



DESIGN AND EVALUATION OF VALSARTAN TRANSDERMAL PATCHES

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ABSTRACT

Transdermal drug delivery systems are also known as patches, containing dispersed or dissolved drug with plasticizers, polymers etc., are intended to deliver a therapeutically effective amount of drug across the skin. Main objective of the present work is to develop transdermal patches of Valsartan with hydrophilic and hydrophobic polymers containing the drug reservoir by solvent evaporation method. Valsartan is a poorly soluble drug with poor bio availability. In this experiment, the membranes of ethylcellulose and Eudragit RS 100 and Eudragit RL 100 along with HPMC combination were used to achieve controlled release of the drug. The prepared patches showed satisfactory physicochemical characteristics of weight variation, thickness, folding endurance, moisture absorption and drug content. Results for *in-vitro* permeation studies were done by using Franz diffusion cell with 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: Valsartan, Transdermal patches, In-vitro diffusion, Kinetic studies, Drug reservoir, Rate control membranes.

INTRODUCTION

Valsartan is rapidly metabolized by first pass metabolism so transdermal route is preferred to reduce first pass metabolism. Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. It acts selectively at the AT1 receptor subtype. Valsartan is a potent and highly selective type I antagonist that lowers blood pressure in hypertensive patients¹. The drug is rapidly absorbed following oral administration². AT2 receptor found in many tissues is not known to be associated with cardiovascular homeostasis. Valsartan has greater affinity for AT1 receptor than AT2 receptor. Increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate unblocked AT2 receptor. Primary metabolite of valsartan is essentially inactive with an affinity for AT1 receptor about 1 to 200th that of valsartan itself³.

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the rennin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. Its action is therefore independent of the pathways for angiotensin II synthesis. Valsartan peak plasma concentration is reached 2-4 hours after dosing. Absolute bioavailability for valsartan formulation is 25%. Food decreases the bioavailability of valsartan by about 40% and peak plasma concentration (C max) by about 50%. 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. Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration⁴. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. The aim of the study is to achieve the objective of systemic medication through topical application and release of drug via skin by developing transdermal drug delivery system. To obtain a controlled, predictable and reproducible absorption and release in to blood stream, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application are some of the potential need to formulate the transdermal drug delivery system.

MATERIALS AND METHODS

Materials

Valsartan is a gift sample procured from Natco Pharma, Hyderabad. Eudragit RS 100, HPMC and, Eudragit RL 100 were procured from Degussa India pvt.ltd, Mumbai. Methyl cellulose and Carboxy methyl cellulose Methanol, were obtained by SD Fine Chem. Ltd. Poly ethylene glycol Di butyl phthalate, poly ethylene Glycol, Span 80 and Tween 80, Karnataka fine chem., Bangalore. The others solvents and chemicals used were of analytical grade.

Methods

Preparation of transdermal patch

Transdermal patches containing valsartan were casted on glass slide by solvent casting 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 valsartan dissolved in 5 ml methanol 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)^{5,6}. After complete drying, patches were cut into small pieces each of 3 square centimeters and stored between sheets of wax paper in a desiccator (Table 1).

Evaluation of patches

The following evaluation tests^{7,8} are performed.

Thickness

The thickness of patches was measured at 3 different places by using micrometer (mitutoyo & co, Japan), and mean value were calculated⁹.

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 without breaking was taken as the value of folding endurance¹⁰.

Moisture pickup studies

The moisture uptake was determined by drying the film at 60°C with a current of air after which the film were subjected to desiccator over anhydrous calcium chloride at 40°C 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 and shown in Table 3.

Table 1: Composition of Transdermal Patches

Ingredients	FORMULATIONS						
	F1	F2	F3	F4	F5	F6	F7
Valsartan	5% of polymer composition	5%	5%	5%	5%	5%	5%
HPMC %w/v	10	-	-	-	-	-	-
MC %w/v	-	10	-	-	-	-	-
S-CMC %w/v	-	-	10	-	-	-	-
HPMC:MC(1:1)	-	-	-	1:1 ratio	-	-	-
Di butyl phthalate %w/v	-	-	-	30%	30%	30%	30%
PEG 200 %w/v	30%	30%	30%	-	-	-	-
Tween 80	1%	1%	1%	1%	1%	1%	1%
HPMC+Eudragit RS 100%w/v	-	-	-	-	10	-	-
HPMC+Eudragit RL 100 %w/v	-	-	-	-	-	10	-
HPMC+Ethyl cellulose %w/v	-	-	-	-	-	-	10

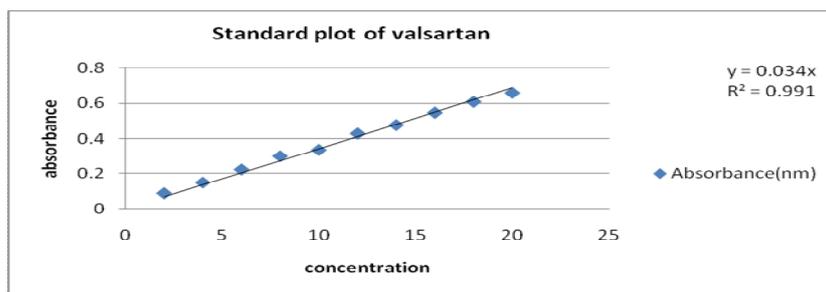


Figure 1: Valsartan Standard Calibration curve in Methanol

Table 2: Physiochemical Characterization of Transdermal Patches

Parameters	F1	F2	F3	F4	F5	F6	F7
Thickness (µm)	110.1±0.3	93.6±0.5	98.5±0.5	96.2±0.05	89.3±0.1	87.2±0.14	83.2±0.2
Weight Variation (mg)	62.1±0.1	56.3±0.2	52.3±0.1	55.2±0.1	51.8±0.2	42.6±0.2	48.2±0.8
Folding endurance	345±4.2	333±2.5	365±1.2	386±7.4	389±1.5	359±4.5	398±2.5
MVT in 24 hours	0.150±0.004	0.130±0.004	0.140±0.005	0.139±0.002	0.128±0.04	0.148±0.005	0.125±0.004
Drug content(%)	98.52	95.6	99.5	96.82	96.58	97.89	99.48

Table 3: Percentage Moisture Pick Up Studies

Parameters	F1	F2	F3	F4	F5	F6	F7
52% RH	9.5	6.5	10.2	10.8	7.5	9.8	10.8
75% RH	12.5	10.2	14.8	14.1	10.5	12.4	14.5
92% RH	15.6	14.6	17.2	16.9	14.5	15.2	18.2

Moisture vapor transmission studies (MVT)

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 assembly was accurately weighed and placed in a humidity chamber (80 ±5 %RH) at 27°C for 24 hours¹¹.

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 45°C. 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 – Visible spectrophotometer (Analytical technologies Ltd)^{12, 13}.

In-vitro permeation studies

Patches of 3 sqcm were subjected to an *In-vitro* permeation studies^{14,15} 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 ±2°C throughout the experiment. The compartment was in contact with the ambient environment. The amount the drug permeated through membrane was determined by withdrawing 1ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples filtered by membrane and the samples were analyzed spectrophotometrically.

Table 4: Cumulative release % of Valsartan Transdermal Patches

Formulations	% Cumulative Release
F1	85.98
F2	92.56
F3	94.55
F4	87.55
F5	52.24
F6	71.25
F7	63.5

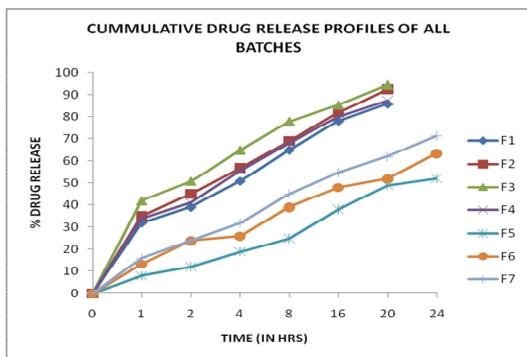


Figure 2: Cumulative drug release profile of all formulations

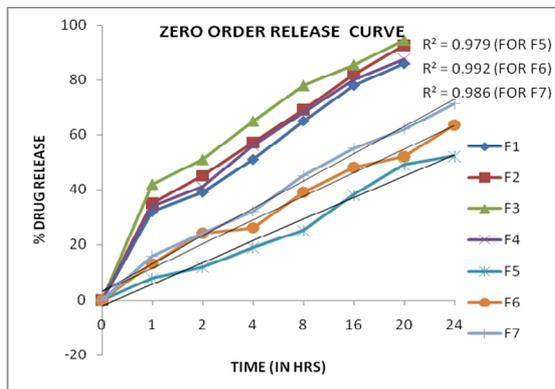


Figure 3: Zero order drug release profile of all formulations

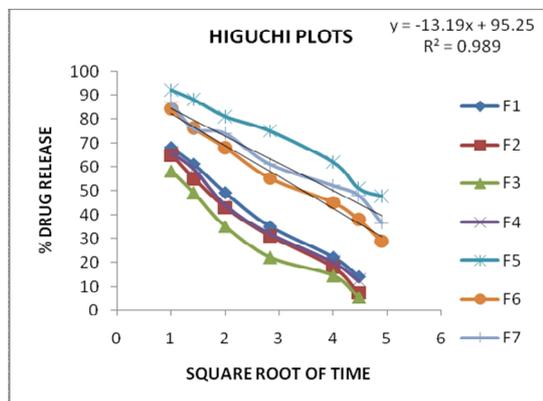


Figure 4: Higuchi plot of all formulations

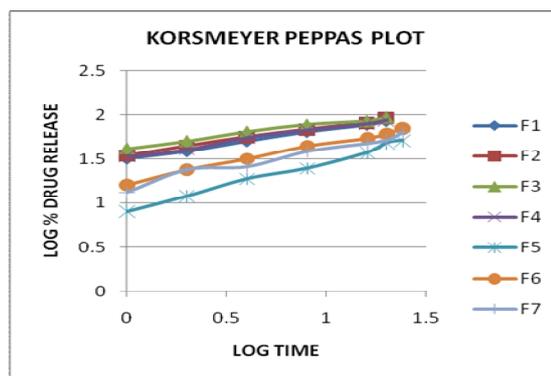


Figure 5: Korsmeyer peppas plot of all formulations

RESULTS AND DISSCUSSION

In the present experiment, transdermal patches of Valsartan were formulated using hydrophilic polymers of HPMC, SCMC, MC and the effect of ethyl cellulose, Eudragit RS 100 and Eudragit RL 100 as the rate controlling membrane was studied. The formulated patches were characterized for physicochemical 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 physicochemical properties of Valsartan transdermal patches were displayed in table 2.

The thicknesses of the prepared transdermal patches are between 110.1±0.3 to 83.2±0.2 (µm). Casting of rate controlling membrane increases the thickness of patches. The weight of prepared patches was not uniform in all seven formulations and varies in the range of 48.2±0.8 to 62.1±0.1 mg per patch. The folding endurance measures the ability of patch to withstand the rupture, folding endurance was in the range between 333±2.5 to 398±2.5, and all of the seven formulation’s folding endurance was satisfactory. The patch formulated with HPMC, SCMC, and MC shows the MVT in decreasing order 0.160, 0.151, 0.130 mg.cm-2h-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 99.48 to 95.6 % per patch. The drug content analysis was uniform in all the patches. The moisture pick up studies were performed and recorded at 52, 75, 92 %RH. Formulations F3, F4, F7 containing S-CMC, HPMC & MC combination and HPMC+EC have shown maximum moisture pickup values. In this study, different formulations released variable amount of Valsartan through membrane into the *in vitro* fluid. To study the drug diffusion kinetics and mechanism the results were fitted to Zero order, Higuchi's and Korsmeyer-Peppas plots.

Drug release profiles from different formulations are shown in figure 2. It was found that 94.55% of drug was released with 24 hours from F3. It means the patch produced burst release. Other formulations F1, F2, and F4 are also showed similar type of faster release 85.98, 92.56, and 87.55 respectively within 24 hours. So the patch shows poor in controlling the release, because the hydrophilic polymers tends to swell in in-vitro medium and immediately the drug was diffused out. The patches containing single polymer having more burst release because it easily dissolves in medium. To control the release of drug two polymers were used in the formulations F5, F6, F7 which showed slower release rate in 24 hours. 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, RL100, and ethyl cellulose as the rate controlling membranes, which was casted over HPMC drug reservoir.

Eudragit RS100, RL100, and ethyl cellulose are 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 (F7) ethyl cellulose was the rate controlling membrane and it has less hydrophobicity which showed a release rate of 63.5% 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. 52.24% for 24 hours.

The data was subjected to Zero order equation and the regression value was found to be in range of ($R^2=0.979-0.992$) which confirms Zero 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 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.

CONCLUSION

The kinetic parameters among the seven formulations showed that all the formulations provided Zero order release kinetics. When the average rate constants of all the formulations were compared, it was found that formulation F5 has slowest release of all the formulations (52.24%). Based on the observations, it is concluded that HPMC+Eudragit RS100 showed better release over other polymer ratio for the development of TDDS for Valsartan and the formulation F5 may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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