# FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF LOSARTAN POTASSIUM

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**Summary**

The aim of the study was to develop suitable transdermal drug delivery system of losartan potassium with a view to prevent its first pass hepatic metabolism, to achieve a controlled drug release and improved bioavailability. The transdermal patches of losartan potassium were prepared by solvent casting technique. A combination of Polyvinyl Pyrrolidone (PVP-K25) and Polyvinyl Alcohol (PVA) with Poly Ethylene Glycol (PEG) as plasticizer was used to design transdermal patches. Four formulations ($F_1$, $F_2$, F3, F4) were developed, with different proportions of polyvinyl pyrrolidone and polyvinyl alcohol .The physicochemical parameters like physical appearance, weight variation, thickness and drug content were studied. In vitro releases from the patches were studied, which showed good sustaining action over a period of 24 hours. After 24 hours, the drug release was found to be 53.73%, 56.3% , 60.45% and 95.29%, respectively.

**Keywords:** Transdermal Patches, Losartan Potassium, Polyvinyl Pyrrolidone, Polyvinyl Alcohol and Poly Ethylene Glycol.

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## Introduction

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. The development of Transdermal drug delivery is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy[1].Transdermal Drug Delivery System is viable drug delivery platform technology and has a strong market worldwide. Transdermal Drug Delivery System is particularly desirable for drugs that need prolonged administration at controlled plasma level that basis make appropriateness to antihypertensive agents for their transdermal development. The principal of transdermal drug transport is to deliver drug across epidermis to achieve systemic effect over a prolong period of time. Controlled zero order absorption, simple administration mode, easy termination in case of failed, avoidance of first pass effects, reduction in side effects, sustained drug delivery, and improved patient compliance make the research interest of researchers. The first patch of scopolamine approved in 1979, and now in the present market there numbers of transdermal patches are available for drug such as scopolamine, nitroglycerin, nicotin, clonidine, fentanyl, estradiol, testosterone, lidocain, and oxbutinin. Limited permeability of human skin is still a fundamental problem limiting its widespread therapeutic use. So it is the very big challenge of creating effective transdermal system because it involves sufficient drug permeability through the stratum corneum[2].

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. Transdermal drug delivery promises many advantages over oral and/or intravenous administration, such as better control of blood levels, a reduced incidence of systemic toxicity, and absence of hepatic first-pass metabolism. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical prerequisites, such as short half- life, small molecular size, and low dose etc[3].

Losartan Potassium 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. 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 administrations with subsequent lack of patient compliance[4-7].

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. Pondicherry. Poly vinyl pyrrolidone (PVP), poly vinyl alcohol (PVA) and poly ethylene glycol 200 (PEG-200) were obtained by SD Fine Chem. Ltd. Mumbai (India). All other chemicals were of analytical grade.

### Preparation of transdermal patch

Transdermal patches containing Losartan were casted on glass slide by solvent ethylene evaporation technique[8]. The drug matrix was prepared by dissolving PVP in distilled water. And PVA was also dissolved in warmed distilled water. Poly ethylene glycol (15%) was used as a plasticizer. The antihypertensive drug 115mg of Losartan was added and the homogenous dispersion was produced by slow stirring with a magnetic stirrer. After complete drying of patches were cut into small pieces each of 1 square centimeter and stored between sheets of wax paper in desiccators.

**Table 1: Composition of Transdermal Patches**

| Formulation No. | PVP(mg) | PVA(mg) | PEG 200 (%) |
|---|---|---|---|
| $F_1$ | 100 | 400 | 15 |
| $F_2$ | 200 | 300 | 15 |
| $F_3$ | 250 | 250 | 15 |
| $F_4$ | 300 | 200 | 15 |

### Evaluation of Losartan Patches

### Thickness

The thickness of patches was measured at 5 different places by using digital micrometer, and mean value were calculated[9].

### Weight Variation

The patches were subjected to weight variation by individually weighing 10 selected patches of 1X1 $cm^2$ randomly. Such variations were carried out for each formulated patches[10].

### 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 without breaking was taken as the value of folding endurance[11].

**Drug Content**

Patches of specified area were dissolved in 7. 2pH Phosphate buffer and the volume were made up with 7.2pH phosphate buffer. Blank was prepared using drug free patch treated similarly. The solution was filtered through membrane, diluted with a suitably and absorbance were measured at 205 nanometer in a double beam UV – Vis spectrophotometer (Shimadzu UV-1700)[12].

**Moisture content**

The film was weighed and kept in a desiccators containing Calcium chloride at 40°C and dried for at least 24 h. Film was weighed until it showed a constant weight. The Moisture content was the difference between the constant Weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content[13].

**Table 2: Physicochemical Characterization of Transdermal Patches**

| Parameters | $F_1$ | $F_2$ | $F_3$ | $F_4$ |
|---|---|---|---|---|
| Thickness(mm) | 0.40 | 0.48 | 0.41 | 0.31 |
| Weight variation(mg) | 18.26 | 32.2 | 15.8 | 23.3 |
| Folding endurance | More than 300 | More than 300 | More than 300 | More than 200 |
| Drug content | 85.51% | 73.32% | 83.86% | 93.20% |

**FTIR Spectroscopy**

From the prepared Patches the best formulation was subjected to FTIR spectroscopic studies, to determine drug-carrier interaction. The FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks, using a fourier transform IR spectrophotometer. The samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 $cm^{-1}$ and the resolution was 2 $cm^{-1}$.

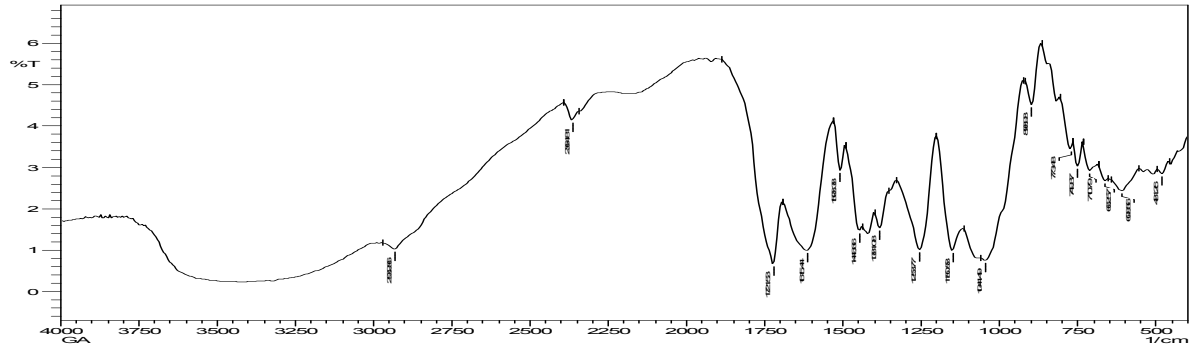


**Fig 1: FTIR Spectra of Pure Losartan Potassium**

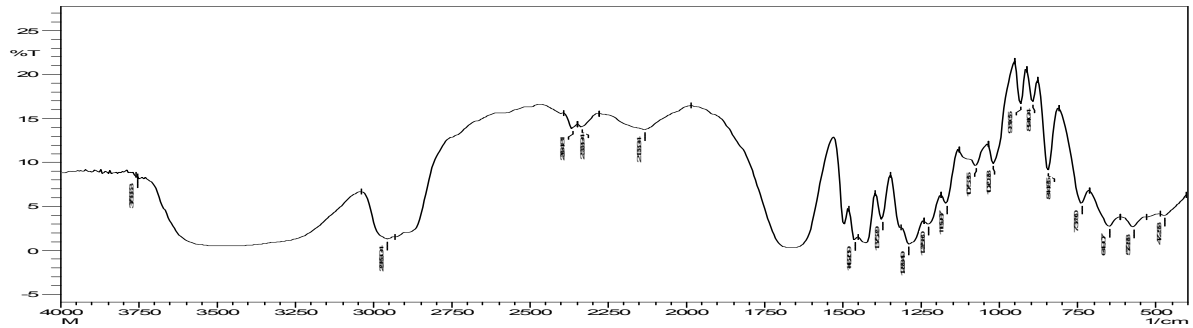


**Fig 2: FTIR Spectra of Polyvinyl Pyrrolidone**

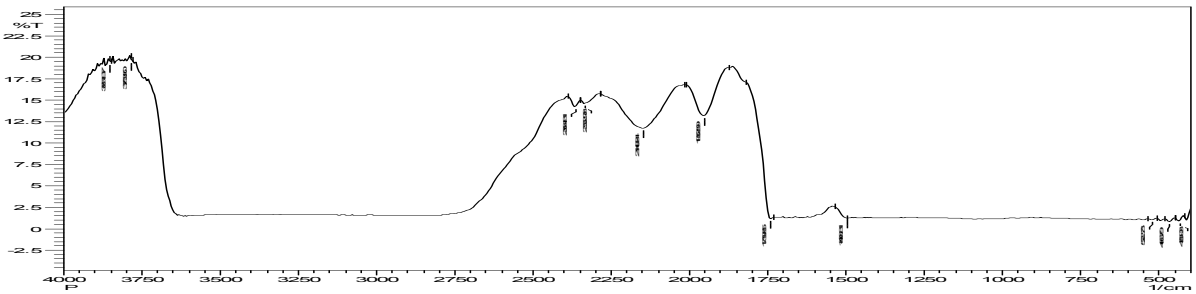


**Fig 3: FTIR Spectra of Polyvinyl Alcohol**

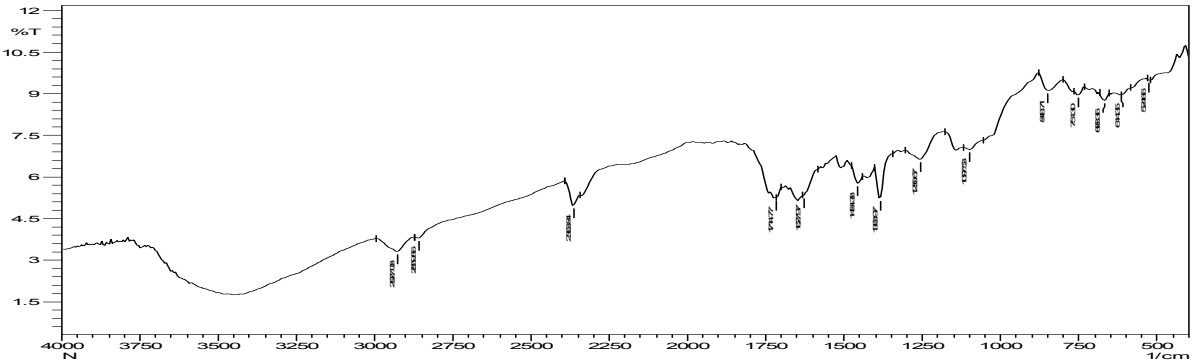


**Fig 4: FTIR Spectra of Losartan Potassium Patch**

### *In-Vitro* Permeation Studies

Patches of 1X1sqcm were subjected to an In-vitro permeation studies by using Franz diffusion cell containing cellophane membrane. The patches were placed in a donor compartment over the membrane. The temperature of the receptor Compartment was maintained at 37 ±2ºC throughout the experiment. The compartment was in contact with the ambient environment. The amount the drug permeated through membrane was determined by a 5 ml aliquot of dissolution medium was withdrawn at different time intervals with pipette containing prefilter and replaced with 5 ml of fresh buffer. Then samples were filtered through 0.5 µm Millipore filter and the filtrate was assayed spectrometrically at 205 nm using buffer as a blank. Each dissolution rate test is repeated for three times[14].

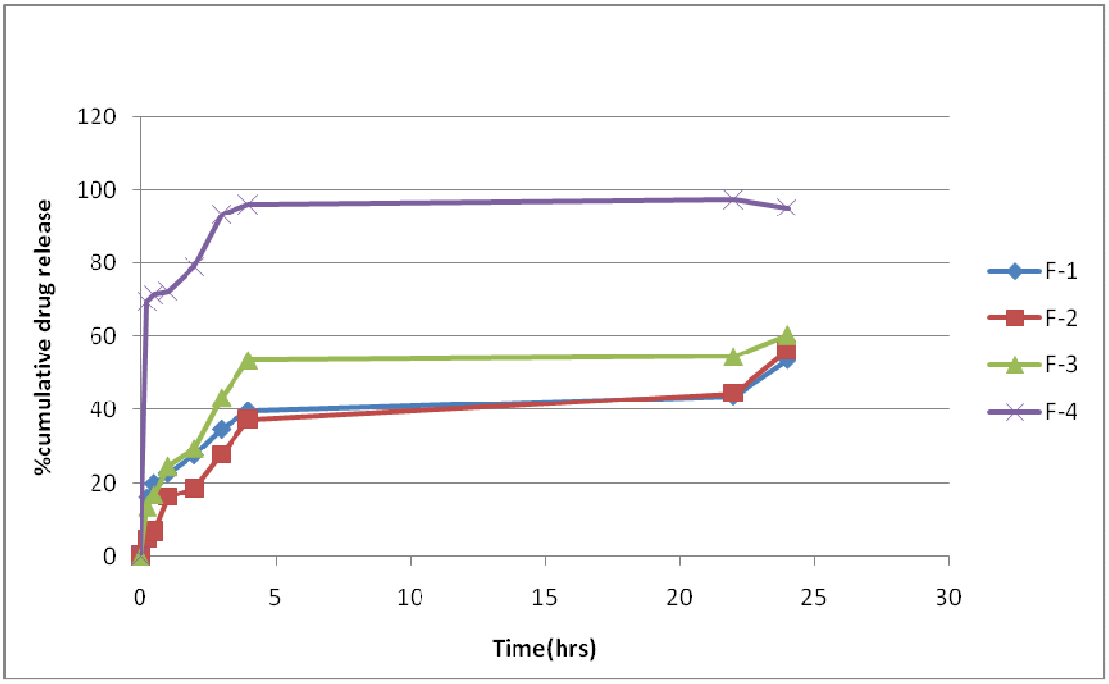


**Fig 5: *In Vitro* Drug Release Study**

## Result and Discussion

In the present study efforts were made to prepare transdermal patches of Losartan Potassium using polymers like PVP and PVA. The drug delivery systems was designed as a matrix and the release was controlled by using polymeric rate controlling membrane, the prepared patches ( F1 to F4 ) were evaluated for physicochemical parameters (Table 2) and *in vitro* diffusion studies using cellophane membrane. The thickness of patches varies from 0.31 to 0.48 mm (n=6), the weight of prepared patches was uniform in all four formulations and varies in the range of 15.8mg to 32.2 mg per patch. The folding endurance was measured to know the ability of patch to with stand the rupture, folding endurance was found more than 300 times in all patches (n=5). For all the prepared formulations the drug content was found to be in the range of 73.32% to 93.20 %. The drug content analysis was uniform in all the patches.

In the present study, the polymeric films of different combinations of PVP and PVA were formulated with constant amounts of Losartan Potassium. Drug permeation study from different formulations was conducted, the cumulative release of drug from different patches (F1 to F4) over 24hours was determined. The data was presented in fig 5. It was observed that as the concentration of PVP increased it resulted in increased drug release. The highest percentage of drug release was found in F4 (95.29%) and least percentage of drug release was observed in F1 (53.73%). The data was subjected to 1st order equation and the regression value was found to be in range of (R2=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 (R2=0.5742-0.9684) guiding the release of the drug through diffusion process. The data was further subjected to korsmeyer's and 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

On the basis of *in-vitro* evaluations of the matrix film formulations, it can reasonably conclude that Losartan potassium can be formulated into transdermal polymeric films for development of a transdermal drug delivery system. The formulation F4 was found to be the best one and it may be employed for further pharmacokinetic and pharmacodynamic studies in suitable animal models and human beings

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