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R E S E A E C H A R T I C L E

Formulation and Optimization of Telmisatran Sustained Release Transdermal Films

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A B S T R A C T

The present investigation was aimed to develop sustained release transdermal therapeutic system containing Telmisartan with different ratios of Eudragit RS 100 and polyvinyl alcohol (PVA) by solvent-evaporation technique. Delivery of the drug via skin would provide a useful alternative to oral delivery, which has undesirable side effects, such as upper respiratory infections and disturbance of normal gut flora. The physicochemical compatibility of the drug and the polymers was by Fourier Transform Infra-Red (FTIR) and DSC. The results suggested no physicochemical incompatibility between the drug and the polymers. Blank films were prepared and evaluated characteristics like smoothness and flexible. Further drug loaded films were prepared and evaluated for thickness, tensile strength, weight uniformity, drug content, moisture content, moisture uptake, swelling index, water vapor transmission and in-vitro-drug permeation study. The results followed zero order kinetics and the mechanism of release was diffusion controlled release and further it was found to be linear with korsemeyer-peppas equation and confirmed that diffusion follows Non-Fickian transport. Based on the in-vitro dug permeation studies using rat skin, F6 formulation (1:5 ratios of PVA and Eudragit RS-100) produce 93% drug release in 7 hours.

Keywords: Telmisartan, Transdermal drug delivery, penetration enhancers, Eudragit RS-100, PVA, Solvent evaporation method

A R T I C L E I N F O

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1. Introduction

Transdermal drug delivery (TDDS) is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. TDDS established itself as an integral part of novel drug delivery systems that breaks many barriers in drug delivery like need of assistance, intermediate dosing and uncomfortable administration [1]. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided [2, 3].

Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1(AT1), with a binding affinity 3000 times greater for AT1 than AT2. It has the longest half-life of any ARB (24 hours) and the largest volume of distribution among ARBs (500 liters). In addition to blocking the RAs, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism [4]. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).

The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from bypassing the first hepatic metabolism [5]. Variables due to oral administration, such as pH, the presence of food or enzymes, and side effects of drug can be eliminated. The aim in the development of new transdermal drug delivery devices is to obtain a controlled, predictable, and reproducible release of the drug into the blood stream of patient.The objectives of the investigations were: To formulate transdermal patches using Eudragit RS 100 and polyvinyl alcohol (PVA), evaluate the patches and study the release profile and release mechanisms from patches.

2. Materials and Methods

Telmisartan IP was obtained as a gift sample from E.Merk(India)Ltd, Rusan Pharma Ltd. Polymer such as Eudragit Rs-100, Poly vinyl alcohol were also obtained as a gift sample from Degussa India Pvt Ltd. Mumbai and other excipients such as Plasticizer Dibutyl Phthalate and solvents methanol and dichloromethane were available in department.

Preparation of Transdermal Patches of Telmisartan:

Transdermal patch is prepared by solvent evaporation method. For this different concentration of polymers were used, which is given in table: 1.

Method of Preparation of Patches

Transdermal drug delivery patches can be prepared by:

Glass Substrate Method: Weighed required quantity of polymers and dissolved in 10 ml of solvent mixture consisting of 1:2 ratios of Dichloromethane and Methanol. The polymeric solutions were kept a side for swelling for 5 Hrs. Then required quantity of plasticizer and drug solution are added and vertexed for 10 minutes. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a previously cleaned petriplate and this was kept aside for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the Petriplate. After over night, the dried films were taken out and stored in desiccators [6].

Preparation of Polymeric Films:

Preparation of polymeric films was carried according to method. The polymers, PVA and Eudragit RS100, were taken in a weighing bottle [7]. About 15ml of solvent mixture of dichloromethane: methanol (1:2) was added and shaked to prevent the formation of lumps, and then kept aside for swelling of polymers. And after complete solublization of polymers in mixture of solvent, added required quantity of dibutyl phthalate to this mixture, and vertexed. Finally weighed quantity of telmisartan was dissolved in 5ml of solvent mixture, added to the polymer solution and mixed well. It was set-aside for some time to exclude any entrapped air and was then transferred into a previously cleaned Petri plate (70.00 sq.cm) and then this was kept aside for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the Petri plate. After 12hrs, the dried films were taken out and stored in a desiccator.

Evaluation of Transdermal Patches

Thickness Variation Test [8]:

The thickness of the films was measured at six different points of the patch by digital screw gauge (Mitutoyo, Japan).

Weight Variation Test:

Each formulated films was prepared in triplicate and then cut 20mm diameter surface area from each film. Their weight was measured using Saritorius digital balance.

Folding Endurance:

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance. The values are reported in Table 2.

Moisture Absorption Studies:

The prepared films were weighed accurately and placed in a desiccator containing saturated solution of Potassium Bromide (84% RH). After three days, the films were taken out and weighed [9].

$$\% \text{ Moisture absorbed} = \frac{\text{Final wt} - \text{Initial wt}}{\text{Initial wt}} \times 100$$

Moisture Loss Studies:

The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40 oC for 24 hr. Then the final weight was noted when there was no further change in the weight of individual patch [10] .The percentage of moisture loss was calculated as

$$\% \text{ Moisture Loss} = \frac{\text{Initial wt} - \text{Final wt}}{\text{Final wt}} \times 100$$

Water Vapor Transmission Rate (WVTR) Studies:

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100 oC for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after storage [11]. The amount of water vapor transmitted was found using following formula.

$$\text{WaterVapor Transmission Rate} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time X Area}}$$

It is expressed as the number of grams of moisture gained/hr/cm.sq.

Drug content Determination:

The prepared patches of specified surface area (3.14 sq.cm) was cut and dissolved in 100 ml of 5% methanol solution, and vigorously shaked for 12hrs, and then sonicated for 15minutes, centrifuged at 5000 rpm for 30 min. Filtered the drug contained polymeric solution through 42 number whatman filter paper, the 1ml of filtrate was taken in a test tube and diluted five times with same solvent [12]. By using double beam Uv-Visible spectrophotometer to determined drug content at λ 234.0 nm. Respected Placebo patch was taken as a blank solution.

Tensile strength:

The films were evaluated using a texture analyzer equipped with a 500 gm load cell. Film strip in 10 mm x 10 mm of dimension and free from air bubbles or physical imperfections, was held between two clamps positioned at a distance of 1 cm. During measurement, the film was pulled by top clamp at a rate of 10 mm/minutes. The force and elongation was measured when the films broke. Measurements were run four times for each film. The tensile strength at break was calculated as below [13].

Tensile strength (kg/mm2) = Breaking force (kg)/ cross section area of sample (mm2)

Swelling Index:

Weighed pieces 1x1 cm2 of film were immersed in distilled water; at 5, 10, 30, 60min. Soaked films were removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately [14]. The swelling index was calculated from the weight increase, as follows.

Swelling Index = (W2-W1)/ W1

Where, W1 and W2 are the weight of the film before and after immersion in the medium, respectively.

In-vitro Drug Diffususion Studies through dialysis membrane:

The drug diffusion studies through dialysis membrane experiments were conducted by using vertical type diffusion cell (Franz type) having receptor compartment dimensions and capacity as follows: 25mm inner diameter and 20ml volume (15ml minimum) with 4.91cm.square area. The receptor compartment was filled with 20ml of phosphate buffer pH 7.4; the activated dialysis membrane was mounted on the flange of the diffusion cell receptor compartment. The prepared Transdermal patch with surface area 3.14 cm2 was placed on center of membrane, the donor compartment was then placed in position and the two valves of the cell clamped together. The whole assembly was kept on a magnetic stirrer and solution in the receptor compartment was constantly and continuously stirred using a magnetic bead and at 32 ± 1oC maintained. 1ml sample was withdrawn at different time intervals and analyzed for drug content at 234.0 nm. Receptor phase was replaced with an equal volume of phosphate buffer at each time interval.

Mechanism of drug release

Various models were tested for explaining the kinetics of drug release.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

(a) Zero Order Release Model: To study the zero–order release kinetics the release rate data are fitted to the following equation

Q= K0 t

Where, Q= amount of drug released at time t

K0=zero order release rate constant

The plot of % drug release versus time is linear.

(b) First Order Release Model: The release rate data are fitted to the following equation

ln(100-Q) = ln100- k1 t

Where, Q= percent drug release at time t

K1= first order release rate constant

A plot of log % drug release versus time is linear.

(c)Higuchi's Release Model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation

Q= KH t1/2

Where, Q= percent drug release at time t

KH= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

(d) Korsmeyer-Peppas Release Model: The release rate data were fitted to the following equation

F= (Mt/M) = Km tn

Where, Mt= drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

Km=constant dependent on geometry of dosage Form

n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swellable & Cylindrical Matrix). In this model, a plot of log (Mt/M) versus log (time) is linear.

Drug-Excipients Interaction Studies:

The FTIR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation (F6) were analyzed between wave numbers 4000.0 and 400.0 cm-1.

Differential Scanning Calorimetry.

Thermo grams of drug and optimized Transdermal patches were recorded. All the samples were hermitically sealed in flat bottomed aluminum pans and heated over a temperature range of 40-240 OC at a rate of 10 OC/min using alumina as a reference standard.

FT-IR and DSC were carried out on the pure drug substance, optimized Transdermal patch and dummy patch, in order to find out the possible interactions between Telmisartan and the polymer.

3. Results and Discussions

Thickness: With the help of Digital calipers, the thickness of patches was measured and the average thickness was noted. The thickness results are given in Table2. The result indicates that there was no much difference in the thickness within the formulations. The order of the thickness of patches is $F_3<F_4<F_6<F_5<F_2<F_1$.

Weight uniformity:

Drug loaded patches (1x1 cm^2) were tested for uniformity of weight and the results of weight uniformity are given in**Table2**. The order of the weight of patches is$F_3 <F_6<F_4 <F_2 <F_5<F_1$. This is in agreement with the uniformity of the thickness.

Folding endurance:

The recorded folding endurance of the patches was shown inTable2. It depicts all formulations have good film properties. The folding endurance of the patches are in the following order $F5<F_3<F_6<F_4<F_2<F_1$. The results indicate, as the PVA concentration increases the folding endurance of the patches increases.

%moisture absorption:

The percentage moisture absorption of the prepared patches are in following order $F_2<F_1<F_3<F_5<F_6<F_4$. The results show the moisture absorption of all the patches are within the acceptable limit.

% moisture loss:

The percentage moisture absorption of the prepared patches are in following order $F_4<F_2<F_3<F_5<F_6<F_1$. The formulation F1 shows significant loss of moisture when compare to other patches.

Drugcontentuniformity:

Drug content of the patch was carried out to as certain that the drug is uniformly distributed into the formulation. The results obtained are represented in the Table 2. From the results obtained, it was clear that there was proper distribution of Telmisartan in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation.

Water vapour transmission rate:

Thewatervapourtransmissionratesofdifferentformulationsw ereevaluatedandtheresultsareshownintable3.TheTelmisarta n patches prepared with combination of eudragitRS100 and PVA shows comparable WVTR. The WVTR was in the following order $F_3<F_1<F_6<F_5<F_4<F_2$.

Tensile strength:

F6 showed highest tensile strength and the F2 showed lowest tensile strength.

Swelling index:

The % swelling index was determined and found to high for F6 and F5. The result from the table clearly indicates the moisture uptake value was found to have direct relationship with swelling index %. As the moisture uptake increases the % swelling index also increases and as the time increases the % swelling index increases.

In-Vitro Diffusion Studies

In-vitro release studies of Telmisartan patches were carried out in diffusion cell using commercial available semi permeable membrane and phosphate buffer (pH7.4) as a diffusion medium. The release profiled at a of Telmisartan were given respectively for patches F_1 to F_6.

Drug permeation profiles for formulations F1 to F_6 were indicated that 92.98% of drug was released within 7hrs, from F_1 to F6 slowly and followed zero-order kinetics with peppas model. This signifies that the patch has to be applied several times a day to maintain the rapeutic levels constant so it lacks patient compliance. To sustain the drug release, hydrobhobic polymer that decreases the release is needed to be added, that is Eudragit RS100 is added. The drug release rate is due to the hydrophilic polymer PVA. Therefore, Eudragit which is hydrophobic in nature was combined with PVA to achieve sustain release of Telmisartan. The sustained drug release could be achieved by increasing the polymerconcentration, which is Eudragit RS 100 in the formulation by keeping the total copolymer concentration same. So it necessitates further study to release the complete drug from the prepared formulations, hydrophilic polymer PVA increased the drug release in the patch. The results as shown in fig 1. Review of literature gave an idea of using permeation enhancer to improve the drug release from the formulation. Different class of enhancers acts by various mechanisms which are described briefly in introduction.

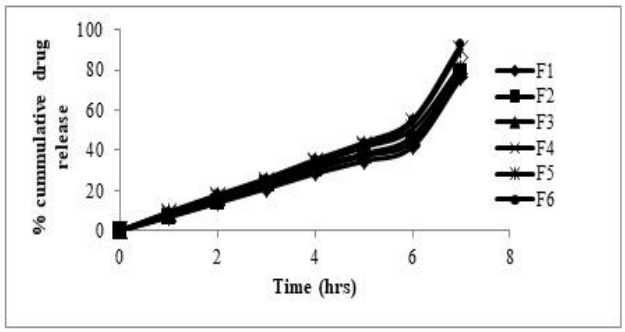

Fig 1: *In vitro* diffusion profiles of Telmisartan transdermal films

The release kinetics was evaluated by making use of zero order, first order, Higuchi's diffusion and Korsemeyer-Peppas equation. Calculated regression coefficient values for different formulations. These values are compared with each other for model and drug equation. Based on the higher regression values (R^2), the best fit model was zero order for F_6 Formulations. The Peppas model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. 'n' value could be used to characterize different release mechanism. The'n' values obtained graphically

from peppas plot were shown. As the values obtained were more than 0.5, this indicates that the release approximates non fickian diffusion. The results as shown in table 4.

Drug excepient interaction studies:

The drug- excepients interactions were studied by FTIR Spectroscopic technique as show in fig 2 and 3. The FTIR spectrum of batch F6 (PVA:Eudragit RS100 ratio 1:5) of transdermal patch there are following characteristics peaks at 3306.3 cm^{-1} for N-H stretching, 2920.6 cm^{-1} for C-H stretching, 1600.7 cm-1 for C=C aromatic bending, stretching, 1332.3 cm^{-1} for methylene groups.

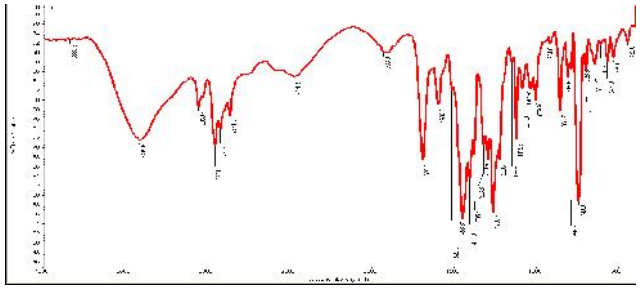

Fig 2:FTIR spectra of Telmisartan

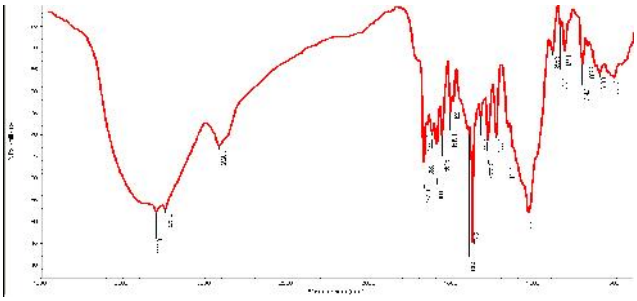

Fig 3: FTIR spectra of optimized formulation F6

From the above graph there is no shift in peaks and intensity of Drug, Physical mixture, and Formulation. Hence there is no physical or chemical change and interactions, drug and excipients are compatable.

Differential Scanning Calorimetry (DSC):-

Thermo grams of drug and optimized Transdermal patches were recorded. All the samples were hermitically sealed in flat bottomed aluminum pans and heated over a temperature range of 40-240 OC at a rate of 10 OC/min using alumina as a reference standard.

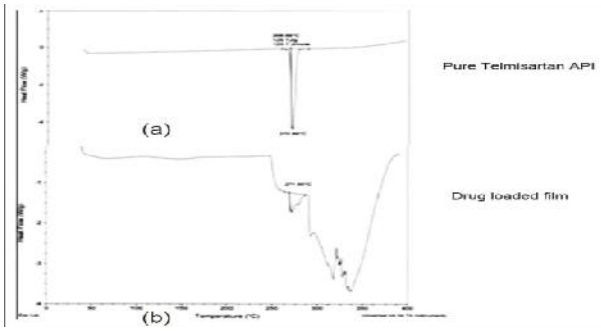

Fig 4: DSC spectra of pure drug and Optimized (F6) formulation

DSC thermogram of Telmisartan and final film F6 is shown is fig. 4. The thermogram of pure drug showed endothermic peak at 270° corresponding to its melting point. DSC thermogram for drug loaded film also shows peak at around 270° indicating compatibility of the drug.

4. Conclusion

The method of preparation of transdermal patches of Telmisartan presented in this research work is simple. All formulation also showed good physicochemical properties like thickness, weight variation, drug content, flatness, folding endurance, moisture content and moisture uptake. The in-vitro release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. The finding of this result revealed that the problems of Telmisartan on oral administration like dissolution rate limited absorption and gastric side effects can be overcome by applying Telmisartan topically in the form of trans dermal patch.

Table 1: Composition of different formulations containing Telmisartan

Formulations (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Telmisartan	200	200	200	200	200	200
EudragitRS100	500	500	500	1000	1000	1000
Poly Vinyl Alcohol (Copolymer)	100	150	200	100	150	200
Dichloromethane (ml)	5	5	5	5	5	5
Methanol (ml)	10	10	10	10	10	10
dibutyl phthalate (%w/v)	5	5	5	5	5	5

Table 2: Physico-chemical properties of prepared formulations

Formulation code	Thickness	Weight uniformity	Folding endurance	% moisture absorption	% moisture loss
F_1	0.21	0.426	157.66	7.75	41.66
F_2	0.19	0.386	122.33	6.67	12.35
F_3	0.17	0.332	82	7.84	12.64

F_4	0.18	0.363	98	12.12	8.60
F_5	0.19	0.395	72.66	9.09	13.54
F_6	0.18	0.347	89.33	10.46	14.58

Table 3: Physico-chemical properties of prepared formulations

Formulation code	Watervapourtransmissionrate	Drug content uniformity	Tensile strength	Swelling index
F_1	6.5×10^{-3}	97.6	3.4	78.5
F_2	7.2×10^{-3}	98.5	3.2	65.8
F_3	6.0×10^{-3}	99.3	3.5	72.5
F_4	7.1×10^{-3}	98.6	4.3	78.5
F_5	7.0×10^{-3}	99.2	4.1	78.7
F_6	6.9×10^{-3}	99.7	4.4	80.0

Table 4: Release kinetics of Telmisartan (F6) Transdermal films

Formulation code	Correlation coefficient (R^2)				'n'
	Zero order	First order	Higuchi	Peppas	
F5	0.9129	0.8815	0.9666	0.7614	**0.652**
F6	0.9554	0.9389	0.9832	0.8726	**0.745**

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