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Development and Physiochemical, *In-Vitro* Evaluation of Antihypertensive Transdermal Patches

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Abstract:
Transdermal patches of Losartan with hydrophilic and hydrophobic polymers containing the drug reservoir were prepared by solvent evaporation method. In this experiment, the membranes of ethylcellose and eudragit RS 100 were used to achieve controlled release of the drug. The prepared patches showed satisfactory physiochemical characteristics of weight variation, thickness, folding endurances, moisture absorption and drug content were uniform in all patches. *In-vitro* permeation studies were done by using Franz diffusion cell having cellophane membrane. The effect of non- ionic surfactant like tween 80 and span 80 on drug permeation were studied. Based on the kinetic studies, the patch containing both HPMC and Eudragit RS100 showed satisfactory drug release patterns.
Keywords: *Transdermal patches, In-vitro diffusion, Kinetic studies, Drug reservoir, Rate control membranes*

Introduction:

Losartan Potassium[1-3] is a novel multiple action cardiovascular drug alternative to ACE inhibitor. This drug is currently approved in India. The decrease in the blood pressure is produced by competitive antagonist action of AT1 receptor and release of aldosterone and adrenaline from adrenal glands, renal action promoting salt and water reabsorption. The multiple action of Losartan may also provide the rational use of drug in the treatment of congestive heart failure[4].

Losartan Potassium is less absorbed from the gastro intestinal tract and the bioavailability is only 33% due to first pass metabolism in liver (cytochrome 450 enzymes). It has a half life of 2.1± 0.70 h[3].

Losartan Potassium was chosen as a model drug for study since it possess near ideal characteristic that a drug must have in formulating a drug delivery system such as low molecular weight, high lipid solubility, effective in low plasma concentration as well as high degree first-pass effect. It also means multiple administration with subsequent lack of patient compliance. The aim of the study was to prevent its first-pass metabolism and achieve control release.

Materials and Methods:

Losartan Potassium was a gift from Tri-Star formulation Ltd. Pondcherry. HPMC, Eudragit RL 100 and Eudragit RS100 were kindly supplied by LOBA Chemie.Ltd. Mumbai (India).Methyl cellulose and carboxy methyl cellulose were obtained by SD Fine Chem Ltd. Mumbai (India). Polyvinyl Pyrrolidone, poly ethylene Glycol, Span 80 and Tween 80 were purchased from QUALIGENS fine chemicals, Mumbai (India). All other chemicals were of analytical grade.

Drug Partition Coefficient[7]:

The partition coefficient studies were performed using n-octanol as the non aqueous phase and water as the aqueous phase. The two phases were mixed in equal quantities and kept for saturation with each other on a water bath at 37ºc for 24 hours with occasional shaking. The saturated phases were separated by centrifugation at 2500 RPM. The standard curves of the drug were plotted from both water and n-octanol. Equal volume (10ml) of two phases was placed in six conical flasks, and 100 mg of drug was added to each flask. The flasks were shaked at 37ºc for 5 hours to achieve complete partitioning at 100 RPM. The two phases were separated by centrifugation at 1000 RPM for 5 minutes and the solution was passed through membrane filter and the filtrate was analyzed for drug content using spectrophotometrically.

Preparation of transdermal patch:

Transdermal patches containing Losartan were casted on glass slide by solvent

evaporation technique. The drug matrix was prepared by dissolving hydroxyl propyl methyl cellulose (HPMC) in distilled water. Poly ethylene glycol (30%) was used as a plasticizer. The antihypertensive drug 30 mg of Losartan dissolved in 5 ml ethanol and the homogenous dispersion was produced by slow stirring with a magnetic stirrer. The rate controlling membrane Eudragit RS 100 and ethyl cellulose was incorporated into the drug reservoir.1% m/v of permeation enhancer of non ionic surfactant (tween 80)[2, 3] were cast on drug reservoir. Formulation f2, f3 was prepared by using Methyl cellulose and sodium carboxy methyl cellulose as hydrophilic polymers respectively. After complete drying of patches were cut into small pieces each of 3 square centimeters and stored between sheets of wax paper in a desiccator(Table-I).

Evaluation of Losartan patches [4, 5]:

Evaluation of all formulated Transdermal patches values were shown in Table-II.

Thickness: The thickness of patches was measured at 3 different places by using micrometer (mitutoyo & co, Japan), and mean value were calculated[6].

Weight variation: The patches were subjected to weight variation by individually weighing 10 selected patches randomly. Such variations were carried out for each formulated patches.

Folding endurance: The folding endurance of patches was determined by repeatedly folding one film at the same place till it tends to break. The number of times the film would be folded at the same place with out breaking was taken as the value of folding endurance[7].

Moisture pick up studies : The moisture uptake was determined by drying the film at 60ºc with a current of air after which the film were subjected to desiccator over anhydrous calcium chloride at 40ºc for 24 hours. Those patches were weighed and exposed to 70 % relative humidity at room temperature. This relative humidity was maintained using saturated sodium chloride solution. After attaining equilibrium under this humidity, patches were weighed for determining the increased in weight. The percentage moisture uptake was calculated[8] and shown in Table –III.

Moisture vapor transmission studies: Moisture vapor transmission means the quantity of moisture transmitted through unit area of patch in unit time. Glass vials were filled with 2 grams of anhydrous calcium chloride and a patch of specified area was affixed into the top of vial brim. The assemble was accurately weighed and placed in a humidity chamber (80 ±5 %RH) at 27ºc for 24 hours[9].

Drug content: Patches of specified area were dissolved in 5 ml of dichloromethane and the volume was made up to 10 ml with 7.4 pH phosphate buffer. Dichloromethane was evaporated using vacuum evaporator at 45ºc. a blank was prepared using drug free patch treated similarly. The solution was filtered through membrane, diluted with a suitably and absorbance were measured at 242 nanometer in a double beam UV – Vis spectrophotometer (analytical technologies Ltd) [10, 11].

In-vitro permeation studies[12, 13]: Patches of 3 sqcm were subjected to an Invitro permeation studies by using Franz diffusion cell containing cellophane membrane. The patches was placed in a donor compartment over the membrane and covered with parafilm. The temperature of the receptor compartment was maintained at 37 ±2ºc through out the experiment. The compartment was in contact with the ambient environment. The amount the drug permeated through membrane was determined by with drawing 1ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples filtered by membrane

Table 1: Composition of Transdermal Patches

Formulation	Drug reservoir	Rate controlling membrane	Permeation enhancer(1% m/v)	Plasticizer (30%)
1	HPMC	----------	Tween 80	PEG 200
2	MC	----------	"	"
3	S-CMC	----------	"	"
4	HPMC:MC(1:1)	----------	"	"
5	HPMC	Eudragit RS 100	"	"
6	HPMC	Ethyl cellulose	"	"

Table 2: Physiochemical Characterization of Transdermal Patches

Parameters	F1	F2	F3	F4	F5	F6
Thickness(μm)	95.5± 0.0	90.7± 0.03	92.4± 0.1	94.2± 0.02	92.6± 0.0	92.3± 0.1
Weight Variation(mg)	57.1± 0.4	49.3± 0.1	53.6± 0.2	58.4± 0.2	57.0± 0.5	57.2± 0.2
Folding endurance	342.4± 8.2	282± 4.1	324.6 ± 5.0	330.7± 4.8	347.1± 3.8	348.3 ± 6.1
MVT in 24 hours	0.160± 0.001	0.130± 0.002	0.151 ± 0.007	0.171± 0.002	0.163± 0.001	0.169 ± 0.005
Drug content	2.85± 0.02	2.85± 0.01	2.81± 0.02	2.84± 0.01	2.84± 0.01	2.85± 0.02
In vitro diffusion release rate	1.06± 0.06	3.18± 0.01	2.91± 0.02	0.98± 0.06	0.82± 0.02	0.91± 0.04

Mean ± SD (n=5)

Table 3: Percentage Moisture Pick Up Studies

Formulations	52% RH	75% RH	92% RH
F1	8.14	14	17.76
F2	12.8	17.47	18.42
F3	10	18.64	20.35
F4	12.39	19.87	20.51
F5	8.16	15	17.50
F6	9.09	16.02	20.13

Mean ±SD (n=5)

Table 4: Release Kinetics of Invitro Losartan Transdermal Patches

FORMULATIONS	%CUMULATIVE RELEASE	1ST ORDER		HIGUCHI'S EQUATION R^2	KORSMEYER'S PEPPAS EQUATION
		R^2	K		
F1	89.21 ± 0.78	0.9258	8.797×10^{-2}	0.8679	0.5776
F2	99.06 ± 0.02	0.917	1.95×10^{-1}	0.5742	0.8432
F3	96.99 ± 4.64	0.9767	1.47×10^{-1}	0.8223	0.8995
F4	75.96 ± 0.31	0.6757	5.527×10^{-2}	0.7666	0.7158
F5	45.55 ± 1.03	0.9184	2.326×10^{-2}	0.9554	0.6292
F6	61.33 ± 1.85	0.9575	3.661×10^{-2}	0.9684	0.6226

and the samples were analyzed spectrophotometrically.

Results and Discussion:

In the present experiment, transdermal patches of Losartan were formulated using hydrophilic polymers of HPMC, SCMC, MC and the effect of ethyl cellulose and eudragit RS 100 as the rate controlling membrane was studied. The formulated patches were characterized for physico chemical properties, in vitro diffusion studies using synthetic membrane.

n-Octanol and *In vitro* study fluid; i.e. water, were considered to be the standard system for determining the drug partition coefficient between cellophane membrane and water. The logarithmic value of partition coefficient (log p) was found to be 4.01±0.01. The data obtained indicate that it possess sufficient lipophilicity to be

designed into a transdermal patch. The physiochemical properties of Losartan transdermal patches were displayed in table 2. The thickness of patches varies from 90.7 to 94.2µm (n=5), casting of rate controlling membrane increases the thickness of patches. The weight of prepared patches was uniform in all six formulations and varies in the range of 49.3 to 58.4 mg per patch. The folding endurance measures the ability of patch to with stand the rupture, folding endurance was in the range between 282 to 348.3 (n=5). The patch (f3) containing methyl cellulose represented the least value. The patch formulated with HPMC, SCMC, and MC shows the MVT in decreasing order 0.160, 0.151, 0.130 mg.cm^{-2}h^{-1} respectively. The MVT can be accelerated due to presence of hydrophilic nature of polymer. Incorporation of hydrophobic polymer as a rate controlling membrane such as Eudragit RS 100, ethyl cellulose reduces the value of MVT rate respectively. Incorporation of non ionic surfactant i.e. tween 80 in the patch increases the MVT. For all the prepared formulations the drug content was found to be in the range of 2.81 to 2.85 mg/patch. The drug content analysis was uniform in all the patches. The moisture pick up studies were analyzed and recorded at 52, 75, 92 %RH.HPMC-MC are having more moisture uptake and reported a maximum value of 12.39, 19.87, 20.51 at 52, 75, 92 %RH respectively.

In this study, different formulations release variable amount of Losartan through membrane into the *in vitro* fluid. To study the drug diffusion kinetics and mechanism the results were fitted to First order, Higuchi's and Korsmeyer-Peppas(Table-IV). Drug permeation profiles from different formulations are shown in fig 1.

It was found that 89.21% of drug was released with 24 hours from F1 (without rate controlling membrane). It means the patch produced burst release. In formulation F2 containing methyl cellulose showed a release of 99.06% for 10 hours. It indicates the patch was to be applied several times a day. Formulation F3 containing SCMC was released at a rate of 96% drug for 15 hours. So the patch shows poor in controlling the release, because the hydrophilic polymers tends to swell in invitro medium and immediately the drug was diffused out. The single polymer having more burst release because it easily dissolves in medium. To control the release of drug two polymers were used in the formulation 4(HPMC: MC) which showed a release rate of 75 % for 24 hours.

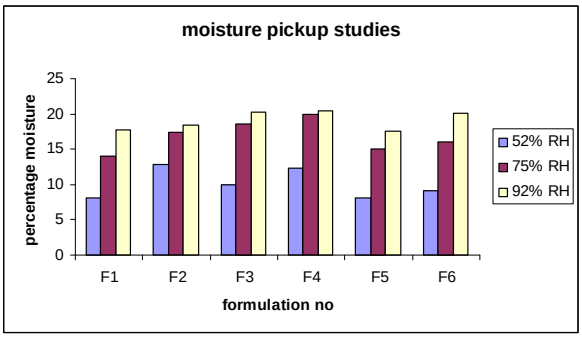

Fig. 1: Moisture pickup studies

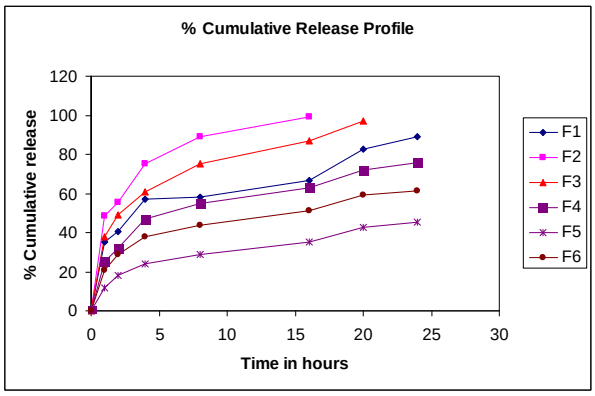

Fig. 2: Percentage Cumulative Release Profile

From the above four formulations it was concluded that the release pattern was not controlled by hydrophilic polymers. So it was necessary to use hydrophobic polymers such as eudragit RS100, ethyl cellulose as the rate controlling membranes, which was casted over HPMC drug reservoir. Eudragit

RS 100, ethyl cellulose was insoluble in diffusion medium. Partitioning between hydrophobic polymers and diffusion medium was very less indicating that the membrane has retarded the release of drug from the reservoir. In the formulation (f6) ethyl cellulose was the rate controlling membrane and it has less hydrophobicity which showed a release rate of 61.3% for 24 hours. In formulation (f5) Eudragit RS100 was the rate controlling membrane because of its high hydrophobicity and cross linking ability which retards the drug release from the membrane drastically i.e. 45.55% for 24 hours.

The data was subjected to 1st order equation and the regression value was found to be in range of (R^2=0.917-0.9767) which confirms 1st order release pattern. Now further investigation was carried to know whether diffusion was involved in the drug release by subjecting the data to higuchi's equation. The lines obtained were comparatively linear (R^2=0.5742-0.9684) guiding the release of the drug through diffusion process. The data was further subjected to korsmeyer's peppas equation for determining the release profile of the drug. Now the release exponent (n) value was determined and this data is used for determining whether the release was fickian or non fickian.

Conclusion:

The kinetic parameters among the formulations showed that all the formulations provided 1st order kinetics. When the average rate constants of all the formulations were compared, it was found that F5 has slowest release of all the formulations. Based on the observations , it is concluded that HPMC:Eudragit RS100 showed better release over other polymer ratio for the development of TDDS for Losartan and the formulation F5 may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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