERL 100, ERS 100), plasticizers (PEG 400), penetrating enhancer (DMF) and solvents (DCM, methanol). All the eleven formulations were checked for physico chemical parameters. [17]

Evaluation of Benazepril hydrochloride transdermal films

Table 2: The physico-chemical evaluation of Benazepril hydrochloride transdermal films

FC	Weight uniformity (mg)	Thickness uniformity (mm)	Drug content uniformity (%)	WVT (gcm/cm²24h)	Folding Endurance
F1	125.0 ± 1.82	0.18 ± 0.0021	98.86 ± 4.5	6.91 ± 0.059	271 ± 4.35
F2	138.6 ± 1.76	0.19 ± 0.0032	98.95 ± 1.9	6.75 ± 0.055	308 ± 3.13
F3	141.2 ± 2.30	0.25 ± 0.0058	97.13 ± 2.6	6.63 ± 0.035	259 ± 5.21
F4	149.5 ± 2.54	0.30 ± 0.0027	98.95 ± 4.1	6.42 ± 0.024	248 ± 3.86
F5	150.0 ± 1.35	0.40 ± 0.0024	98.40 ± 3.4	6.25 ± 0.029	246 ± 4.60
F6	100.0 ± 1.92	0.20 ± 0.0041	96.84 ± 3.7	5.98 ± 0.037	315 ± 4.13
F7	125.1 ± 2.41	0.18 ± 0.0031	97.30 ± 4.8	5.92 ± 0.021	288 ± 3.88
F8	131.4 ± 2.13	0.22 ± 0.0023	98.62 ± 2.5	5.55 ± 0.048	298 ± 5.05
F9	136.7 ± 1.84	0.10 ± 0.0042	97.78 ± 1.6	5.18 ± 0.034	294 ± 5.13
F10	138.2 ± 1.25	0.31 ± 0.0036	97.55 ± 2.7	4.90 ± 0.030	289 ± 4.51
F11	140.0 ± 2.34	0.22 ± 0.0027	96.98 ± 1.6	4.79 ± 0.051	285 ± 5.01

Table 3: *In-vitro* drug permeation studies of Benazepril hydrochloride TDDS formulation

FC	Time (h)							
	0h	2h	4h	6h	8h	10h	12h	24h
F1	0	10.38	26.4	35.4	47.2	53.9	65.6	95.6
F2	0	12.2	28.9	39	49.7	57.85	64.7	96.8
F3	0	6.4	15.4	29.9	41.4	50.2	61.4	85.17
F4	0	1.87	5.17	10.1	14.6	18.9	23.5	74.3
F5	0	0.8	5.3	7.5	10.4	13.5	15.7	53.2
F6	0	8.1	35.4	39.9	47.4	59.7	65.6	92.3
F7	0	7.2	18.9	30.4	44.8	53.9	62.3	80.5
F8	0	4.6	14.1	28.6	40.3	51	60.6	71
F9	0	3.12	6.2	13	38.1	43.7	52.6	64.7
F10	0	0.67	4.2	6.9	10.5	11.1	19.2	41.4
F11	0	5.4	17.1	27.3	43.7	56.9	62.1	70.9

Physical appearance

The transdermal films of all eleven formulations were thin, transparent, flexible, smooth and uniform. Incorporation of PEG 400 yielded smooth and flexible patches. The transparent nature of films may be more prominently attributed to ERL than ERS. The flexibility can be due to HPMC.

Weight uniformity

The weights of all formulations are uniform. The values of all formulations vary from 100 ± 1.92 mg to 150 ± 1.35 mg with F6 showing the minimum variation (Table 2).

Thickness uniformity

The film thickness ensured uniformity of thickness in all developed formulation. The value ranges from 0.1 ± 0.0042 mm to 0.3 ± 0.0027 mm (Table 2).

Drug content uniformity

The transdermal films were dissolved in suitable solvent for 24 h with constant stirring. The amount of drug present was determined by U.V Spectrophotometer at 294 nm. [12]

Water vapour transmission (WVT)

The WVT of all the formulations vary between 4.79 ± 0.051 to 6.91 ± 0.059 gcm/cm² 24 h. ERL film formulations exhibited good water vapour permeation than that of ERS. There was a decrease in Water vapour transmission with increasing film thickness and crosslink density, due to the increased path length for diffusion and increased film rigidity at higher crosslink densities (Table 2).

Folding Endurance

The values of all eleven formulation range between 246 ± 4.60 to 315 ± 4.13. The amount of drug released from transdermal film formulations after 24 hours were 96.8%, 95.6%, 92.3%, 85.17%, 80.5%, 74.3%, 71%, 70.9%, 64.7%, 53.2%, 41.4% respectively. [18] The highest % release from F2 formulation due to the presence of Eudragit and HPMC in almost equal proportions suggesting HPMC is required for the control of rate and Eudragit for the release for sustained and prolonged effect (Table 3).

Release order kinetics

The drug dissolution data fitted into various release order kinetics plots. The slope (n) indicate that the drug released by Fickian diffusion (Figure 1-4).

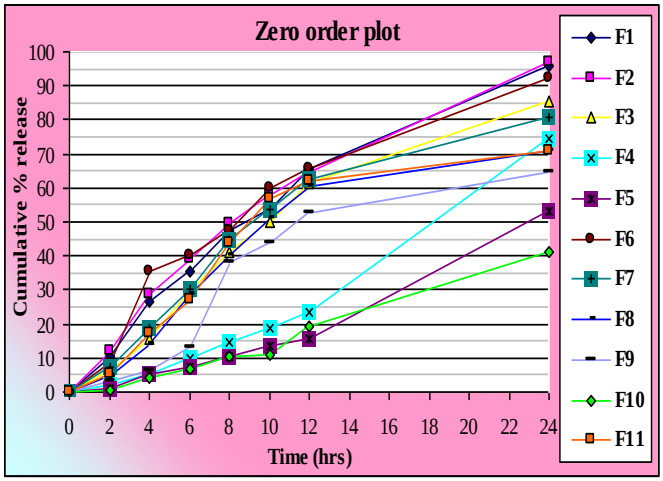

Fig. 1: Zero order kinetics plot of Benazepril hydrochloride transdermal formulation

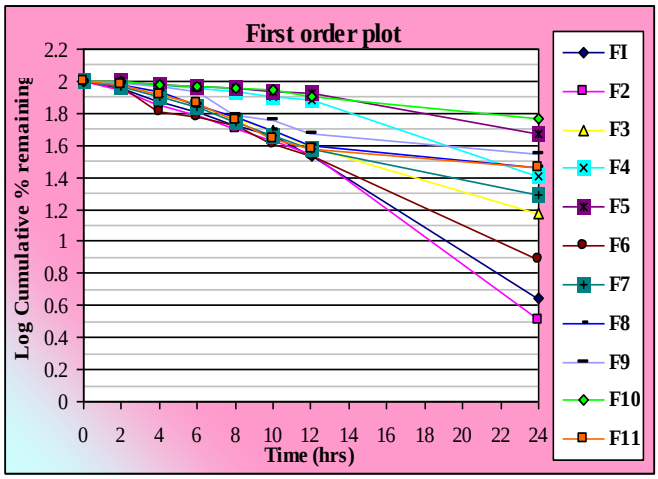

Fig. 2: First order kinetics plot of Benazepril hydrochloride transdermal formulation

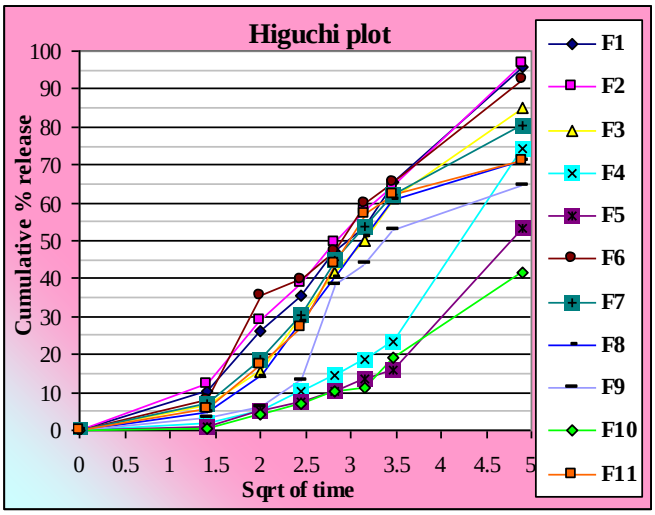

Fig. 3: Higuchi plot of Benazepril hydrochloride transdermal formulation

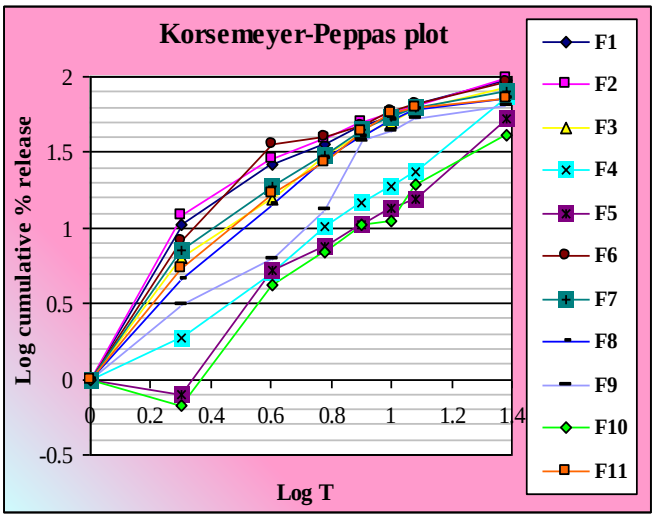

Figure 4: Korsemeyer peppas plot of Benazepril hydrochloride transdermal formulation

Table 4: Stability study data of Benazepril hydrochloride transdermal formulation

Formulation	Time Period			
	Initial	1 month	2 months	3 months
F1	98.86	98.72	97.53	97.40
F2	97.92	97.85	97.79	97.71
F3	97.13	97.02	97.00	96.97
F4	98.95	98.78	98.34	98.11
F5	98.4	98.05	98.00	97.86
F6	96.84	96.65	96.34	96.11
F7	97.30	97.23	97.00	96.76
F8	98.62	98.12	97.86	97.23
F9	98.78	98.34	98.11	98.00
F10	98.55	98.24	98.01	97.90
F11	96.98	96.54	96.31	96.20

Accelerated stability studies

No physical changes in appearance, flexibility and colour were observed. The degradation with respect to drug content was observed negligible (Table 4).

Permeation Data Analysis

The flux values calculated for formulation F4, F5 and F2 meets the required flux of 14.08µg/cm²/h (control). The highest flux of 89.11µg/cm²/h was recorded for F1 formulation.

The permeability coefficient value ranges from 5.67 cm/h to 14.96 cm/h. The minimum value recorded for F2 that is in close relation with the permeability coefficient of the control (5.50 cm/h).

Enhancement ratio values of all formulations ranges from 1.03 to 2.72 with minimum value recorded for formulation F2 (Table 5). Hence Formulation F2 is considered as optimized formulation and subjected to drug compatibility study through FTIR.

Table 5: Permeability parameters of Benazepril hydrochloride transdermal formulation

Formulation code	Drug flux (permeation rate) at steady state(J_{ss})*	Permeability Coefficient (cm/h)	E_r**
Control	14.08	5.50	1
F1	89.11	14.96	2.72
F2	2.53	5.67	1.03
F3	50.8	13.99	2.54
F4	12.38	11.68	2.12
F5	3.75	9.28	1.68
F6	65.35	14.23	2.58
F7	53.84	13.19	2.39
F8	31.45	12.05	2.19
F9	20.26	11.46	2.08
F10	89.08	14.87	2.70
F11	43.36	12.04	2.18

*Drug flux units -µg/cm 2/h; **Er -Enhancement ratio

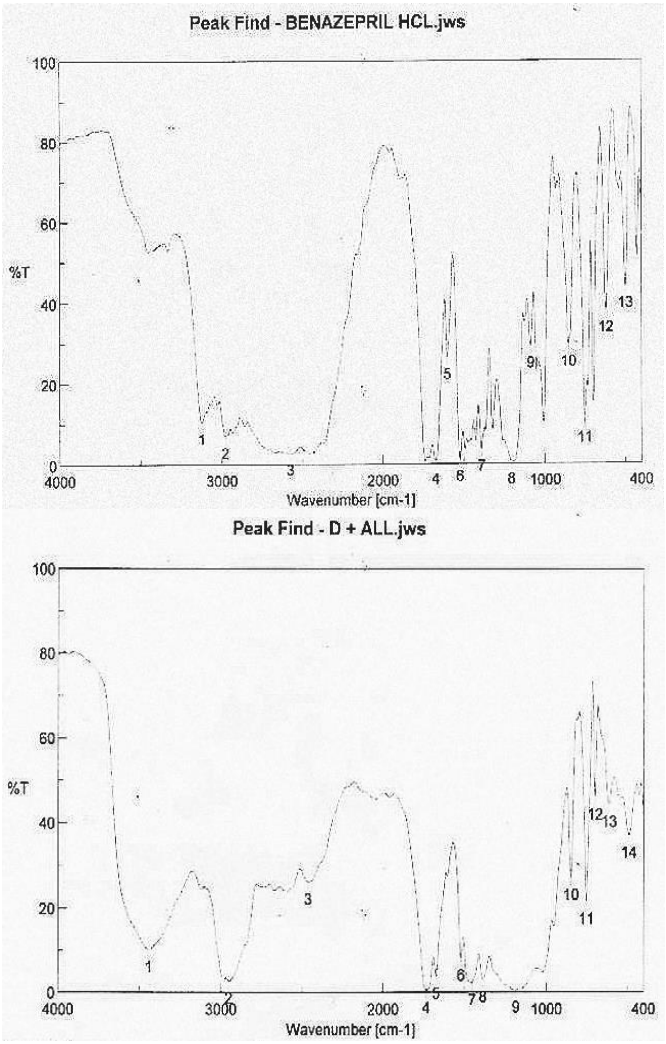

Fig. 5: FTIR of Benazepril Hydrochloride and optimized formulation F2

Drug compatibility study

Benazepril exhibits 3 principle peaks at 1739 cm^{-2} due to -C=O of –C-CO-OCH_2CH_3 ,1674 cm^{-2} due to –COOH, 1211 cm^{-2} due to -CH bending. The same characteristic peaks were shown by the pure drug as that of monograph ensuring its purity. It was observed that characteristic IR absorption peaks of Benazepril were not altered in formulation F2. This indicates the drug is compatible and stable in the formulation (Figure 5).

Comparative drug release study of optimized Benazepril Hydrochloride transdermal formulation (F2) and marketed formulation

The drug dissolution profiles of Benazepril optimized transdermal formulation and marketed tablet formulation were comparable without any significant difference. The drug release at the end of 24 h was found to be 96.8% and 84.81% for optimized and marketed formulations respectively (Figure 6).

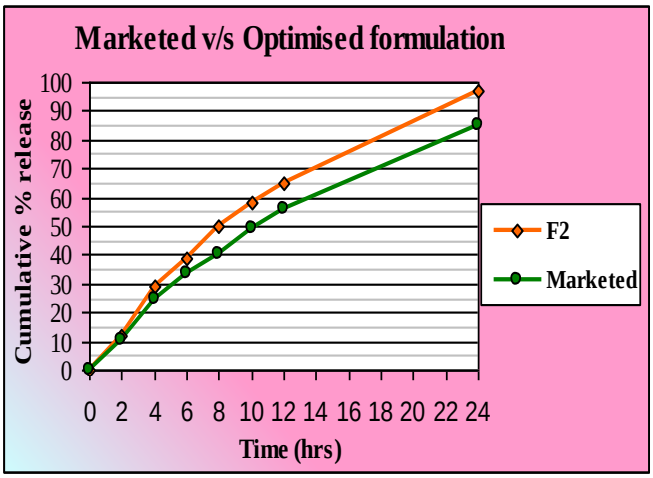

Fig. 6: Comparative *in-vitro* study plot of optimized transdermal formulation (F2) and conventional marketed tablet formulation

DISCUSSION

The results of Benazepril transdermal films indicate that these TDDS systems provide better compliance than existing conventional drug delivery system. The transdermal films of Benazepril Hydrochloride formulated using HPMC E15, ERL 100, ERS100 and subjected to physicochemical evaluation followed by *in vitro* study. The physico chemical properties shown by all formulations were satisfactory. The prepared patches were permeable to water vapour depending upon the thickness and crosslink density. F2 formulation was the best formulation as per the diffusion profile. The Permeation Data Analysis also reveals that the formulation F2 have comparable Drug flux, Permeability Coefficient and Enhancement ratio with the control. Hence innovative and promising transdermal drug delivery formulation of Benazepril Hydrochloride was developed for the effective treatment of hypertension.

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