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Research Article

Development and evaluation of transdermal drug delivery system of metoprolol

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ABSTRACT

Metoprolol (MP) is a potent ill-selective adrenergic blocking agent with proven antihypertensive activity. However, it undergoes extensive hepatic first-pass metabolism and has a short biological half-life, which necessitates frequent dosing to attain adequate therapeutic blood levels. To overcome this problem, the feasibility of systemic delivery of MT via the transdermal route was explored. In the present work, efforts have been made to prepare a transdermal drug delivery system of MT using various blends of polymers such as Eudragit RS 100, Hydroxy propyl methyl cellulose and Poly vinyl pyrrolidone using propylene glycol as a permeation enhancer. The prepared patches were evaluated for various physicochemical properties and *In-vitro* drug release studies. The releases were fitted to statistical treatment such as Zero order kinetics, Higuchi's and Peppa's plot. The optimized formulation from the *In-vitro* drug release study is used to carry out *In-vitro* skin permeation study using porcine ear skin, snake shed skin and rat skin. The *In-vivo* evaluation of formulation F 1 (1% Eudragit RS 100, 1.5%HPMC & 0.5% PVP) show better correlation with the *In-vitro* drug release which confirms the achievement of targets of the present study such as the controlled prolonged zero order release, reduced frequency of administration, greater therapeutic effect, overcome the side effects, simplify the treatment regimen and thus may improve patient compliance.

Keywords: HPMC; Metoprolol tartrate; Transdermal Patch; Zero order kinetic

INTRODUCTION

Transdermal drug delivery system (TDDS) is an appealing alternative to minimize and avoid the limitations allied with oral and parenteral administration of drugs. Later delivery systems, suffer from certain restrictions like peak and valley phenomenon, i.e. they exhibit fluctuations in plasma drug levels and do not render sustained effect while the TDDS meets the requisitions and provides a proper and prolonged delivery of drug, in a steady-state profile and reduces the prospects of peak-associated side effects, and ensures that the level of the drug is above the minimal therapeutic concentration. Overall, as a form of controlled drug delivery, transdermal patches are extremely commodious, user-friendly and provides the ease of termination, if need arises (e.g. systemic toxicity) with less pain sensation while administrating drug candidates (Amit Alexander *et al.,* 2012). Metoprolol tartrate is a drug used in the treatment of mild to moderate essential hypertension. It acts by blocking the β_1 adrenoreceptors and is almost completely absorbed (95%) after oral administration, although the systemic bioavailability varies widely owing to extensive presystemic metabolism (40–50%). Peak plasma concentrations are achieved after 2–3 h. The plasma half-life is about four hours (C. Dollery, 1991), which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long-term treatment.

The aim of the present study was to develop and evaluate transdermal drug delivery of MT using various polymers such as Hydroxy propyl methyl cellulose (HPMC K4M), Poly vinyl pyrollidine (PVP K30), Eudragit RS 100 in various proportion and combinations.

EXPERIMENTAL WORK

Materials and Methods

Metoprolol tartrate was gift from Madras Pharmaceuticals Ltd, Chennai (India). Hydroxy propyl methyl cellulose (HPMC K4M), Poly vinyl pyrollidine (PVP K30), Eudragit RS 100 was purchased from Loba Chemie Ltd. (India). All other chemicals used for this study were of analytical grade.

Preformulation Studies

Drug partition coefficient

The partition co-efficient of the drugs was determined using n-octanol: Phosphate buffer (pH 7.4) system. The n-octanol- Phosphate buffer partition coefficient serves as a parameter of lipophilicity. n- Octanol and Phos-

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phate buffer were presaturated with each other for at least 24 h before the experiment. An accurately weighed quantity of each drug was dissolved in 10 ml of the n-octanol phase and shaken at 37°C for 24 h against 10 ml buffer in a sealed container. The separated n-octanol phase was assayed by UV spectroscopy to determine its residual concentration and hence the amount partitioned into the buffer (Marin *et al.,* 1998, McDaid *et al.,* 1996). The partition coefficient was expressed as the concentration of drug in the n-octanol phase (% w/v) divided by the concentration in the aqueous phase.

Drug–excipient interaction study

The pure drug, MT and a mixture of it with the polymers, HPMC, PVP and CP were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying pressure in a hydraulic press (Jagmohan *et al.,* 2003). The pellets were scanned over a wave number range of 4000-400 cm^{-1} in Shimadzu Japan, FTIR instrument.

Fabrication of transdermal patches

Transdermal patches composed of different polymers containing MT were prepared by Solvent Casting technique as illustrated in Table 1. Firstly, drug was dissolved in ethanol. Base materials were added into the solution and swelled in ambient temperature. Permeation enhancers and plasticizer were added to the solution, and then agitated in a sonicator. This was casted on a glass surface containing ring, it was covered by funnel to control evaporation of solvent and allowed to dry at room temperature overnight. The films were separated, and the backing membrane used was aluminium foil and the formulations were stored in a desiccator. After being dried, the single-layer patch was obtained (Anitha P *et al.,* 2011).

Table 1: Composition of transdermal patches using Metoprolol Tartrate

Formulation Code	Eudragit RS 100	HPMC	PVP	Propylene glycol
F 1	1.0	1.5	0.5	30% w/v of polymer
F 2	1.0	0.5	1.5	
F 3	1.0	1.0	1.0	
F 4	1.0	2.0	-	
F 5	1.0	-	2.0	
F 6	1.5	1.5	-	
F 7	1.5	-	1.5	
F 8	-	1.5	1.5	
F 9	2.0	0.5	0.5	
F 10	2.0	1.0	-	
F 11	2.0	-	1.0	

Physicochemical evaluation of the prepared films

Thickness and weight variation

The thickness of the patch at three different points was determined using thickness gauge, and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation (Mundada *et al.,* 2009).

Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times until it broke (Ubaidulla *et al.,* 2007). The test was carried out to check the efficiency of the plasticizer, and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

Percentage Moisture Loss

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days (Kusum Devi *et al.,* 2003). The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

Percentage moisture uptake

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days (Biswajit Mukherjee *et al.,* 2005). The test was carried out in triplicate. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Water absorption capacity

Three film units of each formulation were kept in an atmosphere of relative humidity RH = 82% for one week and the difference in weight of the film was taken as the water absorption capacity for that film (Udupa *et al.,* 1992).

Water vapor transmission rate

For water vapor transmission studies glass vials of equal diameter were used as transmission cell (Kulkurni Raghavendra *et al.,* 2000). These transmission cells were washed thoroughly and dried in an oven. About 1 gm of anhydrous calcium chloride was taken in the cell and the polymer film was fixed over the brim with the help of the solvent. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7th day. Water vapor transmission rate usually expressed as the number of grams of moisture gain/h/sq.cm.

$$W\ V\ T = WL/S$$

Table 2: Physicochemical evaluation of transdermal films

F Code	Thickness (mm) ± SD	Weight Uniformity ± SD	Folding Endurance ± SD	Drug Content (%)	Percentage Moisture Loss ± SD	Percentage Moisture Uptake ± SD	Water Vapour Transmission Rate (mg/cm^2/hr)
F 1	0.32±0.01	321.0±0.31	350 ±1.0	99.67	7.77±0.01	8.21±0.01	7.10 x10^{-3}
F 2	0.36±0.03	343.4±0.21	370± 2.0	99.16	8.86±0.01	7.32±0.02	7.29 x10^{-3}
F 3	0.33±0.01	331.7±0.18	344 ±2.0	98.77	8.15±0.01	8.26±0.03	7.26 x10^{-3}
F 4	0.39±0.05	298.6±0.27	320 ±2.0	99.08	6.21±0.01	9.12±0.01	6.93 x10^{-3}
F 5	0.32±0.05	297.5±0.32	368 ±2.0	98.66	9.63±0.01	7.02±0.02	8.96 x10^{-3}
F 6	0.36±0.02	312.2±0.23	380±1.0	98.44	6.52±0.01	9.07±0.03	6.64 x10^{-3}
F 7	0.32±0.01	291.0±0.51	329 ±1.0	99.60	9.12±0.01	7.18±0.01	8.58 x10^{-3}
F 8	0.37±0.04	311.7±0.26	346± 2.0	98.31	5.83±0.01	10.21±0.02	6.28 x10^{-3}
F 9	0.37±0.04	325.1±0.46	373 ±2.0	98.72	10.22±0.01	6.32±0.01	9.56 x10^{-3}
F 10	0.38±0.08	312.2±0.48	328 ±2.0	98.30	9.95±0.01	6.55±0.01	9.78 x10^{-3}
F 11	0.35±0.07	317.0±0.19	327 ±2.0	98.64	10.65±0.01	6.08±0.02	9.99 x10^{-3}

Where, W is water vapor transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm^2.

Drug content

Films of specified area were cut and the pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h (Mazzo *et al.,* 1994). A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the drug content was analyzed at 223 nm by UV spectrophotometer.

In vitro drug release studies

The *In-vitro* release studies were carried out by using Keshary chein apparatus. The receptor compartment was maintained at 37±1°C by means of a water bath, circulator, and a jacket surrounding the cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. The solution in the receptor compartment was continuously stirred at 60 rpm by means of Teflon coated magnetic stirrer, in order to avoid diffusion layer effects. The Commercial Semi-permeable membrane were mounted between the donor and receptor compartment and secured in place by means of a clamp. The patch was placed on one side of the semi-permeable membrane (Ji-Hui Zhao *et al.,* 2007*,* Yanli Gao *et al.,* 2000). Aliquots of 1ml were removed from the receptor compartment by means of a syringe and replaced immediately with the same volume of buffer solution kept at 37± 1°C. Test samples were taken from the medium at predetermined time intervals over a period of 24 h and the samples were analyzed for MT content by UV spectrophotometer at 223 nm (Vlassios Andronis *et al.,* 1995). The diffusion kinetics of the MT was analyzed by graphical method for zero order, Higuchi and Peppa's exponential equation.

In vitro Transdermal permeation

The hairs of the male Wistar albino rat were cleared by using scissors. After cleaning the skin with Phosphate buffer pH 7.4, animal was sacrificed by excessive ether inhalation. An incision was made on the flank of the animal and the skin was separated. The prepared skin was washed with Phosphate buffer pH 7.4 and used (Yanli Gao *et al.,* 2009).

Snakeskin, (Hatanaka T *et al.,* 2006) offers considerable advantages over human material, as it is relatively abundant. In shed snake, the permeability co-efficient of lipophilic drugs was in the same range as those through the human skin. Shed skin of "NAJA NAJA" was collected and soaked in pH 7.4 Phosphate buffer for half an hour and then used. The shed skin was mounted in such a way that the ventral surface side of the skin was kept intimate contact with the formulation and keeping the dorsal region of skin being contact with the release surface of the donor compartment.

Albino porcine ear, (Jagadish Singh *et al.,* 1999) was obtained from a local slaughter house. The epidermis was prepared by a heat separation technique. The whole skin was soaked in water at 60ºC for 45 seconds, followed by careful removal of the epidermis. The epidermis was washed with pH 7.4 Phosphate buffer and used.

The transdermal permeation was performed in Chein Diffusion cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment (Ke *et al.,* 2005). Receptor compartment contains phosphate buffer pH 7.4 and samples were withdrawn at regular time intervals and replaced the same with receptor fluid. The samples

were analyzed at 223 nm against blank by UV spectrophotometer (Srinivas Mutalik *et al*., 2006).

In vivo studies

Primary Skin Irritation Test

The dorsal part of rabbit was carefully shaved, and patch was applied on the shaved skin for 7 days. After the patch was removed, conditions of the dorsal skin were observed and are evaluated most often by modification described by Draize (Draize JH, 1944) and his colleagues in 1944, which is based on scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring.

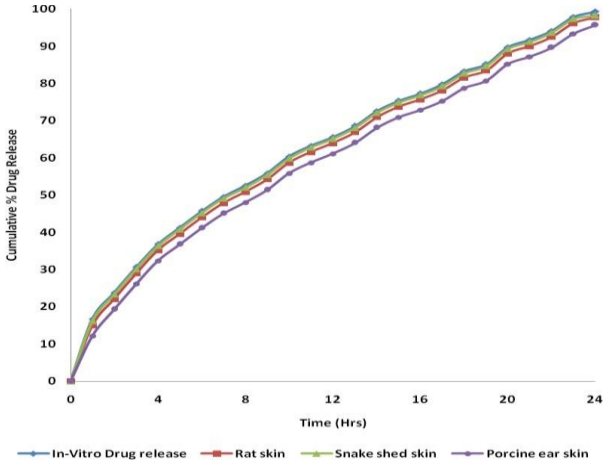

Figure 1: Comparative *In-vitro* drug diffusion through artificial semipermeable membrane and various biological skins

Selection of animals

Rabbit's (crytolagus cuniculus) of male sex 10-12 weeks old weighing 1-2 kg were selected. They were kept with husk bedding and were fed with standard rodent pellet diet and water. Light & dark cycles with 12 h light and 12 h dark were maintained. The temperature and relative humidity conditions were 28 ± 2°C and 60 ± 15% respectively. The protocols for all animal studies were approved by Institutional Ethical Committee (1220/a/08/CPCSEA).

Method

A set of healthy rabbits were selected. They were checked to ensure that they were free from disease. The dorsal surface of the selected rabbits was cleaned and hair was removed. The dose of MT was calculated according to the body weight (Anitha P *et al.,* 2011; Jayaprakash *et al.,* 2010). The patch F 9 (HPMC 1.5%, Eudragit RS 100 1.5%) was placed on the dorsal surface. At specific time interval the patch was removed from the rabbit carefully and analyzed for remaining drug content. Initial drug content was determined before placing the film. The remaining drug content was subtracted from the initial drug content of the film. The value obtained denotes the amount of drug in diffused from the patch into the body (Chakkapan *et al.,* 1994).

RESULTS AND DISCUSSION

In the present work efforts have been made to prepare transdermal drug delivery system of MT using various blends of polymers such as Eudragit RS 100, Hydroxy propyl methyl cellulose and Poly vinyl pyrrolidone. Permeation enhancer used was Propylene glycol.

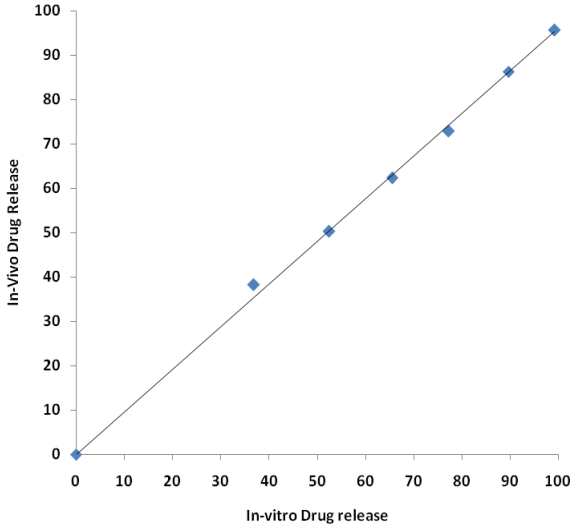

Figure 2: *In-vitro In-vivo* Correlation of F 1

The observed partition coefficients of MT using n-octanol/Phosphate buffer pH 7.4 found to give log K values 2.4**.** The physicochemical compatibility of the drugs and the polymer was established through FTIR studies which show no interactions. Physico-chemical evaluation data of table 2 indicates that thickness of the patches varied from 0.32 ± 0.01 to 0.39 ± 0.05. Folding endurance values of matrix films was found within 320 ± 2.0 – 380 ± 1.0 numbers of folds, indicating good strength and elasticity. The drug content analysis and the weight uniformity of the prepared formulation have shown that the process adopted for casting the films in this investigation is capable of giving films with uniform drug content and with minimum intra batch variability. The percentage Moisture uptake in the formulation F 8 has shown the highest value of moisture absorption 10.21±0.02 which may be due to higher polydispersity index and solubility parameter of HPMC, PVP. The formulation F 11 (1.5% HPMC, 1.5% PVP) shows higher value of Moisture loss 10.65±0.01 which may be due to presence of higher concentration of hydrophilic polymers and formulation F 8 shows low value of 5.83±0.01.

The formulation F 11 (1.5% HPMC, 1.5% PVP) has shown maximum water vapor transmission of 9.99×10^{-3} among all the patches which may be due to presence of higher concentration of hydrophilic polymers and F 8 has less water vapor transmission of 6.28×10^{-3}. The *In-vitro* release plots of all other formulations were suggestive of zero order release and are diffusion mediated which was confirmed from the regression value

of Higuchi's plot. All the formulations undergo non-fickian type of release which is confirmed from the slope values obtained from the Peppa's plot. The cumulative percentage of drug released in 24 h was found to be the highest for Formulation F 1 which has shown the drug release of 99.31%. The *In-vitro* drug release plot indicates that the drug release followed zero order kinetics, which was envinced from the regression value of the above mentioned plot. Hence formulation F 1 was selected as the optimized formulation by virtue of its drug release kinetics. *In-vitro* transdermal permeation study was carried out in rat skin, Snake shed skin and porcine ear skin the formulation F 1 showed drug diffusion for 24 h up to the extent of 97.81%, 98.23% and 95.65% respectively. The comparative *In-vitro* drug diffusion data has been illustrated in Figure 1. The variation among the used biological membrane could be attributed to the fat content and thickness of the membrane used. The result obtained from the primary skin irritation studies revealed that neither the adhesive nor the drug MT caused any noticeable irritation on the rabbit skin throughout the study. *In-vivo* study was carried out in rabbit, at the end of 24^{th} h the drug release was found to be 96.23 %. The results which are illustrated in Figure 2 indicated that the *In-vitro* and *In-vivo* correlation was very good which reveals the reproducibility of drug release even in biological environment.

CONCLUSION

In conclusion, formulation F 1 has achieved the targets of present study such as controlled release, prolonged zero order release, reduced frequency of administration, greater therapeutic effect, overcome the side effects, simplifies the treatment regimen and thus may improve patient compliance.

REFERENCES

Amit Alexander, Shubhangi Dwivedi, Ajazuddin, Tapan K. Giri, Swarnlata Saraf, Shailendra Saraf, Dulal Krishna Tripathi. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release. 2012; 164: 26–40.

Biswajit Mukherjeea, Sushmita Mahapatraa, Ritu Guptab. Comparison between povidone-ethyl cellulose and povidone-Eudragit transdermal Dexamethasone matrix patches based on in vitro skin permeation. European Journal of Pharmaceutics and Biopharmaceutics 2005; 59: 475–483.

Chakkapan S, Kiran Gandhi, Suja Thomas, Katkam RR, Puri CP, Srivastava R. Studies in transdermal drug delivery system for estradiol. Indian Journal of Pharmaceutical sciences 1994; 56(4): 121-125.

Dollery C, Therapeutic Drugs, Churchill Livingstone. New York 1991. 115–118.

Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes, Journal of Pharmacology and Experimental Therapeutics, 1944; 82: 377–390.

Hatanaka T, Panomsuk S, Opanasopit P, Rojanarata T. Comparison of the percutaneous absorption of hydrophilic and lipophilic compounds in snake shed skin and human skin. Pharamzie 2006; 61: 331 -335.

Jagadish Singh, Kaidi Zha. *In-vitro* percutaneous absorption enhancement of Propanolol HCl through Porcine epidermis by Terpenes/ethanol. Journal of Control Release 1999; 62: 359 – 366.

Jagmohan. Organic Spectroscopy. Edn 2, Narosa Publications, Inc., New Delhi, 2003; 212-232.

Jayaprakash S, Mohamed Halith S, Mohamed Firthouse PU. Preparation and evaluation of celecoxib transdermal patches. Pakistan Journal Pharmaceutical Sciences 2010; 23(3): 279-283

Ji-Hui Zhao, Ji-Hua Fu, Shu-Ming Wang. A novel transdermal patch incorporating Isosorbide dinitrate with Bisoprolol: In vitro and In vivo characterization. International Journal of Pharmaceutics 2007; 337: 88–101.

Ke GM, Wang L, Xue HY, Lu WL, Zhang X, Zhang Q, Guo HY. In vitro and In vivo characterization of a newly developed Clonidine transdermal patch for treatment of attention deficit hyperactivity disorder in children. Biological and Pharmaceutical Bulletin. 2005; 28: 305–310.

Kulkurni Raghavendra, Doddaya H, Marihal SC, Patiln CC, Habhu PV. Comparative evaluation of polymeric films for transdermal application. The Eastern Pharmacist 2000; 516: 109 – 111.

Kusum Devi V, Saisivam S, Maria GR, Depti PU. Design and Evaluation of Matrix diffusion Controlled Transdermal patches of Verapamil Hydrochloride. Drug Development and Industrial Pharmacy 2003; 29: 495 – 503.

Marin EL, Modamio P. Transdermal absorption of celiprolol and bisoprolol in human skin in vitro. International Journal of Pharmaceutics 1998; 173: 141–148.

Mazzo DJ, Obetz CL, Shuster J, Brittain HG. Analytical profiles of drug substances and excipients. San Diego CA: Academic Press Inc. 1994; 23: 53.

McDaid DM, Deasy DM. An investigation into the transdermal delivery of nifedipine. Pharmaceutica Acta Helvetiae. 1996; 71: 253-258.

Mundada AS, Avari JG. Damar Batu as a novel matrix former for the transdermal drug delivery: *In-vitro* evaluation. Drug Development and Industrial Pharmacy 2009; 35: 1147–1154.

Posina Anitha, Sundarapandiyan Ramkanth, Mohamed T S Saleem, Kommireddy Umasankari, Boddu Praveen Reddy, Madhusudhana Chetty. Preparation, *In-vitro* and *In-vivo* characterization of transdermal patch containing glibenclamide and MT: a combinational approach. Pakistan Journal of Pharmaceutical Sciences. 2011; 24 (2): 155-163.

Srinivas Mutalik, Narayanabhirama Udupa. Formulation development, in vitro and in vivo evaluation of membrane controlled transdermal systems of Glibenclamide. Journal of Pharmaceutical sciences 2005; 8 (1): 26-38.

Srinivas Mutalik, Nayanabhirama Udupa, Sharath Kumar, Sunil Agarwal, Ganesh Subramanian, Averineni K. Ranjith. Glipizide matrix transdermal systems for diabetes mellitus: Preparation, *In-vitro* and preclinical studies. Life Sciences 2006; 79: 1568–1577.

Ubaidulla U, Reddy MVS, Ruckmani K, Ahmed FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPS PharmSciTech 2007, 8: 1–8.

Udupa N, Koteshwar KB, Vasantha kumar. Formulation and Evaluation of Captopril Transdermal preparations. Indian Drugs 1992; 29: 680 – 85.

Vlassios Andronis, Mounir S. Mesiha. Design and evaluation of transdermal Chlorpheniramine maleate drug delivery system. Pharmaceutics Acta Helvetiae 1995; 70: 301-306.

Yanli Gao, Jinying Liang. Double-layer weekly sustained release transdermal patch containing gestodene and ethinylestradiol. International Journal of Pharmaceutics 2009; 377: 128–134.