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RESEARCH ARTICLE

DEVELOPMENT AND *IN-VITRO* EVALUATION OF MATRIX-TYPE TRANSDERMAL PATCHES OF LOSARTAN POTASSIUM

Fatima A. Adamude[1], Uhama Kingsley Chukwuka[2]
[1]*Department of Biochemistry, Federal University Lafia, Nigeria.*
[2]*Department of Biochemistry, Anambra State University Uli, Nigeria.*

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***Address for Correspondence:**
Fatima A. Adamude, Department of Biochemistry, Federal University Lafia, Nigeria, E-mail: *fatteeyjibamin@gmail.com*

Abstract

Objective: The aim of present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of Losartan potassium.
Methods: Four transdermal patches formulations of Losartan potassium were prepared by using different polymers using blends of different polymers like polyvinylpyrrolidone K30 (PVP K30) and ethylcellulose (EC), hydroxypropyl methyl cellulose and chitosan. Physical studies including thickness, folding endurance moisture content, tensile strength and flatness were performed on all formulations. *In-vitro* diffusion study of 10 hrs was performed by means of Franz diffusion cell.
Results: Thickness of four prepared patches lies in the range of 0.30 to 0.33 mm. Percent moisture content was found to be in the range of 2.56 to 3.44. The cumulative percent drug release after 10 hrs in between 38.41 to 80.41%.
Stability study performed on selective batch, TP1 for 12 weeks at different temperature indicates stability of transdermal patches at room temperature.
Conclusion: Present study concluded that Losartan potassium can be formulated into the transdermal matrix type patches to sustain its release characteristics. Polymeric composition of batch TP1 (PVP K30: Chitosan: 70:30) was found to be the best choice for manufacturing transdermal patches of Losartan potassium among the formulations studied.
Keywords: Franz diffusion cell, *in-vitro* diffusion, losartan potassium, skin, transdermal drug delivery system.

INTRODUCTION

Skin is an effective medium from which absorption of the drug takes place and enters into systematic circulation over a period of time[1]. Transport of compounds via skin is considered to be a complex phenomenon, which allows the passage of certain chemicals into and across the skin. Transdermal drug delivery is the noninvasive delivery of medications from the surface of skin the largest and most accessible organ of human body through its layers, to the circulatory system[2]. Transdermal patches are designed to slowly deliver the active substance(s) through the intact skin, resulting in a prolonged and adequately constant systemic absorption rate, reduced number of doses and side effects of drug and improved therapeutic efficacy[3]. At present scenario more than 74% of drugs are taken orally and are found not to be as valuable as desired. To advance such characters transdermal drug delivery system was introduced. A Transdermal patch is an adhesive patch that has a coating of drug that is placed on the skin to deliver specific dose into the systemic circulation over a period of time[4]. Losartan potassium is an orally active angiotensin-II receptor antagonist used in the treatment of hypertension due to mainly blockade of AT_1 receptor[5]. It is readily absorbed from the gastrointestinal tract[6]. The main reason for low therapeutic effectiveness of Losartan potassium is its narrow absorption window, narrow therapeutic, index, poor bioavailability as 25-35%, and short biological half life of 1.5-2 h[7].
So in present work Losartan potassium was selected for development and evaluation of matrix-type transdermal patches in order to improve its bioavailability and reduce frequency of administration.

MATERIALS AND METHODS

Losartan potassium was obtained from Bond Chemical Industries Limited, Lagos, Polyvinylpyrrolidone K30 and HPMC K100 was received from Afrik

Pharmaceuticals Limited, Nigeria. Ethyl cellulose, and Chitosan from Dana Drugs Limited, Nigeria. Castor oil and propylene glycol was received from Food and Pharma Nig. Limited, Lagos, Nigeria. All other reagents used were of analytical grades.

Preparation of the Losartan potassium transdermal patches: Polymers in different ratio (Table 1) were taken with plasticizer and Losartan potassium and dissolved in different solvents. Solution was then poured onto a glass petri dish and then placed in an oven. An inverted funnel was placed on the petri dish to facilitate the evaporation of the solvent at the controlled rate over the drying periods of 12 hrs at 40°C. The film thus formed was collected with a sharp razor blade[8].

Table 1: Compositions of the Losartan potassium transdermal patches.

Code	Polymers ratio (%)	Solvent	Plasticizer (20%)	Propylene glycol (%)
TP1	PVP K30 : Chitosan:: 70:30	Dichloromethane (2% w/v)	Castor oil	30
TP2	PVP K30: Chitosan:: 30:70	Dichloromethane (2% w/v)	Glycerine	-
TP3	HPMC: Ethyl cellulose::70:30	Acetic acid (1 % w/v)	Castor oil	-
TP4	HPMC: Ethyl cellulose::30:70	Acetic acid (1 % w/v)	Glycerine	30

Evaluation of transdermal patches

Determination of patch thickness

Patch thickness of Losartan potassium transdermal patches was measured using a digital micrometer (Mitutoyo, Japan). A mean of three readings was obtained[9].

Weight variation: Uniformity of weights of Losartan potassium transdermal patches were determined by weighing five matrices of each formulation. After each film unit was weighed individually on a digital balance, the average weight of film was taken as the weight of the film[10].

Evaluation of drug content

A known area of each patch was weighed accurately and dissolved in 2 ml chloroform followed by dilution with distilled water and then filtered. Drug content was analyzed by UV spectrophotometer (PerkinElmer, USA) at 250 nm. A drug-free film was used as control. A mean of three readings was recorded. The results are reported as mean of six readings[11].

Folding Endurance

Three Losartan potassium transdermal patches of each batch were taken for this study. Folding endurance was determined by repeatedly folding one film at the same place till it break. The number of times the film could be folded at the same place without breaking gave the value of folding endurance[12].

Flatness

Longitudinal strips of 1.8 cm in length were used out from the prepared Losartan potassium transdermal patches and then variation in the lengths due to the non-uniformity in flatness was measured[13].

Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{l1 - l2}{l2} X100$$

Where, l_1 = final length of each strip, and l_2 = initial length

Determination of tensile strength

The tensile strength of Losartan potassium transdermal patches was evaluated using Instron 4204 Tensile tester, with a 50KN load cell (Instron, UK). Six samples of each formulation were tested at an extension speed of 5 mm/min[14]. The test was carried out at 25±2°C and 56±2% RH and tensile strength calculated –

$$\tau = \frac{Lmax}{Ai}$$

Where τ is the tensile strength; Lmax is the maximum load; and Ai is the initial cross sectional area of the sample.

Measurement of moisture content

Each patch was weighed and kept in a desiccator containing fused calcium chloride at 40°C for 24 h. The patches were reweighed until a constant weight was obtained. A mean of three readings was taken[15]. The results are reported as mean of six readings.

Water vapor transmission rate

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 2 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm^2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h. The vials were removed and weighed at 24 h time intervals to note down the weight gain[16].

***In-vitro* diffusion study**

The diffusion studies of Losartan potassium transdermal patches were done to get an idea of permeation of drug through barrier from the transdermal system[17]. Franz-diffusion cell which is also called Keshary–Chein cell was used to study the *in-vitro* release profile for a 10 hrs study. The cell consisted of sampling port and temperature maintaining jacket[18]. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. Receptor compartment, which was maintained at 37ºC. The patches of diameter of 2 cm. Every hour 1 ml of the receptor fluid was withdrawn and replaced with 1 ml of fresh drug free buffer (pH 7.4) solution to maintain constant volume. The withdrawn sample was analyzed spectrophotometrically at 250 nm.

Stability study

The transdermal patches of Losartan potassium were subjected to accelerated stability study at (40°C/75% RH) conditions for 90 days. The patches were packed in aluminum foil and kept at accelerated conditions. The patches were analyzed for drug content at 0, 30, 60

and 90 days respectively by a UV spectrophotometer method[19].

Statistical analysis

The results obtained were treated statistically using one-way analysis of variance (ANOVA). Post-hoc Tukey-HSD (Honestly Significant Difference) test was performed when there was a statistically significant difference, which was set at $p \leq 0.05$.

RESULTS AND DISCUSSION

Four transdermal patches formulations of Losartan potassium were prepared by using different polymers i.e. PVP K30, EC, chitosan, HPMC in different ratio. Dichloromethane (2% w/v) and acetic acid (1% w/v) were used as the solvent based on the solubility of the polymers. Propylene glycol (30%) was used as permeation enhancer. Thickness lies in the range of 0.30 to 0.33 mm. Average thickness was almost uniform within same formulation a small variation in thickness was observed with different formulations. The variations in thickness may be due to viscosity of polymer solutions of different formulations. Patch thickness should also be appropriate because increased film thickness will increase compaction and reduce the mobility of molecules, which can decrease drug release from the patch[20]. Mean drug content of in all the patches was found to be greater than 94.81 %. The weight of patches lies in the range of 42.3 to 46.57 mg (Table 2). The % drug content lies in the range of 93.81 to 96.77. Content uniformity studies proved that the amount of Losartan potassium in each patch of 2.009 cm^2 was found to be fairly uniform. Percent moisture content was found to be in the range of 2.56 to 3.44. Moisture content depends on type and concentration of plasticizer[21]. In present study castor oil and glycerin were used as plasticizer. Since patch with too much of water is prone to microbial growth while too less amount of water is prone to cracking and chances to absorb water from our skin[22]. Therefore, it is important to perform physicochemical studies in order to determine the suitable patch therapy over longer period of time without losing integrity of the polymeric composition of the transdermal patches. The folding endurance represents the elasticity of the patches. Formulation of batches TP1 and TP2 has shown higher folding enduarance (greater than 280) reason may be elastic nature of chitosan present in these two batches. This test is performed to check the suitability of sample to withstand folding and brittleness[23]. Tensile strength lies in the range of 4.39-6.37 MPa. According to American Society for Testing Materials (ASTM), materials with tensile strength > 4.0 MPa possess an elastic characteristic[24]. Patches should be elastic in order to withstand external forces such as wear and tear during handling, storage or use. Water vapor transmission rate was found to be maximum for formulation of batch TP1. The *in-vitro* diffusion of Losartan potassium transdermal patches formulation was studied using locally fabricated Franz diffusion cell. The cumulative percent drug release after 10 hrs in between 38.41 to 80.41%. Maximum in batch TP1 (80.41%) indicates the effects of propylene glycol as permeation enhancer. Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred.

Table 2: Physical Characterization of Losartan potassium transdermal patches.

Parameter	TP1	TP2	TP3	TP4
Physical Appearance	Uniform, opaque, slightly sticky, flexible	Uniform, opaque, slightly sticky, flexible	Uniform, translucent, slightly sticky, flexible	Uniform, translucent, slightly sticky, flexible
Thickness (mm)	0.30±0.37	0.31±0.27	0.32±0.08	0.33±0.09
Weight (mg)	45.3±0.28	43.7±0.34	42.3±0.26	46.57±0.13
% Drug content	96.77±0.31	95.42±0.18	96.42±0.42	94.81±0.12
Folding endurance	> 288	> 285	> 122	> 150
Flatness	100%	100%	100%	100%
Tensile strength (MPa)	4.39±0.58	5.21±0.32	6.37±0.43	5.47±0.09
% Moisture Content	3.44±0.25	2.56±0.26	2.78±0.25	2.88±0.25
WVTR ($g/cm^2/hrs$)	$1.621x10^{-4}$±0.12	$1.489 x10^{-4}$±0.27	$1.543x10^{-4}$±0.08	$1.443x10^{-4}$±0.12

(Mean±S.D., n=3)

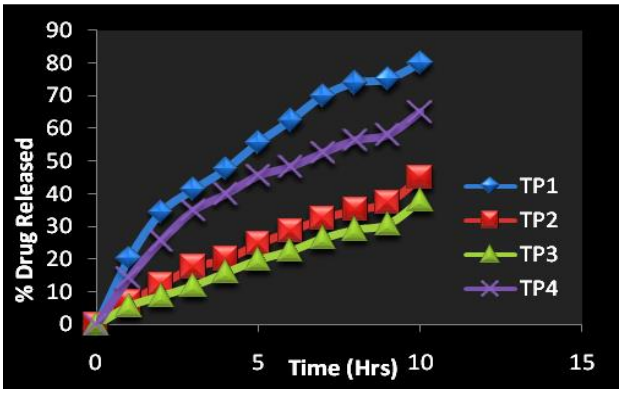

Figure 1: *In-vitro* diffusion profile of Losartan potassium transdermal patches.

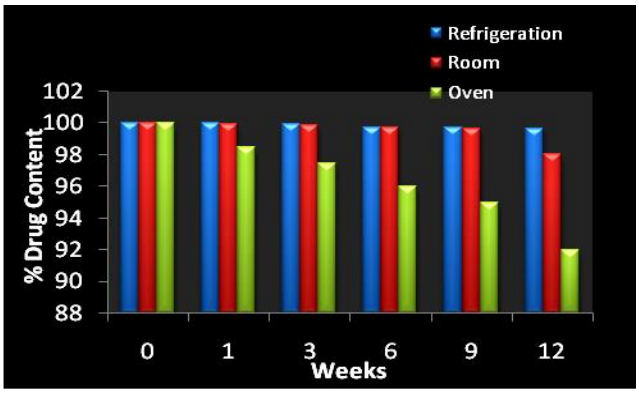

Figure 2: Stability study of optimized Losartan potassium transdermal patches of batch TP1.

In general the release of the drug depends upon hydrophobic and insoluble nature of the polymers used[25]. The drug release increases on increasing the concentration of hydrophilic polymer in the polymer matrix. Drug release increased with increase in the content of PVP K30 due to the hydrophilicity of PVP K30 which facilitates water absorption thus promoting drug dissolution and drug release from the patch. Furthermore, as PVP leaches out, pores are created in the matrix for drug to diffuse out of the patch; thus, drug release is increased.

Stability studies performed on optimized formulations TP1 shows 97.62% drug content at refrigeration condition, 92.52% drug content at oven condition and 98.43% drug content at room temperature during the studies performed for 12 weeks (figure 2). Hence it is concluded from the obtained data that the optimum storage condition for transdermal patches was found to be room temperature.

CONCLUSIONS

Transdermal drug delivery systems continue to deliver patients' increased compliance by providing predictable and reliable therapeutic dosages. The prepared transdermal drug delivery system of Losartan potassium using different polymers such as HPMC, EC, Chitosan and PVP had shown good promising result for all the evaluated parameters. Based on the *in-vitro* drug release and drug content, formulation TP1 was concluded as an optimized formulation. The study concluded that proper combination of hydrophilic and hydrophobic polymers is required in formulation development of transdermal patches of Losartan potassium. However, further *in vivo* and *in-vitro* investigations are required.

AUTHOR'S CONTRIBUTION

Fatima AA: writing original draft, conceptualization, methodology, investigation. **Chukwuka UK:** Writing, review, and editing, supervision, resources. Final manuscript was read and approved by all authors.

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DATA AVAILABILITY

The data supporting the findings of this study are not currently available in a public repository but can be made available upon request to the corresponding author.

CONFLICT OF INTEREST

None to declare.

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