RESEARCH ARTICLE

Formulation and Evaluation of Prolonged Release Transdermal Drug Delivery System of Telmisartan for the Treatment of Hypertension

Asheesh Singh*[1], Parul Singh[2]

[1]*Glenmark Pharmaceutical Limited, Pithampur, Indore (MP), India- 454775*
[2]*Department of Pharmacy, Guru Ghasidas University, Bilaspur (India)-495009.*

ABSTRACT

The objective of the present study was to formulate and evaluate controlled and prolonged release transdermal drug delivery system of Telmisartan for effective management of hypertension. The administration of Telmisartan via transdermal patch facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration. To fulfill above objective transdermal patches of Telmisartan were prepared by solvent evaporation method using combinations of Eudragit RL100, Ethyl cellulose and PVP in different proportions. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, water vapour transmission and tensile strength were evaluated. In-vitro Diffusion Study, skin irritation test and stability studies were also performed. In PVA and Eudragit RL 100 patches the water vapor transmission rate was found to be higher at 75% RH, RT conditions. Therefore at both % RH, RT conditions the PVA and Eudragit RL 100 patches provide the best resistance to water vapor.

KEYWORDS

Telmisartan, Eudragit RL100, Ethyl Cellulose, PVP, Transdermal Patch, *In-Vitro* Permeation Study

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].

*Address for Correspondence:
Asheesh Singh,
Research Officer, Department of Analytical Research Formulation
Glenmark pharmaceutical Limited, Plot No.2
Pharma Zone Pithampur-454775.
E-Mail Id: asheesh_parihar@yahoo.com

Transdermal delivery can also increase the therapeutic value of many drugs by avoiding specific problems associated with the drugs like gastrointestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects and short half life necessitating frequent dosing etc[4]. Above all this drug input can be terminated at any point of time by removing transdermal patch. However, to deliver drugs through transdermal route, it must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult[5-6]. Hence relatively potent drugs are only suitable candidates for TDDS.

Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1(AT_1), with a binding affinity 3000 times greater for AT_1 than AT_2. 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. 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).

Telmisartan's activity at the peroxisome proliferator-activated receptor delta (PPAR-δ) receptor has prompted speculation around its potential as a sport doping agent as an alternative to GW 501516. Telmisartan activates PPAR-δ receptors in several tissues

The polymeric film containing Eudragit RL 100, Ethyl cellulose, PVP and drug (Table. 1) were selected for transdermal administration based on evaluation studies. The polymeric films were prepared by mercury substrate method employing PEG-400 as plasticizer. Two different penetration enhancers Urea and Dimethyl sulphoxide (DMSO) were employed in the study. The dried polymeric film was evaluated using different parameters including thickness uniformity, drug content of the film, in vitro drug release from films and in vitro skin permeation of drug[7-9].

MATERIAL AND METHODS

Materials

Telmisartan was obtained as a gift sample from Ipca laboratories limited Sejavta, Ratlam India. Eudragit RL100 and Eudragit RS (S. D. Fine Chem. Ltd., Mumbai), Ethyl cellulose, PVP K-30 (S. D. Fine Chem. Ltd., Mumbai), Urea and Dimethyl sulphoxide (DMSO) (S. D. Fine Chem. Ltd., Mumbai) were procured for above study. All other chemicals used were of analytical grade.

Preparation of Telmisartan-Containing Transdermal Patches

The transdermal patch was prepared by solvent evaporation technique on mercury substrate. Polymer solution was prepared in ethanol (10 ml) and to it telmisartan was added. The plasticizer and permeation enhancer were added during patch casting. The solution was poured on glass rings placed on mercury surface and allowed to dry in air for 24 h. Circular patches of 2 cm diameter (3.14 cm^2) were cut from semi dried patches and placed in vacuum desiccators.

Evaluation of Patch

Measurement of Thickness and Weight Variation

Thickness was measured using micrometer screw gauge (Mitutoyo, Japan). Each patch was measured for thickness at six different points to ascertain thickness uniformity in patch[10-11]. Weight variation was determined by weighing three patches individually, from each batch and the average weight was calculated (Table 2).

Tensile Strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength[12]. The tensile strength of the patches was determined by using a tensile strength instrument as described by Agarwal et al (Figure 1). Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

$$T.\ S. = break\ force/\ a.b\ (1+\Delta L/L)$$

Where a, b and L are width, thickness and length of the patch respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg)[13].

Table 1: Composition of transdermal patches Telmisartan

Formulation code	% ERL 100	% EC	% PVP	Telmisartan	% PEG 400	% Urea	% DMSO
F1	10	-	-	70 mg	-	-	1
F2	9	-	1	70 mg	1	1	2
F3	8	-	2	70 mg	2	2	4
F4	7	-	3	70 mg	3	3	6
F5	6	-	4	70 mg	4	4	8
F6	5	-	5	70 mg	5	5	10
F7	-	5	5	70 mg	5	5	10
F8	-	6	4	70 mg	4	4	8
F9	-	7	3	70 mg	3	3	6
F10	-	8	2	70 mg	2	2	4
F11	-	9	1	70 mg	1	1	2
F12	-	10	-	70 mg	-	1	1

Table 2: Characterization of transdermal patches

| Code	Wt. variation (mg)	Thickness (mm)	Tensile strength (kg/m^2)	Folding Endurance	Water vapour transmission (gm/cm^2.24h)	Drug Content (%)
F1	160.8±1.24	0.312±0.0024	0.413±0.0062	258 ±4.23	4.12 X 10^{-4}	95.54
F2	160.2 ±1.76	0.303 ±0.0024	0.473 ±0.0036	272 ± 4.34	4.81 X10^{-4}	98.87
F3	153.1 ±1.25	0.318 ±0.0021	0.463 ±0.0045	265 ± 3.11	4.93 X10^{-4}	97.92
F4	176.3 ±2.34	0.352 ±0.0023	0.449 ±0.0057	259 ± 5.23	5.19 X10^{-4}	97.11
F5	157.0 ±1.84	0.334 ±0.0031	0.435 ±0.0069	248 ± 3.88	5.56 X10^{-4}	98.92
F6	168.9 ±1.92	0.331 ±0.0042	0.426 ±0.0071	246 ± 4.61	5.93 X10^{-4}	98.40
F7	165.3 ±2.41	0.236 ±0.0027	0.421 ±0.0028	315 ± 4.12	5.99 X10^{-4}	96.87
F8	168.7 ±2.13	0.242 ±0.0036	0.409 ±0.0035	309 ±3.86	6.25 X10^{-4}	97.32
F9	158.4 ±1.35	0.239 ±0.0032	0.394 ±0.0046	298 ±5.02	6.36 X10^{-4}	98.67
F10	173.9 ±2.54	0.241 ± 0.0041	0.38 6±0.0055	294 ±5.11	6.53 X10^{-4}	98.77
F11	166.2 ±1.82	0.248 ±0.0058	0.377 ±0.0072	289 ±4.51	6.88X10^{-4}	98.55
F12	171.6 ±1.42	0.292 ±0.0012	0.312 ±0.0036	285 ±3.78	6.92 X10^{-4}	97.54
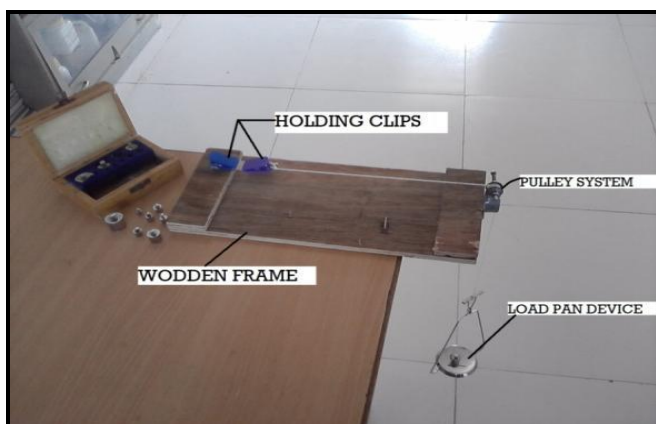
Figure 1: The tensiometer used to measure the tensile strength

Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. This was determined by repeatedly folding one patch at the same place till it break (Table 2). The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance[14-15]

Water Vapour Transmission

The water vapour transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics[16]. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. About 1 gm of fused calcium chloride as a desiccant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These pre-weighed vials were stored in a humidity chamber at RH of 80% with the temperature set to 30ºC for a period of 24 hours (Table 2). The weight gain was determined every hour up to a period of 24 hours. The water vapour transmission was calculated using the equation

$$Rate = WL/S$$

Where W is gm of water permeated / 24 hr. L is thickness of the patch S is exposed surface area of the patch.

Drug Content Uniformity

In order to ascertain the uniform distribution of the drug in the patches, the content uniformity test was carried out utilizing the pharmaceutical standard by means of a UV/Visible spectrophotometer. The transdermal patch of specified area (3.14 cm²) was dissolved in 100 ml pH 7.4 phosphate buffers. This was then shaken in a mechanical shaker for 2 hrs to get a homogeneous solution and filtered (Table 2). A blank was performed using a drug free patch treated similarly. The drug content in each formulation was determined by measuring the absorbance at 274 nm after suitable dilution using a UV/visible spectrophotometer[17-19].

In-vitro Diffusion Study

The in-vitro diffusion study is carried out using Franz Diffusion Cell (Ponmani & Co, Coimbatore). Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment.
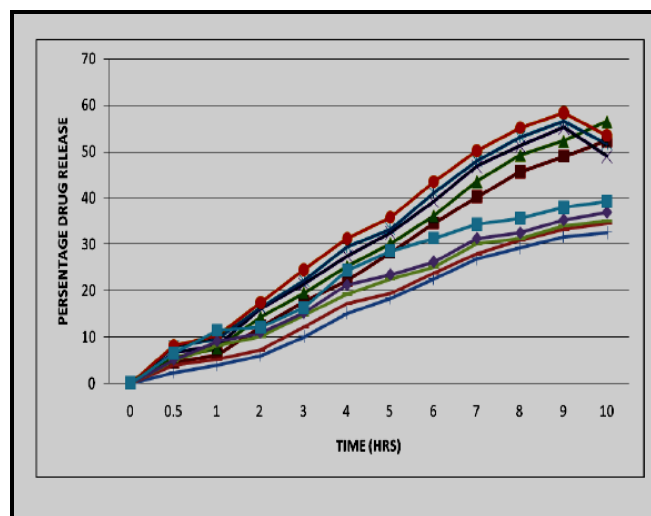

Figure 2: *In-Vitro* diffusion studies of various Telmisartan transdermal patches

131

Table 3: *In-Vitro* diffusion studies of various Telmisartan transdermal patches

S. No.	Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
					Drug Release						
1	0	0	0	0	0	0	0	0	0	0	0
2	0.5	4.58	5.55	6.78	7.98	8.14	2.45	3.98	4.90	5.12	6.45
3	1	6.26	7.56	8.22	9.55	10.45	4.03	5.25	8.14	9.11	11.41
4	2	12.22	14.26	16.25	16.34	17.41	6.06	7.22	10.22	10.97	12.08
5	3	17.56	19.45	21.40	22.14	24.51	10.09	12.25	14.65	15.26	16.25
6	4	22.26	25.16	27.48	29.42	31.26	15.18	17.26	19.24	21.26	24.26
7	5	28.26	30.20	32.55	33.27	35.85	18.37	19.56	22.59	23.45	28.47
8	6	34.56	36.08	39.21	41.12	43.56	22.60	23.78	25.04	26.24	31.24
9	7	40.22	43.57	46.79	48.06	50.21	26.90	28.04	30.22	31.26	34.22
10	8	45.65	49.25	51.24	53.11	55.22	29.28	30.87	31.26	32.44	35.58
11	9	48.95	52.26	55.21	56.54	58.42	31.72	33.26	33.99	35.26	37.89
12	10	52.39	56.49	48.98	51.68	53.49	32.56	34.58	35.09	36.89	39.21

A weighed amount of transdermal patch is placed on one side of membrane. The receptor medium is PBS pH 7.4. The receptor compartment is surrounded by water jacket to maintain the temperature at $37 \pm 0.5°C$. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. During each sampling interval, samples were withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The sample withdrawn was analyzed spectrophotometrically at 274 nm (Table 3, Figure 2).

Skin Irritation Test

The skin irritation test was performed on a healthy rabbit weighing between 2 to 3 kg. Drug loaded polymeric film of 3.14 cm^2 was placed on the left dorsal surface of the rabbit. The patch was removed after 24 h with the help of telmisartan swab. The skin was examined for erythema and oedema[20].

Stability Studies

All the films were exposed to three selected temperatures of 4°C, 27°C and 40°C. Transdermal films were kept in the oven for period of 45 days. The films were analyzed for the drug content on 0, 15, 30 and 45 day of storage. The averages of triplicate readings were taken (Table 4).

Table 4: Stability studies data for F5

Days	% Drug Remained		
	4°C	27°C	40°C
0	98.92	98.92	98.92
15	98.20	97.88	96.58
30	97.82	97.16	95.12
45	97.66	96.42	94.56

RESULTS AND DISCUSSION

The main goal of the present investigation efforts was to develop and evaluate new patches comprising of telmisartan containing Eudragit RL 100, Ethyl Cellulose and PVP in various combinations. The physicomechanical evaluation (Table 2) indicates that the weight variation of these formulated patches varied between 153.1±1.25 (F 3) and 173.9±2.54 (F10). The thickness of these patches varied between 0.239±0.0032 and 0.352±0.0023mm, the thinnest being formulation F9 and the thickest being formulation F4. Folding endurance was measured manually. The highest folding endurance was observed in the case of F7 and the lowest in the case of F1. The range of folding endurance study ensured flexibility of these formulated patches. The drug content (%) in all formulations varied between the range 96.87% and 98.87. This indicates that the drug dispersed uniformly throughout the polymeric film.

The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics that was performed in a humidity chamber at RH of 80% with the temperature set to 30ºC for a period of 24 hours. The maximum water vapour transmission was found with F1 while least was observed with formulation F12.

The in vitro drug release pattern of telmisartan from formulated transdermal patches is shown in Figure 2. All of these patches slowly released the drug, incorporated and sustained over a period of 10 h. The drug release from patches varied with respect to the polymer composition and nature. An increase in drug release from the patches was found with increasing concentration of polymers that are more hydrophilic in nature. Among all formulations, the maximum in vitro drug release (56.49mg) over a period of 10 h was observed in the case of formulation no. F2, while the minimum in vitro drug release (32.46mg) over a period of 10 h was found in the case of formulation F6. The in vitro drug release was more sustained for the telmisartan patches which were composed with high proportion of Eudragit RL 100. The *in vitro* permeation data shows that the release of telmisartan with polymer of eudragit and PVP is more sustain compare to EC and PVP. The increase in proportion of PVP shows more diffusion of drug. Skin irritation test on rabbit showed no sign of skin reaction and erythema hence the fabricated transdermal patch was suitable for further studies.

SUMMERY AND CONCLUSION

Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Matrix type transdermal patches containing telmisartan were prepared by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, tensile strength, folding endurance, drug content, water vapour transmission and skin irritation studies.

The permeability of Telmisartan was increased with increase in PVP content. The burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug which results in the formation of pores and thus leads to the decrease of mean diffusion path length of the drug molecules to permeate into dissolution medium and higher permeation rates. Based on the above observations, it can be reasonably concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Telmisartan.

ACKNOWLEDGEMENT

REFERENCES

1. Aqil, M., Ali, A., Sultana, Y., & Najmi, A. K. (2004). Fabrication and evaluation of polymeric films for transdermal delivery of pinacidil. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *59*(8), 631-635.

2. Arabi, H., & Seyed'ali Hashemi, N. A. (2001). Preparation of a transdermal delivery system and effect of membrane type for scopolamine drug. *Iranian Polymer Journal, 11*(4), 245-249.

3. Budavari, S., O'Neil, M. J., Smith, A., & Heckelman, P. E. (1989). *The merck index* (Vol. 11, pp. 2330-31). Rahway, NJ: Merck.

4. Chandrashekar, N. S., & Rani, R. S. (2005). Design, Fabrication and Calibration of Modified Franz Diffusion Cell for Transdermal Diffusion Studies. *International Journal of Pharmaceutical Excipients*, 104-106.

5. Crawford, R. R., & Esmerian, O. K. (1971). Effect of plasticizers on some physical properties of cellulose acetate phthalate films. *Journal of Pharmaceutical Sciences*, *60*(2), 312-314.

6. Kusum Devi, V., Saisivam, S., Maria, G. R., & Deepti, P. U. (2003). Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Development and Industrial Pharmacy*, *29*(5), 495-503.

7. Eliassaf, J. (1972). Detection of small quantity of Poly (vinyl alcohol) in poly (vinyl chloride) resins. *Polymer Letter*, *16*, 225-235.

8. Gupta, S. P., & Jain, S. K. (2004). Development of matrix-membrane transdermal drug delivery system for atenolol. *Drug Delivery*, *11*(5), 281-286.

9. Krishna, R., & Pandit, J. K. (1994). Transdermal delivery of propranolol. *Drug Development and Industrial Pharmacy*, *20*(15), 2459-2465.

10. Madison, K. C. (2003). Barrier function of the skin: "la raison d'etre" of the epidermis. *Journal of Investigative Dermatology*, *121*(2), 231-241.

11. Mamatha, T., Venkateswara Rao, J., Mukkanti, K., & Ramesh, G. (2009). Transdermal Drug Delivery System forAtomoxetine Hydrochloride–In vitro and Ex vivo Evaluation. *Current Trends in Biotechnology and Pharmacy*, *3*(2), 188-196.

12. Mishra, A.N. & Jain, N.K. (1997). Transdermal Drug Delivery: Controlled and Novel Drug Delivery. CBS Publisher and Distributor, New Delhi. 100-101.

13. Munden, B. J., Dekay, H. G., & Banker, G. S. (1964). Evaluation of polymeric materials I. Screening of selected polymers as film coating agents. *Journal of Pharmaceutical Sciences*, *53*(4), 395-401.

14. Murthy, S. N., & Hiremath, S. R. (2002). Preformulation studies of transdermal films of hydroxypropyl methylcellulose and sodium carboxymethyl cellulose. *International Journal of Pharmaceutical Excipients*, *1*, 34-8.

15. Raghuraman, S., Velrajan, G., Ravi, R., Jeyabalan, B., Johnson, D. B., & Sankar, V. (2002). Design and evaluation of propranolol hydrochloride buccal films. *Indian Journal of Pharmaceutical Sciences*, *64*(1), 32-36.

16. Rao, P. R., Ramakrishna, S., & Diwan, P. V. (2000). Drug release kinetics from polymeric films containing propranolol hydrochloride for transdermal use. *Pharmaceutical Development and Technology*, *5*(4), 465-472.

17. Saini, T.R. Seth, A.K. (1985). Evaluation of free films. *Indian Drugs, 23*(1), 45-47.

18. Samanta, M. K., Dube, R., & Suresh, B. (2003). Transdermal drug delivery system of haloperidol to overcome self-induced extra-pyramidal syndrome. *Drug Development and Industrial Pharmacy*, *29*(4), 405-415.

19. Stücker, M., Struk, A., Altmeyer, P., Herde, M., & Lübbers, D. W. (2002). The cutaneous uptake of atmospheric oxygen contributes significantly to the oxygen supply of human dermis and epidermis. *The Journal of Physiology*, *538*(3), 985-994.

20. The Indian Pharmacopoeia. 4th ed. (1996). *The Controller of Publications*. Ministry of health and family welfare, Govt. of India. New Delhi. 72-74.