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DEVELOPMENT AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF CAPTOPRIL

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KEYWORDS:

Anti-hypertensive Drug, Transdermal Drug Delivey System (TDDS), Eudragit RL100 and Eudragit RS100.

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ABSTRACT

The aim of the present investigation was to prepare Captopril transdermal patches using the eudragit RL100 and eudragit RS100 in different proportion by solvent evaporation method. Captopril is a drug of choice in anti-hypertensive therapy and is reported for potential administration through transdermal route. The investigation was carried out to study the effect of different proportion of eudragit RL100 and eudragit RS100 on drug release pattern. The backing membrane is prepared by using polyvinyl alcohol and dibutyl phthalate is used as a plasticizer. Several Physicochemical parameters like moisture content, moisture loss, thickness, folding endurance, tensile strength, flatness were studied. For all the formulations, *in vitro* drug release was studied using modified diffusion cell. Formulations with highest proportion of eudragit RL100 shows faster release whereas increasing proportion of eudragit RS100 produces a prolonged regimen of sustained drug delivery through transdermal route for a period of 24 hrs.

1. INTRODUCTION:

The transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. The transdermal route is ideally suitable for drugs that need to be administered for diseases those are chronic in nature and required a steady state drug concentration throughout the treatment [1]. The present study is an attempt to develop a transdermal system capable of delivering the selected anti-hypertensive drug in the desired therapeutic concentration for prolong period. Captopril, an orally active inhibitor of an angiotensin converting enzyme (ACE) has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered a drug of choice in anti-hypertensive therapy due to its effectiveness and low toxicity [2].

Captopril shows 75% bioavailability but presence of food reduces the oral absorption by 30-50%. According to a previous research, the oxidation rate of Captopril in dermal homogenate is significantly lower than the intestinal homogenate because the oxidative product of Captopril, a Captopril disulfide shows poor absorption from the intestine. Captopril when administered initially causes hypotension, which can prove to be harmful in diuretic treated and congestive heart failure patients. Persistent hypotension may cause some trouble in myocardial infarction patients [3]. Therefore, the use of transdermal drug delivery system, can reduce the side effects associated with Captopril.

MATERIALS AND METHODS:

Captopril, Eudragit RS100 and Eudragit RL100 were purchased from Balaji Drugs Gujrat, Di-n-butylphthalate, Central Drug House (p) Ltd. New Delhi.

PREPARATION OF BACKING MEMBRANE:

A 4% (w/v) solution of polyvinyl alcohol (PVA) in distilled water was prepared using mechanical stirrer. Then 2ml of the solution was poured in both side open glass moulds, having specific diameter (2.8 cm), one side of which is previously covered by aluminium foil. It was placed in dryer at 60ºC±2ºC for drying over a period of 6 hrs. After 6 hrs moulds were removed from dryer and air dried for 24 hrs [4].

FORMULATION OF DRUG LOADED TRANSDERMAL PATCHES

Matrix type transdermal patches of Captopril were prepared by using two polymer composition, containing eudragit RS100 and eudragit RL100 in different ratios as shown in the Table 1 by solvent evaporation technique in cylindrical both side opened glass moulds. The bottom of the mould was wrapped with aluminium foil on which the backing membrane was cast by pouring

4% (w/v) PVA solution followed by drying at 60°C for 6 hrs. The two polymers were weighed in requisite ratio and they were then dissolved in ethanol as a solvent. Dibutyl phthalate 30% (w/w) of polymer composition was used as a plasticizer. The drug was added 20% (w/w) of the total weight of polymer, in the homogeneous dispersion, by slow stirring with a magnetic stirrer. The uniform dispersion (2 ml each) was casted on the PVA backing membrane casted earlier and dried at 40°C for 6 hrs. After drying patches were removed from the mould, wrapped with aluminium foil and kept in desiccators until they were used for further study. All the patches obtained from this composition were smooth, elastic and were easily removed from glass moulds [4].

Table 1: Formulation of drug loaded transdermal patches using E RL100 and E RS100

Sr. No.	Formulation Code	Ratio of E RL100 and E RS100	Total weight of E RL100 and E RS100	Solvent (ethanol)	Plasticizer (%w/w) of total polymer	Drug (% w/w) of total polymer
1	F1	1:1	500 mg	10 ml	30	20
2	F2	1:2	500 mg	10 ml	30	20
3	F3	1:3	500 mg	10 ml	30	20
4	F4	1:4	500 mg	10 ml	30	20
5	F5	2:1	500 mg	10 ml	30	20
6	F6	3:1	500 mg	10 ml	30	20
7	F7	4:1	500 mg	10 ml	30	20

EVALUATION OF DRUG LOADED TRANSDERMAL PATCHES:

Thickness uniformity [5]:

The thickness of the drug-loaded polymeric films were measured at three different places using a Vernier caliper and mean values were calculated.

Uniformity of weight [6]:

Five films from each batch were weighed individually and the average weight was calculated.

Percent flatness study [7]:

Longitudinal strips were cut out from each transdermal patch, one from the centre and two from the either side. The length of each strip was measured and the variation in the length because of non-uniform in flatness was measured by determining % constriction, considering 0% constriction is equivalent to 100% flatness.

Folding endurance [8]:

The folding endurance was measured manually for the prepared patches. The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gave the value of folding endurance.

Drug content uniformity [9]:

The patches were tested for the content uniformity. The patches of size 1 cm^2 was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24 hrs to dissolve the patches. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 212 nm using UV-visible spectrophotometer. The experiment was repeated three more time to validate the result.

Percent moisture content (%MC) [10]:

The patches were weighed individually and kept in desiccators containing 10 gm of calcium chloride as desiccant at 37°C for 24 hrs. The patches were weighed again and again individually until it showed a constant weight. The final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\% MC = (X-Y/Y) \times 100$$

Where, X = initial weight,Y = final weight

Percentage moisture uptake [8]:

The patches were weighed accurately and placed in a desiccator where a humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

$$\% MU = (X-Y/Y) \times 100$$

Where, X = initial weight, Y = final weight

Percentage moisture loss [10]:

The patches were weighed individually and kept in a desiccator containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

Water vapour transmission (WVT) rate [5]:

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapour transmitted was calculated by the difference in weight using the formula.

$$WVT\ rate = WL/S$$

where; W = water vapour transmitted in gm., L = thickness of the transdermal patch in cm., S = exposed surface area in cm^2.

Tensile strength and percentage elongation [4]:

The tensile strength measurement was made using an instrument assembled in the laboratory. The films were fixed individually to the assembly. The required weights to break the films were noted. Tensile strength was calculated by using the following formula.

$$Tensile\ strength = (break\ force/a \times b) \times (1+L/I)$$

Where, a, b, L and I are the width, thickness, length and elongation of the films.

***In vitro* drug release [4]:**

Modified diffusion cell was used in our studies for *in vitro* drug release. The cell consists of two chambers, the donor and the receptor. The donor compartment is open at the top and is exposed to the atmosphere, maintaining the temperature at $37^oC \pm 2^oC$ and is provided with a sampling port. The diffusion medium was phosphate buffer of pH 7.4, which was stirred with magnetic bead (operated by a magnetic stirrer). A semi-permeable parchment paper previously soaked overnight in 0.1(N) HCL was placed between the two chambers. Diffusion media was stirred to prevent the formation of concentrated drug solution just beneath the membrane. Samples from the receptor compartment were taken at various intervals of time over a period of 24 hrs and the concentration of the drug was determined by UV Spectrophotometric method using the standard curve at 212 nm. Amount of drug diffused at various time intervals was calculated and plotted against time.

RESULTS AND DISCUSSION:

Table 2: Thickness uniformity, folding endurance, weight variation, percentage moisture content (%MC), percentage moisture uptake (%MU), percentage moisture loss (%ML) of drug loaded transdermal patches.

S. No.	Formulation code	Thickness (mm)	Weight (gm)	Folding endurance	%MC	%MU	%ML
1	F1	0.22	0.143	>300	1.527	1.123	1.242
2	F2	0.19	0.123	>300	2.611	1.451	1.854
3	F3	0.2	0.164	>300	2.647	1.562	1.872
4	F4	0.18	0.16	>300	2.826	1.846	1.896
5	F5	0.13	0.18	>300	2.106	1.516	1.524
6	F6	0.12	0.156	>300	2.351	1.582	1.643
7	F7	0.24	0.20	>300	2.582	1.621	1.812

Table 3: Water vapour transmission rate (WVTR), Percent flatness, Tensile strength, and drug content of drug loaded transdermal patches of E RL100 and E RS100.

S.No	Formulation code	WVTR (gm/cm/h)	%Flatness	Tensile Strength (gm/cm^2)	%Elongation	%Drug Content
1	F1	1.201×10^{-4}	100	294.2	18.84	99.23
2	F2	1.226×10^{-4}	98.7	214.1	23.69	97.48
3	F3	1.229×10^{-4}	96.9	228.2	23.12	96.54
4	F4	1.310×10^{-4}	97.8	243.3	22.72	97.87
5	F5	1.208×10^{-4}	98.2	259.4	19.74	95.65
6	F6	1.216×10^{-4}	98.8	274.3	19.56	95.67
7	F7	1.218×10^{-4}	99.6	284.8	18.97	96.8

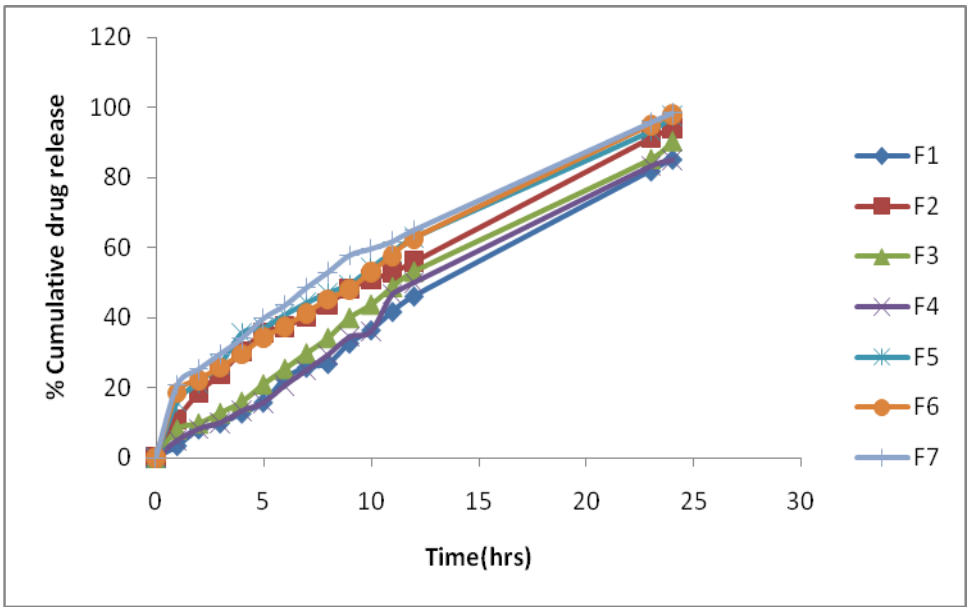

Fig-1: *In vitro* cumulative drug release profile of formulations F1-F7 using dialysis membrane.

In this study transdermal patches of Captopril with variable combinations of E RL100 and E RS100 were prepared and prolonged release of the drug through the matrix films was demonstrated. The compatibility between the Captopril and polymers were confirmed by IR spectrophotometer. The physicochemical parameters and the release characteristics were studied on the fabricated patches. The thickness, weight variation, folding endurance, moisture content and the moisture loss were observed (Table 2). The thickness of the formulated patches F1 to F7 was found to be in between 0.12-0.24 mm, the folding endurance value of all the patches was found satisfactory which ensures that patches prepared using plasticizer dibutyl phthalate (30% w/w of polymer) were having optimum flexibility and were not brittle. The moisture content of the prepared formulations was low and found to be in between 1.527-2.826% w/w (Table 2), which could help the formulations remain stable and reduce brittleness during long-term storage. The percent moisture uptakes (% w/w) of the formulated patches prepared with E RS100 and E RL100 in different ratios were also found low in between 1.123-1.846% (Table 2), which could protect the formulations from microbial contamination and reduce bulkiness. Thus, these formulations can maintain a smooth and uniform surface when applied onto skin. The water vapour transmission through the different patch formulations prepared taking E RL100 with E RS100 in different compositions showed that the patches were permeable to water and showed uniform flatness without any observed constriction (Table 3). The uniformity in flatness of the prepared patches indicates that the formulation by solvent casting and solvent evaporation technique is reproducible and the formulation can maintain satisfactory surface smoothness. The percentage drug content of all the formulations was found in between 95.65-99.23% (Table 3). The drug content of all the formulations was found satisfactory. The tensile strength of the patches was found in between 214.1-294.2 gm/cm^2 (Table 3). The *in vitro* drug release from the formulated patches were carried out in modified diffusion cell through dialysis membrane using 100 ml phosphate buffer (pH 7.4) as diffusion media for a period of 24 hrs. It was observed that the patches prepared with equal proportion of both E RL100 with E RS100 showed a controlled release of the loaded drug over an extended period of 24 hrs, in this respect formulation F1 showed best result amongst all the formulations (Fig 2).

CONCLUSION:

In conclusion, *in vitro* drug release of Captopril from its transdermal patches showed that the films containing equal proportions of E RL100 and E RS100 showed suitability for a prolonged regimen of sustained drug delivery through transdermal route for a period of more than 24 hrs. The results of the study give a rational guideline for formulating a sustained release transdermal

therapeutic system of Captopril for effective therapy and prophylaxis of angina pectoris, cardiac arrhythmia and hypertension.

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