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FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM CAPTOPRIL AS ANTI- HYPERGLYCEMIC AGENT

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Abstract:

The present study was aims to formulate and evaluate transdermal drug delivery 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 Hydro Propyl Methyl Cellulose (HPMC) K15M, Poly Vinyl Pyrrolidone (PVP) K30, ethyl cellulose a hydrophobic and hydrophilic polymer respectively. Transdermal patches were prepared using different combination of the three polymers by solvent evaporation technique. Dibutyl phthalate and PEG400 were added as plasticizers. Tween-80 and dimethyl sulphoxide (DMSO) were applied as a penetration booster. Several Physicochemical parameters like moisture content, moisture loss, thickness, film folding endurance, tensile strength, flatness was studied. For all the formulations, in vitro drug release was studied using modified diffusion cell. Transdermal patches extended 24-hour drug release was demonstrated in vitro. The formulation F4 performed well in assessment studies, according to the findings of the current experimental inquiry. So, the optimized formulation was the F4 formulation. It was discovered that the penetration of captopril from transdermal formulations follows zero order release and the diffusion mechanism. Therefore, we conclusion that the drug carrier for captopril would be a transdermal delivery method.

Keywords: Captopril, Anti-hypertensive drug, Tween-80, DMSO, Dibutyl phthalate and PEG400

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INTRODUCTION:

For Thousands of years, human civilizations have applied substance to the skin as cosmetic and medicinal agents. However, it was not until the twentieth century that the skin came to be used as a drug delivery route. In fact, Marian Webster dates the word "transdermal" to 1944 highlighting that it is a relatively recent concept in medical and Pharmaceutical practice [1]. TDDS delivers drugs through the skin as an alternative for more traditional route like orals, intravascular, subcutaneous and transmucosal [2]. A Transdermal Drug Delivery Systems (TDDS) or transdermal patch is defined as flexible, multilaminated. Pharmaceutical preparation of varying size containing one or more drug substance to be applied to the intact skin for systemic circulation to maintain the plasma level. This is normally formulated with pressure sensitive adhesive that assures the adhesion of the preparation for the skin [3]. In the present scenario, very few transdermal patches are commercially available.

Captopril is ACE inhibitor to treat hypertension, cardiac conditions such as CHF and after myocardial infraction prevention of kidney function in diabetic nephropathy. Congestive heart failure is manifested more frequently during the night or early in the morning. Blood pressure which arises notably just waking up is usually responsible for the attacks [4]. However, for such diseases, conventional drug delivery system is inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened, because during this time, the patient is sleep. Short biological half-life of 1-2 hrs. is one of the important drawbacks of captopril which requires frequent administration of the drug and it leads to poor patient compliance [5,6]. With regards to the drawbacks of captopril including short half-life and narrow absorption window, a sustained release drug delivery system would be beneficial. Simple drug-matrix dispersion type of transdermal drug delivery system (TDDS) of Captopril was formulated for prolonged periods of maintenance therapy alternatives to conventional oral dosages forms. Moreover, the physicochemical characteristics of Captopril also comply with the general requirement for formulating a TDDS to a good extent [7].

MATERIALS AND METHODS:

Materials

Captopril was purchased from Micro labs Pharmaceutical Ltd. HPMCK15M, Polyvinyl pyrrolidone K30, Ethyl Cellulose from S.D. Fine Chemicals. Polyethylene glycol- 400, Dibutyl phthalate from Loba Chemie Pvt Ltd, Mumbai.

Methods

Compatibility study

Utilizing an FTIR spectrophotometer, the mixed combination of captopril and polymer was recorded [8].

Preparations of transdermal patches

By using the solution casting process on a glass substrate (covered in aluminium foil), the transdermal patches of the arrangement stated were created. Captopril-containing membrane-type transdermal systems were created utilising HPMC alone as well as dissimilar proportions of HPMCK15M, PVPK30, and ethyl cellulose [9,10]. Captopril was added to the uniform polymeric solution after the polymers had been precisely weighed, dissolved in a suitable solvent, and thoroughly mixed to create a uniform solution. Dibutyl phthalate and PEG400 were added as plasticizers. Tween-80 and DMSO were applied as a penetration booster. A sufficiently flat, hard, rigid surface was chosen for the placement of the bangles, and the polymer solution was poured into them. The patches were then cured for 24 hours at room temperature. To prevent the solvent from quickly evaporating, a funnel that was upside down was positioned over the bracelets. Patches measuring 3.14 cm^2 were cut, enfolded with aluminium foil, and kept in a desiccator.

Table No. 1 Formulation of transdermal patches for captopril

Formulation (mg/ml)	F1	F2	F3	F4	F5	F6	F7
Drug	60	60	60	60	60	60	60
HPMCK15M	500	450	400	300	-	-	-
PVPK30	-	50	100	200	400	300	200
EC	-	-	-	-	100	200	300
PEG-400	0.18	0.18	0.18	0.18	-	-	-
Dibutyl phthalate	-	-	-	-	0.3	0.3	0.3
Tween 80	0.14	0.14	0.14	0.14	-	-	-
DMSO	-	-	-	-	0.10	0.10	0.10
Methanol	15	15	15	15	-	-	-
Chloroform	-	-	-	-	5	5	5

Thickness of patches

At three different locations, the thickness of Patches was determined using digital vernier callipers with a least count of 0.001 mm. An average of the three readings was taken, and a standard deviation was calculated [11].

Weight variation

For a weight variation test, three 3.14 cm2 discs were sliced and balanced on an electronic scale.

Drug content

Individually balanced patches were dissolved in PBS pH 7.4 solutions with a minimum of methanol to make a volume of 100 ml; 10 ml was then moved to a flask and completed to volume. The absorbance measurement was made at 243 nm. With the exception of using drug-free patches, the blank solution was prepared in the same way [12].

Moisture content percentage

The films were balanced and dried in desiccators with $CaCl_2$ at 40°C for minimum 24 hours or longer till their weight remained consistent. The percentage by weight moisture content was considered as the change among the original mass and the constant mass taken [13].

Swelling index

The 3.14 cm2 patches were balanced, inserted to a petri dish with 10 ml of double-distilled water, and penetrated to grip moisture. After a set period of time, the patches' weight was checked to see if it had increased. Repeat this method until the same weight is seen and the weight stays the same throughout time. By using the formula, the swelling index (% S) was calculated.

$$S\ \% = Wt - Wo / Wo \times 100$$

Where,

S -% swelling,

Wt - patch mass at time t.

Wo - patch mass at time zero.

Folding endurance

This resulted from repeatedly folding one patch in the same location without letting go of it, giving folding endurance its worth. This test, which was accepted out to examine the folding capacity of transdermal patches, also shows how brittle they are, with more brittle patches showing lower folding endurance values [14].

Percentage Elongation

On a glass plate, a film strip (4 x 1 cm) was sliced using a sharp blade. By using a formula and a pointer on graph paper to measure the length just earlier the breaking point, the % elongation break can be calculated [15].

$$\% \text{ elongation} = IB - Io / Io \times 100$$

Where-

Io = Original film length.

IB = Length of film at disruption when pressure is applied.

Tensile Strength

A flat wooden stage with a secure scale and attachments for 2 pins that grip the transdermal patch under test made up the equipment. Both clips could be moved, but one was fixed. One end of the pulley had weights hanging from it, and the further end was fastened with a moveable clip. The wooden platform was so securely fastened that it did not budge throughout the experiment. Cut 3 patch strips that were 0.5 cm wide and 4 cm long. The strips' width and thickness were measured at each place, and an average value was computed. Two cm separately and

one cm at either end of the strips were marked with ink [16].

The markings on each strip were hardly discernible due to the manner they were clipped together. The gadget consistently changed the stress at a rate of 0.5 gramme every 2 minutes. The total weights were calculated and the elongation was measured. Utilising, the tensile strength was calculated [17].

Tensile stress (S) = Applied force /Cross sectional area = m × g /b × t

Where,

S = tensile stress in dynes/cm^2

M = mass in grams

G = acceleration due to gravity (dynes/cm^2)

B = breadth of strip in centimetres

T = width of strip in centimetres

Stability studies

Studies on stability were conducted under various storage conditions. 90 days at 25°C, 20°C, 60% RH, and 40°C, 20°C, 75% RH were tested on batches of optimized formulation (F4&F5). Thickness, drug content, assay, moisture content, absorption, and in vitro drug penetration are the factors that stability studies take into consideration [18].

RESULTS AND DISCUSSION:

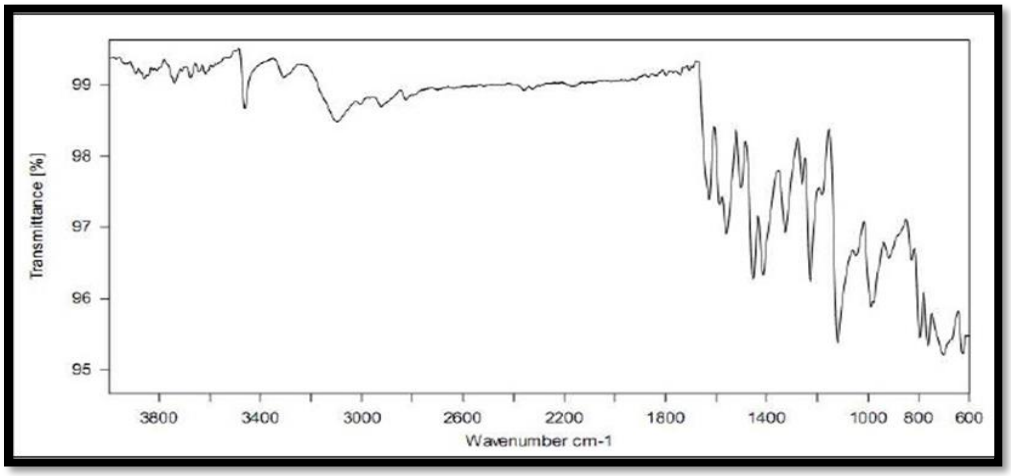

Figure No 18. FTIR spectra of Captopril

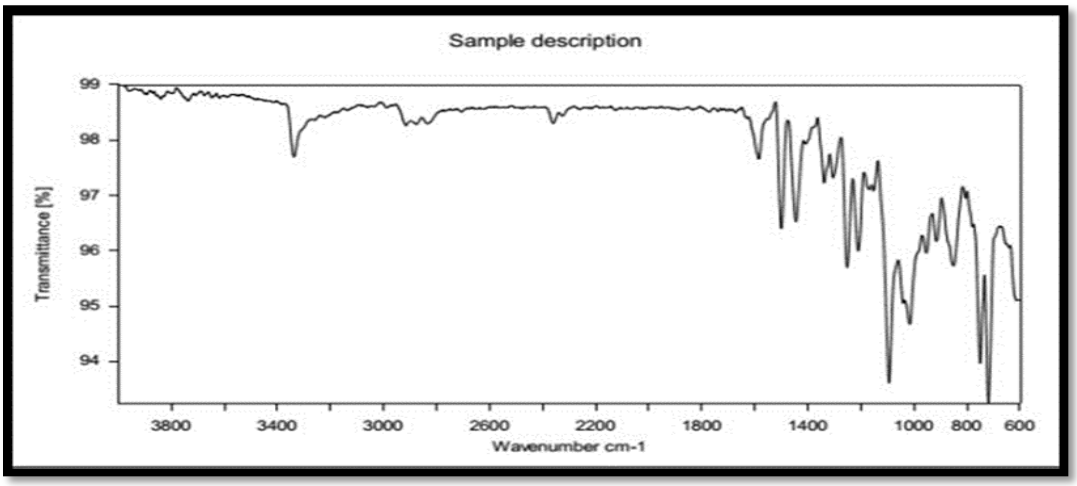

Figure No 24. FTIR Spectra of Optimized formulation

The medication and polymer's FT-IR spectra did not reveal the presence of any new functional group-related peaks. These findings imply that drugs and polymers are compatible.

Table No. 2 Relative FTIR data of medication and polymer

Name of Compound	N-H cm^{-1}	C-H cm^{-1}	C=C cm^{-1}	NO_2 cm^{-1}	C-N cm^{-1}
Captopril	3332	2918	1645	1564	1248
Optimized Formulation	3335	2910	1626	1551	1236

Preparations of Transdermal Patches

Seven different Captopril formulas As a casting solvent, HPMCK15M, PVP K30, ethyl cellulose, chloroform, methanol, and dichloro methane were used to cast patches made of various polymers. The plasticity of patches is provided by PEG400 and dibutyl phthalate, while the medication penetration through transdermal systems is improved by DMSO and Tween 80. In order to prevent the solvent from quickly evaporating, an upturned funnel was positioned over the polymeric solution-filled bangles before they were set in an appropriate flat, hard, dust-free area to dry for 24 hours. Patches measuring 3.14 cm^2 were cut, wrapped with aluminium foil, and stored in a desiccator.

Figure No 1. Captopril Transdermal patch

Table No. 3 Physicochemical Valuation of Transdermic Patches ofCaptopril

Formulation	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm^2
F1	0.11±0.02	0.14±0.02	96.02±3.25	56.8±3.12	2.38±0.78
F2	0.19±0.02	0.148±0.005	96.59±3.14	36.6±21.0	2.80±0.80
F3	0.15±0.05	0.149±0.15	96.96±1.24	37.5±16.15	2.35±0.65
F4	0.16±0.010	0.159±0.09	98.95±2.36	59.5±22.25	3.92±1.75
F5	0.36±0.10	0.150±0.09	99.02±2.12	57.8±22.12	3.88 ±1.78
F6	0.36±0.004	0.155±0.009	98.02±1.36	56.8±10.35	2.78±1.78
F7	0.34±0.003	0.149±0.008	99.05±1.36	58.8±10.35	2.88 ±1.82

Table No. 4 Physicochemical Assessment data of Transdermal Patches

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F_1	23.98±1.48	1.78±0.40	4.78±2.24	23.78±1.4
F_2	22.92±2.20	2.5±0.68	3.5±2.8	24.96±0.84
F_3	24.96±2.58	3.0±1.32	5.2±1.08	24.90±1.08
F_4	25.65±4.08	3.1±1.78	4.6±0.12	22.92±0.82
F_5	27.94±3.52	3.18±2.64	5.6±1.38	21.896±1.30
F_6	24.86±4.20	2.6±0.86	4.8±1.12	23.98±1.28
F7	23.75±3.22	2.7±0.88	4.68±1.24	25.20±1.4

The patches have a thickness that varies from 0.12 to 0.37 mm. In table no.6.5, the thickness values for each batch are listed. Patches' low SD values provide thickness homogeneity throughout each formulation (Table 6.5). It was discovered that the weight variance ranged from 0.148±0.005 to 0.160±0.011mg. The study's findings showed that all systems had homogeneous drug content and reasonably low SD values, ranging from 95.92±3.32 to 99.65±2.42. The values for folding endurance were found to range from 36.62±1.0 to 602±4.33 folds. The patches demonstrated decent mechanical strength and flexibility, according to the findings.

The range of patches' tensile strengths was determined to be 2.40±0.70 to 3.92±1.84 Kg/mm2. The best tensile strength was demonstrated by the formulations F4 and F5. The formulation's percent elongation ranged from 24.25±4.18 to 28.04±4.71%. The organizational integrity of the patches was examined using % moisture content testing under dry conditions. The range of the moisture content was 1.85±0.35 to 3.23±2.78. To verify physical stability under humid conditions, the% moisture uptake investigation was carried out.

Stability Study

The purpose of the current experiments was to assess the preparation constancy of the optimised lots F4 and F5 under accelerated temperature and humidity settings at a three-month interval.

Table No. 5 Stability Study of batch F4 & F5

S. no	Evaluation Parameter	F4		F5	
		At 0 day	After 90 days	At 0 day	After 90 days
1	Thickness (mm)	0.16±0.01	0.15 ± 0.08	0.34±0.1	0.33 ± 0.04
2	Weight variation	0.325±0.08	0.324 ± 0.08	0.224±0.020	0.223± 0.009
3	% Medicine Content	99.48±2.30	98.88 ± 1.18	95.8±2.10	95.5 ± 1.0
4	Folding endurance	38±4.3	37 ± 2.10	57±1.22	56 ± 1.08
5	Tensile Strength Kg/mm^2	2.38±2.12	1.82 ± 1.56	2.42±0.9	2.41 ± 1.58
6	% Elongation	25.3±3.08	24.5 ± 3.8	27.92±3.52	27.08 ± 3.2
7	% Moisture content	3.1±1.78	3.0 ± 0.88	3.15±1.66	2.4 ± 0.10
8	% Moisture uptake	4.6±0.9	4.4 ± 2.15	5.6±1.38	4.92 ± 2.2
9	Swelling index	22.9±0.68	21.90 ± 0.68	23.2±1.3	22.8 ± 0.12

CONCLUSION:

Transdermal matrix patches were eventually efficiently built and developed using the approach of experimental and error founded on results of many assessments characteristics similar thickness, strength, elongation, upgraded compatibility, and stability. The patches had homogeneous medication content and good tensile strength and thickness. Transdermal patches were created using a variety of ratios of the polymers HPMCK15M, PVPK30, and EC. Transdermal patches extended 24-hour drug release was demonstrated in vitro. The formulation F4 performed well in assessment studies, according to the findings of the current experimental inquiry. So, the optimized formulation was the F4 formulation. It was discovered that the penetration of captopril from transdermal formulations follows zero order release and the diffusion mechanism. Therefore, we conclusion that the drug carrier for captopril would be a transdermal delivery method.

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