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FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM OF AN ANTI-HYPERTENSIVE DRUG

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The present study was aims to formulate and evaluate transdermal drug delivery for sustained release of an anti-hypertensive drug Captopril, it is considered as 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 ethyl cellulose and PVP a hydrophobic and hydrophilic polymer respectively. Transdermal patches were prepared using different combination of the two polymers by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as a plasticizer. Several Physicochemical parameter like moisture content, moisture loss, thickness, film 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 polyvinyl pyrolidone shows faster release whereas increasing proportion of ethyl cellulose produces a prolonged regimen of sustained drug delivery through transdermal route for a period of 24 hrs.

Keywords: Captopril, transdermal therapeutic system, ethyl cellulose (EC), polyvinyl

INTRODUCTION

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.[1] The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, TDDS offer many advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance. 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.[2]

Captopril, an orally active inhibitor of an angiotensin converting enzyme has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity. It has a mean half life of 2-3 hrs but action lasts for 6-12 hrs. 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.[3] So, the use of transdermal drug delivery system, can reduce the side effects associated with captopril.

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MATERIAL AND METHODS

Captopril was purchased from Balaji Drugs. Polyvinyl pyrrolidone K-30 (PVP K-30), Central Drug House (P) Ltd. New Delhi; Ethyl cellulose LR (EC), Central Drug House (P) Ltd. New Delhi; 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 2 ml 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 aluminum foil. It was placed in dryer at 60ºC±2º C 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 transdermal patches

Matrix type transdermal patches of Captopril were prepared by using two polymer compositions, containing EC and PVP in different ratios as shown in the Table I by solvent evaporation technique in cylindrical both side opened glass moulds. 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 mold, 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]

Evaluation of transdermal patches

Thickness uniformity:[4]

Thickness uniformity of the transdermal patches was measured with micrometer with least count of 0-0.01 mm. The thickness of the patch at five different points was measured and the average of five readings with the standard deviation was calculated. The procedure was followed for all the formulation batches.

Uniformity of weight:[5]

The patch of size 1x1 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

Percent flatness study:[6]

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:[7]

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 exact value of folding endurance.

Drug content uniformity:[8]

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):[9]

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.

$$\%MC = \frac{X - Y}{Y} \times 100$$

Where, X = initial weight, Y = final weight

Table I: Formulation of drug loaded transdermal patches using EC and PVP

Formulation Code	Ratio of EC: PVP	Total weight of EC & PVP (mg)	Ethanol (ml)	Plasticizer (% w/w) of total polymer	Drug (% w/w) of total polymer
F1	1:1	500	10	30	20
F2	1:2	500	10	30	20
F3	1:3	500	10	30	20
F4	1:4	500	10	30	20
F5	2:1	500	10	30	20
F6	3:1	500	10	30	20
F7	4:1	500	10	30	20

Percentage moisture uptake: [9]

The patches were weighed accurately and placed in a dessicator 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.

$$\%MU = \frac{X - Y}{Y} \times 100$$

Where, X = initial weight, Y = final weight

Percentage moisture loss:[5]

The patches were weighed individually and kept in a dessicator 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.

$$\%ML = \frac{X - Y}{Y} \times 100$$

Where, X = initial weight, Y = final weight

Water vapour transmission (WVT) rate:[10]

The study were performed taking 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 desecrator 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.

$$Tensile\ strength = \left(\frac{break\ force}{a \times b}\right) \times \left(\frac{1 + L}{I}\right)$$

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

Table II: Different evaluation parameters of drug loaded transdermal patches

Formulation code	Thickness (mm)	Weight (gm)	Folding endurance	% MC	%MU	%ML
F1	0.2	0.21	>300	3.97	4.48	4.29
F2	0.18	0.20	>300	4.67	5.82	4.56
F3	0.19	0.156	>300	5.00	5.97	4.79
F4	0.15	0.21	>300	5.59	6.36	5.23
F5	0.21	0.186	>300	4.34	4.51	4.34
F6	0.21	0.226	>300	3.57	4.12	4.12
F7	0.19	0.19	>300	3.15	3.58	3.81

RESULTS

***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. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37°C±2°C 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 0.1N 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.

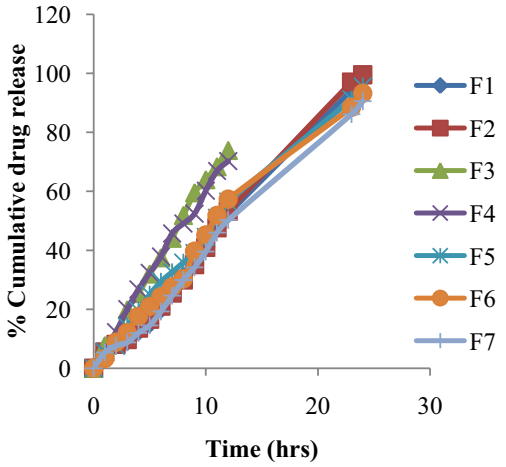

Fig I: *In vitro* cumulative drug release profile of formulations F1-F7 using dialysis membrane

DISCUSSION

In this study transdermal patches of Captopril with variable combinations of EC and PVP were prepared and prolonged release of the drug through the matrix films was demonstrated. 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 II). The thickness of the formulated patches F-1 to F-7 was found to be in between 0.15-0.21mm, the folding endurance value of all the patches was found satisfactory which ensures that patches prepared using plasticizer dibutylphthalate (DBP) (30% w/w of polymer) were having optimum flexibility and were not brittle. The percent moisture content (% w/w) of the formulated patches were found in between 3.58-6.36 % (Table II). In moisture uptake study it was observed that moisture uptake value increases with gradual increase in concentration of hydrophilic polymer PVP. The water vapour transmission through the different patch formulations prepared taking EC with PVP in different compositions showed that the patches were permeable to water and showed uniform flatness without any observed constriction (Table III). 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 95.48-99.69 % (Table III). The drug content of all the formulations was found satisfactory. The tensile strength of the patches was found in between 210.92-277.76 gm/cm^2 (Table III). It was observed that with increase in concentration of hydrophilic polymers the tensile strength of the patches decreases gradually. 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 hydrophilic polymer in a higher concentration like formulations F2, F3, F4 where concentration of PVP is in gradual increasing order the release was very quick and the patches releases more than 98 % of the loaded drug far before 24 hrs and drug release is not in a controlled manner. But in case of the patches prepared with hydrophobic polymer, EC concentration in a gradual increasing order like formulation F5, F6, F7 showed a controlled release of the loaded drug over an extended period of 24 hrs, in this respect formulation F7 showed best result amongst all the formulations (Fig I).

CONCLUSION

In conclusion, *in vitro* drug release of Captopril from its transdermal patches showed that the patches containing higher proportion of EC 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.

Table III: Water vapour transmission rate (WVTR), Percent flatness, Tensile strength, and drug content of drug loaded transdermal patches of EC and PVP

Formulation code	WVTR (gm/cm/h)	% Flatness	Tensile Strength (gm/cm^2)	% Elongation	% Drug Content
F1	$1.4423x^{10-4}$	99.2	236.85	23.8	95.50
F2	$1.9445\ x^{10-4}$	98	228.34	24.7	96.12
F3	$1.8742\ x^{10-4}$	97.9	220.89	26.3	96.68
F4	$1.6048\ x^{10-4}$	97.3	210.92	29.4	95.48
F5	$1.2040\ x^{10-4}$	98.6	241.59	22.4	98.37
F6	$1.1928\ x^{10-4}$	99.1	256.26	20.8	96.88
F7	$1.1054\ x^{10-4}$	100	277.76	19.2	99.69

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