Research Article

Formulation and evaluation of Diltiazem Hydrochloride transdermal patch for treating hypertension

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Abstract

Objective: Hypertension is one of the largest deaths causing disease for the mankind. Since it is a chronic disease it necessitates long term treatment. Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. The purpose of this research was to develop a matrix-type transdermal therapeutic system containing Diltiazem HCL with different ratios of hydrophilic and hydrophobic polymeric systems. **Materials and methods:** The ingredients of transdermal patch were Diltiazem HCL, HPMC and Ethyl cellulose. Solvents like Ethanol, Chloroform and Methanol were used throughout the study. After the pre-formulation study drug loaded matrix type transdermal films of Diltiazem HCL were prepared by solvent evaporation method and evaluated for various physicochemical characteristics. In-vitro permeation studies of formulations were performed by using Franz diffusion cells and dialysis membrane was used as barrier membrane. **Results and conclusion:** Formulation prepared with polymer HPME E15 and ethyl cellulose by using PEG 400 as a plasticizer showed best in vitro skin permeation through Dialysis membrane as compared to all other formulations. The Cumulative drug release from formulation F8 was found to be 98.93% after 8 hrs. Therefore, Diltiazem HCL patch may be a potential formulation for the management of patients with hypertension as a long term release formulation in transdermal drug delivery system.

Keywords: Diltiazem HCL, Transdermal Film, Solvent evaporation technique, In-vitro permeation study

Introduction

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin in to the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin (Nanda et al., 2012). Transdermal drug delivery has been accepted as a potential non-invasive route of drug administration with an advantage of prolonged therapeutic action, decreased side effects, easy use, better patient compliance, constant blood level, avoidance of first pass metabolism and no dose dumping (Prabhakar et al., 2013). Now a day about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Transdermal drug delivery system (TDDS) involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect, while a very major fraction of drug is transported into the systemic blood circulation (Shingadi et al., 2012).

Hypertension is one of the largest deaths causing disease for the mankind. Since it is a chronic disease it necessitates long term treatment (Selvam et al., 2010). Diltiazem is a non-DHP member of the group of drugs known as benzodiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris and some types of arrhythmias. It is also an effective preventive medication for migraine. It is a class 3 anti-angina drug, and a class IV antiarrhythmic. Diltiazem acts as an inhibitor of the CYP3A4 enzyme. The biological half-life of Diltiazem is 3-4.5 hrs which makes it a suitable candidate for administration by

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transdermal route (Ahad et al., 2010).

Materials

Diltiazem HCL was received as a gift samples from Tianjin Tianyao pharmaceutical Co.Ltd. Hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose were obtained from Swastic Acids and Chemicals, Nagpur. Other solvents like Ethanol, Chloroform, and Methanol were obtained from Upper India Scientific, Nagpur. Disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate, Nacl and distilled water were used throughout the study.

Methods

Fabrication of medicated patch

Drug loaded matrix type transdermal films of Diltiazem HCL were prepared by solvent evaporation method. The polymer like EC and HPMC were dissolved in particular solvents with the help of magnetic stirrer followed by the addition of drug in to the polymeric solution. Then the plasticizers were incorporated with continuous stirring for 2-3 hr and the volume was made up to 10 ml. The resultant solution was casted on to the petridish containing backing layer. After 24 hours the films were removed by using sharp knife by inserting along the edge of the films and kept in desiccators to remove any adhering solvent. Then the films were wrapped in aluminium foil, packed in self sealing cover and kept in desiccator (Ahad et al., 2010; John et al., 2012; Zhang et al., 2014).

Table 1. Formulation of Diltiazem HCL transdermal patch

Ingredients (mg/ml)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	30	30	30	30	30	30	30	30
HPMC E15	600	200	300	300	400	-	-	-
HPMC K4M	-	-	-	-	-	300	500	-
HPMCK15M	-	-	-	-	-	-	-	200
EC		200	200	100	200	200	300	200
PEG400	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	10	-	-	-	-	-	-	-
Chloroform	-	7	7	7	7	7	7	7
Methanol	-	3	3	3	3	3	3	3

Backing layer

The main function of backing layer is to protect the patch from external environment**.** The backing layer must be impermeable to drug and permeation enhancers. The backing membrane serves the purpose of holding the entire system together and at the same time protects the drug reservoir from atmospheric exposure, which could result in the breakage or loss of the drug by volatilization.

Fabrication of backing layer

Ethyl cellulose polymer was dissolved in particular solvent with the help of magnetic stirrer followed by the addition of plasticizer with continuous stirring for 2 hrs. The resultant solution was casted on to the petridish drying for 2-3 hrs (Care should be taken that the backing layer must not be over dried).

Table 2. Formulationof backing layer

Ingredients	Quantity taken
Ethyl cellulose	300 mg
Propylene glycol	2.5 ml
Toluene	10 ml

Table 3. Preformulation study

Identification tests	Observed Result
Appearance	Fine powder
Melting point	212^{oc}
Colour	White
Solubility	Soluble in H2O & organic solvent
Odour	Characteristics

Standard calibration curve

The present analytical method obeyed Beer's law in the concentration range 2-10 µg/ml and is suitable for the estimation of Diltiazem from different solutions. The correlation coefficient (r) was found to be 0.9993, indicating a positive correlation between the concentration of Diltiazem and the corresponding absorbance values (Amjad et al., 2011).

Preparation of standard stock solution

Standard drug solution of Diltiazem HCL was prepared by dissolving 10 mg of Diltiazem HCL in 100 ml of phosphate buffer pH 7.4 to obtained stock solution of 100 ug/ml concentration.

Preparation of phosphate buffer pH 7.4

Dissolve 2.38 g of disodium hydrogen orthophosphate, 0.19 g of potassium dihydrogen orthophosphate and 8.0 g of Nacl in sufficient water to produce 1000 ml and adjust the pH if necessary (I.P, 2010).

Evaluations parameters

A. Physical appearances

All the prepared patches were visually inspected for colour, clarity, flexibility and smoothness (John et al., 2013).

B. Thickness

The thickness of three randomly selected transdermal patches from every batch was determined using a standard screw gauge. The average thickness was calculated and summarised (Ramkanth et al., 2012; Sharma et al., 2012).

C. Weight uniformity

For the weight uniformity study of patch three patches from every formulation were taken out and weighted individually on electronic balance. The average weights were calculated and summarised (Dhiman et al., 2011; Ramkanth et al., 2012).

D. Drug content

The patches (1.5 cm^2) were cut and added to a beaker containing 100 ml of phosphate buffer saline (PBS) of pH 7.4. The medium was stirred with magnetic stirrer for 6 hrs. Then, 1 ml sample was pipette out and diluted up to 10 ml with phosphate buffer pH 7.4. The resulting solution was filtered through a 0.45µm Whatman filter paper. The drug content was then determined at 237nm using UV- spectrophotometer (Patel and Kavitha, 2011; Shingade et al., 2012).

E. Flatness

Three longitudinal strips were cut out from each film: 1 from the centre, 1 from the left and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction with 0% constriction equivalent to 100% Flatness. Three patches from every formulation were taken out and the average flatness study were calculated and summarised.

% constriction= L1–L2 X 100/L2

L2 = Final length of each strip; L1 = Initial length of each strip (Patel and Kavitha, 2011; Sharma et al., 2013).

F. Folding indurance test

The folding endurance measured manually for the prepared film. A strip of film is cut evenly and folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance (Dhiman et al., 2011).

G. Moisture content

The films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100 (John et al., 2013).

H. Moisture uptake

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% Relative Humidity (RH). After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] × 100 (Dhiman et al., 2011; Shingade et al., 2012).

I. Water vapour transmission rate

WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time. A modification of the method used by Kanig and Goodman was employed for the determination of vapour transmission from the patch. Glass-bottle (length=5 cm, narrow mouth with internal diameter = 0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive spread across its rim was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber for 24 hrs. The vials were removed and weighted after 24 hrs to note down the weight again and transmission rate was found out (John et al., 2013).

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{area}} X100$$

J. 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 (Ramkanth et al., 2012).

K. In vitro drug diffusion study

Franz diffusion cell

The in vitro release was carried out with the dialysis membrane using Franz diffusion cell. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The Temperature was maintained at 37 ± 0.5°C and receptor compartment was provided with sampling port. The diffusion medium used was PBS pH 7.4 solution. The drug containing film was kept in the donor compartment and it was separated from the receptor compartment by dialysis membrane. The dialysis membrane was previously soaked for 24 hours in PBS pH 7.4. The donor and receptor compartment hold together. The receptor compartment with 18 ml capacity was maintained at 37 ± 0.5 °C and stirred with magnetic capsule operated by magnetic stirrer to prevent the formation of concentrated drug solution Layer below the dialysis membrane. Samples of 4 ml were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by UV

Spectrophotometrically. Cumulative percentage drug released were calculated and plotted against time. The data was fitted to different kinetic models to explain the release mechanism (Amjad et al., 2011; John et al., 2013; Zhang et al., 2014).

Results and discussion

Spectrum measurement

UV Spectroscopy

UV absorption spectrum of Diltiazem drug sample in phosphate buffer pH 7.4 shows maximum at 237 nm specified in the range of 220 to 280 nm. Thus 237 were found to be in specification of drug. So it is further selected as λ max of Diltiazem hydrochloride.

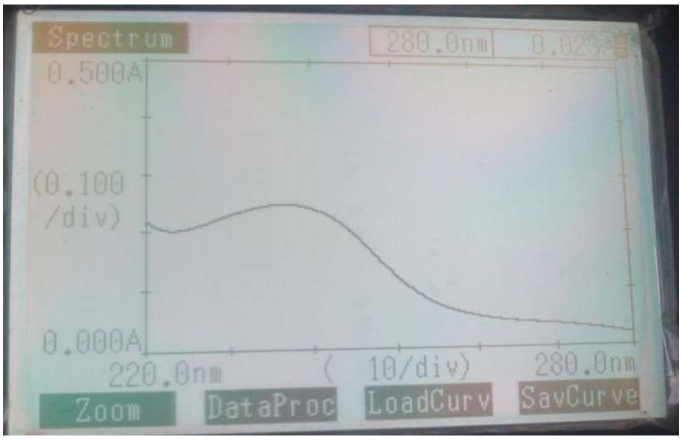

Figure1. UV Scan for Diltiazem HCL

Table 4. Data for standard calibration curve of Diltiazem HCL

Concentration (µg/ml)	Absorbance at 237 nm
2	0.125
4	0.221
6	0.328
8	0.426
10	0.529

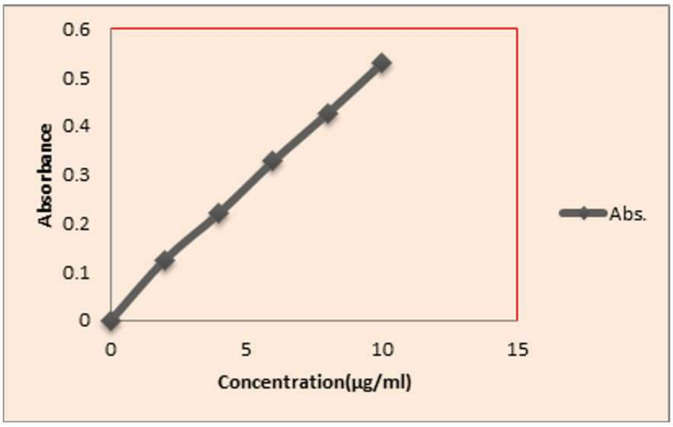

Figure 2. Stdandard Calibration Curve for Diltiazem HCL

Table 5. Physicochemical characteristic of transdermal patches of Diltiazem HCL

Batch code	Thickness (µm)	Weight uniformity (mg)	Folding endurance	Flatness	%Drug content
F1	0.14±0.09	0.52±0.022	216	97.18	69.71
F2	0.52±0.09	0.57±0.03	98	99.11	95.31
F3	0.23±0.04	0.46±0.02	289	99.12	99.77
F4	0.15±0.07	0.47±0.08	102	87.85	92.08
F5	0.19±0.09	0.59±0.01	99	100.02	100.22
F6	0.24±0.07	0.55±0.11	201	96.03	88.18
F7	0.17±0.07	0.48±0.031	298	98.05	98.81
F8	0.69±0.08	0.61±0.022	144	79.94	98.02

Table 6. Physicochemical characteristic of Transdermal Patches of Diltiazem HCL

Batch code	Moisture content (%)	Moisture uptake (%)	WVTR (g/cm2/hrs)	Water absorption capacity
F1	1.561	2.338	0.0278	3.2
F2	1.566	3.174	0.138	5.24
F3	1.597	2.210	0.099	3.1
F4	1.58	3.130	0.055	0.9
F5	1.413	4.125	0.055	2.11
F6	1.564	6.145	0.138	1.21
F7	1.471	5.219	0.083	7.24
F8	1.63	2.758	0.138	4.21

Table 7. Cumulative % drug release profile

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	6.14	2.29	31.02	5.42	40.79	5.23	20.21	30.39
2	8.58	6.42	40.65	5.69	42.12	9.38	29.16	39.42
3	18.90	7.58	57.52	5.77	50.50	10.38	30.18	58.32
4	24.68	9.05	69.14	6.61	59.22	11.61	49.02	63.52
5	30.32	12.52	76.31	10.15	62.18	45.46	60.11	72.31
6	37.15	20.31	76.31	10.77	68.98	62.68	71.76	79.00
7	49.02	20.31	97.07	20.44	76.31	78.67	88.16	83.61
8	58.07	64.38	98.93	31.52	85.62	86.64	92.38	92.36

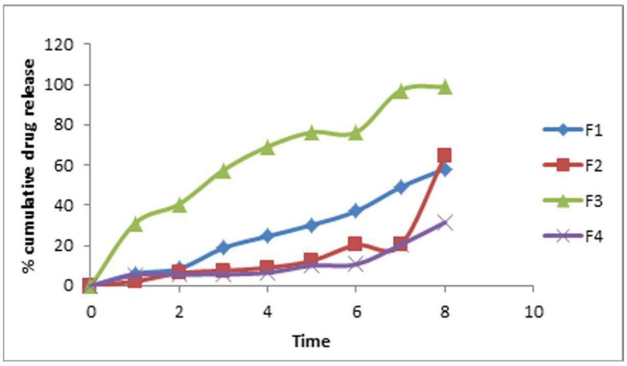

Figure 3. % Cumulative drug profile of Batch F1 to F4

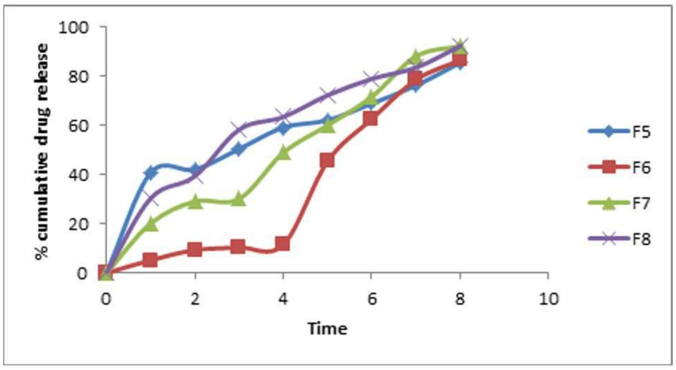

Figure 4. % Cumulative drug profile of Batch F5 to F8

Batch F6, F11, and F12 follow zero order kinetic model Batch F7 and F8 follow first order kinetic and batch F9, F10, and F13 was follow Higuchi model fitting.

Table 8. Drug release kinetic

Batch no	Zero order (R2)	First order (R2)	Higuchi model (R2)	Hixon-crowel (R2)
F6	0.9826	0.9780	0.8695	0.9800
F7	0.9732	0.9743	0.9188	0.9740
F8	0.9496	0.9930	0.9876	0.9884
F9	0.7953	0.8000	0.8766	0.7985
F10	0.7890	0.8881	0.9548	0.8578
F11	0.6716	0.6201	0.5092	0.6367
F12	0.9548	0.9431	0.9203	0.9517
F13	0.9318	0.9852	0.9881	0.9748

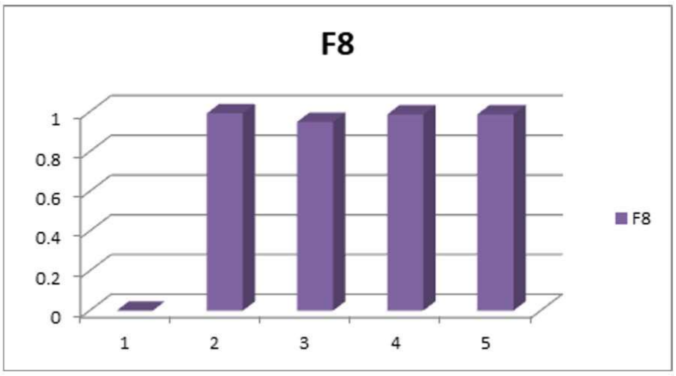

Figure 5. Drug release kinetic of Optimised batch F8

Appearance

The patches from all the batches were translucent and flexible without any sign of crack.

Conclusion

It can be concluded that the formulation has achieved of TDDS i.e. extended release and reduced frequency of administration and has also avoided the first pass effect. Batch F8 containing drug and polymer HPMC E 15 and ethyl cellulose in the ratio of 3:2 emerged as the most satisfactory formulation in so far as its technological properties were concerned. On the stability studies it concluded that there is no change in the physical characteristics of Diltiazem HCL patches and the cumulative % drug release. Thus the formulated patches were stable. Therefore, Diltiazem HCL patch may be a potential formulation for the management of patients with hypertension as a long term release formulation in TDDS.

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Conflict of Interest

Authors have no conflict of interest to declare.

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