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FORMULATION AND EVALUATION OF DILTIAZEM HYDROCHLORIDE TRANSDERMAL PATCH

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ABSTRACT

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In the current research Diltiazem hydrochloride was loaded in transdermal patch and they are prepared by solvent casting method using aluminum foil as the backing membrane. Eudragit RS100 and HPMC were weighed in requisite ratios and they were then dissolved in methanol as solvent using magnetic stirrer.Four optimized transdermal patches were formulated with different drug-polymer ratios. Diltiazem Hcl (20mg) was added into homogenous dispersion under slow stirring with a magnetic stirrer. Dibutyl phthalate 30%w/w of polymer composition was used as plasticizer, added to the above dispersion under continuous stirring. Invitro and physico-chemical evaluation methods were performed. Finally F3 formulation showed higher drug release (83.4 %),thickness (0.45±0.04), weight (532.6±0.36), folding endurance(5),drug content(86.23±0.08)%MC (4.66±0.04),%MA (8.24±0.75),%ML (3.97±0.02),WVTR(2.07±0.01) and drug permeation (1173 µg/ml) than the remaining formulations. Hence, F3 can be selected as best formulation among the four optimized formulations.

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INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. In the Drug Quality Reporting System (DQRS), the United States Food and Drug Administration (FDA) has received numerous reports of "adhesion lacking" for transdermal drug delivery systems. This article provides an overview of types of transdermals, their anatomy, the role of adhesion, the possible adhesion failure modes and how adhesion can be measured. Excerpts from FDA reports on the lack of adhesion of transdermal system products are presented. Pros and cons of in vitro techniques, such as peel adhesion, tack and shear strength, in vivo techniques used to evaluate adhesive properties are discussed. To see a decrease in "adhesion lacking" reports, adhesion needs to become an important design parameter and suitable methods need to be available to assess quality and in vivo performance. This article provides a framework for further discussion and scientific work to improve transdermal adhesive performance.

MATERIALS AND METHODS:

PREPARATION OF STANDARD GRAPH OF DILTIAZEM HCl

100 mg of Diltiazem Hcl was accurately weighed and dissolved in 100 ml standard volumetric flask using methanol to get stock solution (1 mg/ml). From the stock solution, working standards of various concentrations such as 10, 20, 30, 40 and 50 μg/ml were prepared by diluting stock solution with methanol, each sample was then analyzed spectrophotometrically at 237 nm using Shimadzu double beam UV-Vis spectrophotometer.

Table : 1 Formula of Transdermal Patch

Ingredients	F1	F2	F3	F4
Diltiazem.Hcl(mg)	20mg	20mg	20mg	20mg
Eudragit RS 100(mg)	420	360	320	250
HPMC(mg)	40	60	80	100
Dibutyl phthalate(%w/w)	30	30	30	30
Propylene glycol(%w/w)	20	25	30	35

PREPARATION OF TRANSDERMAL PATCH ENRICHED WITH DILTIAZEM HCL

Drug partition coefficient

Partition coefficient study was performed using n-octanol as the oil phase and phosphate buffer (pH 7.4) as the aqueous phase. The two phases were mixed in equal quantities and were saturated with each other on a mechanical shaker at 37^0c for 24h. The saturated phases were separated by separating funnel. Standard plots of the drug were prepared from both phosphate buffer pH 7.4 and n-octanol. Equal volume (10mL) of the two phases were placed in triplicate in conical flasks and, to each, 100mg of drug was added. The flasks were shaken occasionally for 24h to achieve complete partitioning. The two phases were separated by centrifugation at 1500rpm for 5min and were then analyzed for respective drug content.

Method of preparation of transdermal patch

Transdermal patches containing Diltiazem Hcl were prepared by solvent casting method using aluminum foil as the backing membrane. Transdermal patches were prepared according to the formula shown in Table 6. Eudragit RS100 and HPMC were weighed in requisite ratios and they were then dissolved in methanol as solvent using magnetic stirrer. Diltiazem Hcl (20mg) was added into homogenous dispersion under slow stirring with a magnetic stirrer. Dibutyl phthalate 30%w/w of polymer composition was used as plasticizer, added to the above dispersion under continuous stirring.Different concentrations of propylene glycol was incorporated. The uniform dispersion was casted on aluminum backing membrane. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccators.

PHYSICOCHEMICAL EVALUATION

The films were evaluated for the following physicochemical properties:

Thickness:

The thickness of patches was measured at five different places using a micrometer (Mitutoyo Co; Japan) and mean values were calculated.

Weight variation study:

The patches were subjected to weight variation by individually weighing five different randomly selected patches. Such determination was carried out for each formulation.

Folding endurance:

This was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking/cracking gave the value of folding endurance.

Drug content uniformity:

Transdermal patches with an area of 2cm was cut into small pieces and transferred into 100ml phosphate buffer (pH 7.4) and shaken for 6h to extract the drug. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45μm membrane, diluted suitably and absorbance was measured at 210nm in a UV-Vis Spectrophotometer (Shimadzu, Japan).

Moisture content:

The prepared films were marked, then weighed individually and kept in desiccator containing activated silica at room temperature for 24h. The films were weighed again, until constant weight is achieved. The % moisture content was calculated as a difference between initial and final weight with respect to final weight.

% Moisture content (MC) = Initial weight - Final weight

Percentage moisture absorption:

The films were weighed accurately and placed in the desiccator containing 100mL of saturated solution of aluminum chloride, which maintains 79.50%RH. After, three days, the films were taken out and weighed.

Percentage moisture absorption = Final weight - Initial weight.

Percentage moisture loss:

The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and weighed.

Percentage moisture loss = Final weight - Initial weight.

Water vapour transmission rate:

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was

placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage.

Water vapour transmission rate = Final weight - Initial weight.

Water vapour transmission rate is usually expressed as the number of grams of moisture gained/h/cm^2.

SKIN IRRITATION TEST

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on healthy rabbits weighing 1.3 to 1.5 kg. Drug free polymeric film of diameter 4.1cm were used as control. The dorsal surface of rabbits was cleared well and the hair was removed by using a depilatory preparation. The skin was cleared with rectified spirit. The patches were applied to the shaved skin of rabbits and secured using adhesive tape USP (LeucoplastTM). On one side of the back control patch (without any drug, group I) and on the other side an experimental patch (group II) were secured. A 0.8%v/v aqueous solution of formaldehyde was applied as a standard irritant (group III) and its effect was compared with test. The animals were observed for any size of erythema or oedema for a period of 7days. All the experimental protocols involving laboratory animals were approved by the IAEC.

IN VITRO PERMEATION OF DILTIAZEM HCL THROUGH EXCISED HAIRLESS MOUSE SKIN

Preparation of mice skin:

The Swiss albino mice with a weight range of 20-25gm were decapitated. The abdominal skin of excised hairless mice skin was separated along the epidermal junction and it was kept in water bath, which was maintained at 60^oC for 50sec. The heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution for flattering and smoothing.

Permeation studies:

Permeation studies were carried out using vertically assembled Keshary-Chein diffusion cells having diffusional surface area of 5.31cm^2. The full thickness skin samples with surface area of 5.31cm^2 was mounted on Keshary-Chein diffusion cell, with the stratum corneum side in intimate contact with the Diltiazem Hcl releasing surface of the film and the dermal side facing

the receptor solution. The receptor compartment of the cell was filled with 60mL of saline phosphate buffer (pH 7.4) and the temperature was maintained at 37±2^{o}c. The samples were withdrawn from receptor side at predetermined intervals (1, 2, 4, 6, 8, 12 and 24hr) and replaced with same volume of fresh pre-warmed saline phosphate buffer (pH 7.4) to maintain the sink condition. The samples were then analyzed by UV-Vis spectrophotometer at 237nm.

RESULTS AND DISCUSSION

PREPARATION OF STANDARD PLOT OF DILTIAZEM HCL

A standard plot of Diltiazem Hcl was plotted for the concentrations of 10, 20, 30, 40 and 50 µg/ml with the absorbance measured at 237 nm. The calibration equation for the standard graph was found to be y = 0.0215x + 0.182 and the regression coefficient (R^2 = 0.9961) was used in all the calculations. The standard plot of Diltiazem Hcl is given in Fig 1.

Table2 : Standard plot of Diltiazem Hcl in methanol

S.No	Concentration (mcg/ml)	Absorbance
1	10	0.217
2	20	0.395
3	30	0.606
4	40	0.782
5	50	0.954

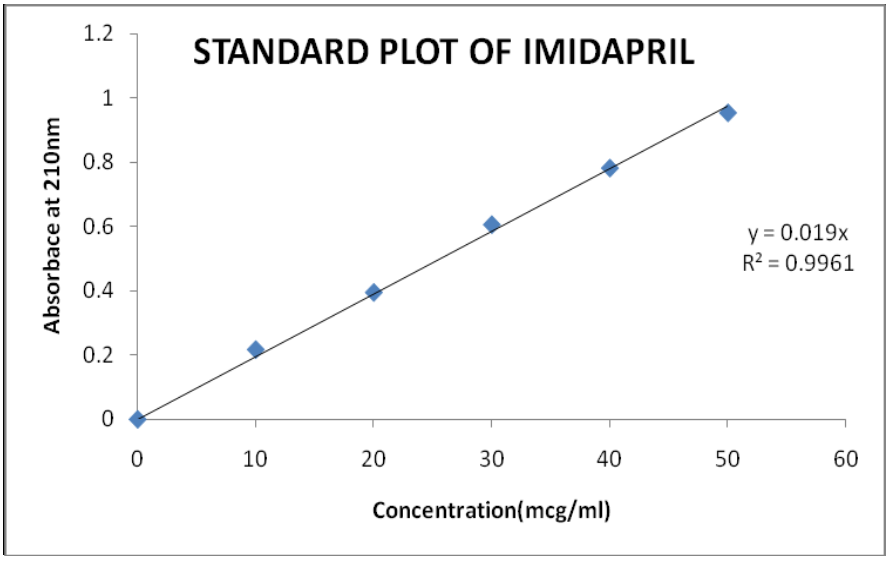


Fig1 : Standard plot of Diltiazem Hcl

PREPARATION OF TRANSDERMAL PATCHS ENRICHED WITH OPTIMIZED DILTIAZEM HCL

FORMULATIONS:

The transdermal patch formulations are designated as F1, F2, F3 and F4.

Table3 : Transdermal patch formulation

Ingredients	Transdermal patch containing Diltiazem Hcl			
	F1	F2	F3	F4
Diltiazem Hcl(mg)	20	20	20	20
Eudragit RS 100 (mg)	420	360	320	250
HPMC (mg)	40	60	80	100
Dibutyl phthalate(%w/w)	30	30	30	30
Propylene glycol(%w/w)	20	25	30	35

CHARACTERIZATION OF THE TRANSDERMAL PATCHES CONTAINING DILTAIZEM HCl FOR TOPICAL DELIVERY.

Drug partition coefficient:

n-octanol and phosphate buffer (pH 7.4) are considered to be the standard system for determining the drug partition coefficient between skin and invitro fluid. The logarithmic rule of the partition coefficient (logP) was found to be 0.80±0.02. The results revealed that the drug possesses sufficient lipophilicity, which meets the requirement of formulating it into a transdermal patch.

Physical parameters:

The physicochemical properties of Diltiazem Hcl trandermal patches were presented in the Table (9,10). They were found to be uniform in their weight and thickness with low SD values.

The folding endurance measures the ability of patch to withstand rupture. The folding endurance was found to be increased with increasing HPMC concentration.

The WVTR was found to be increased with increasing in HPMC concentration; which might be attributed to the hydrophilic nature of the HPMC. It was found that the %MA

Form.code	*1%MC	*2%MA	*3% ML	*4 WVTR(gm/cm^2/h) x10-4
F1	3.66±0.12	6.25±0.18	1.48±0.28	1.15±0.04
F2	4.26±0.04	7.40±0.04	2.35±0.03	1.59±0.02
F3	4.66±0.04	8.24±0.75	3.97±0.02	2.07±0.01
F4	4.50±0.08	7.95±0.04	3.09±0.03	1.95±0.04

and %ML was increased with increasing in HPMC concentration.

Table4 : *Average of three observation. Physical parameters of transdermal patch containing Diltiazem Hcl

The results revealed that the drug content was almost uniform in all the patches with low SD values

Table 5: Physical Parameters of transdermal patch containing imidapril – SLN *Average of three observation; 1 – Percentage moisture content; 2 – Percentage moisture absorption; 3- Percentage moisture loss; 4-water vapour transmission rate.

The diffusion coefficient, permeability coefficient and enhancement ratio of transdermal patch

Form.code	Thickness (mm) *	Weight (mg) *	*Folding endurance	* Drug content
F1	0.41±0.04	530.6±0.36	3	82.18±0.04
F2	0.43±0.05	531.0±0.32	4	85.26±0.09
F3	0.45±0.04	532.6±0.41	5	86.23±0.08
F4	0.44±0.05	529.2±0.41	3	85.22±0.009

were presented in table (11).

Table 6 : Diffusion coefficient, Permeability coefficient, enhancement ratio of transdermal formulation

Form.code	Diffusion coefficient(cm^2/h) ±S.D.	Permeability coefficient (cm/h) ±S.D	Enhancement ratio±S.D
F1	6.97±0.03	22.68±0.03	1.03±0.04
F2	7.05±0.01	29.68±0.02	1.16 ±0.02
F3	8.95±0.03	28.71±0.04	2.05±0.27
F4	7.50±0.01	28.27±0.07	1.30±0.03

IN VITRO DRUG PERMEATION STUDIES:

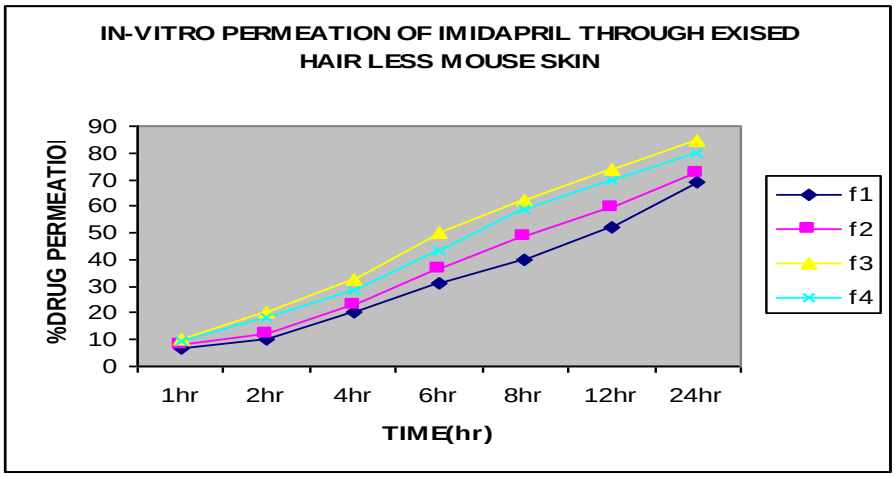
In vitro permeation of Diltiazem Hcl through excised hairless mouse skin revealed that with decreasing in the concentration of Eudragit RS100, the Diltiazem Hcl release also increased. It might be due to lower proportion of quaternary ammonium in Eudragit RS100 for prolonged release of Diltiazem Hcl and that with increasing in the concentration of HPMC th Diltiazem Hcl Diltiazem Hcl released also increased. It might be attributed due to the hydrophilic nature of HPMC. In the formulation of F3, containing Eudragit RS100 and HPMC in the ratio of 4:1, showed 84.50 % Diltiazem Hcl release at the end of 24hr study.

Table 7: in vitro drug permeation studies

Time (hours)	Cumulative percentage of drug released							
	F1		F2		F3		F4	
	Avg (%)	S.D.	Avg (%)	S.D.	Avg (%)	S.D.	Avg (%)	S.D.
1	8.52	1.3426	10.07	1.3426	12.40	1.3426	11.62	2.3255
2	13.25	1.4145	15.73	1.2808	20.61	3.6794	18.99	2.8890
4	22.24	1.3626	24.96	1.2808	41.93	4.8466	37.82	5.7169
6	35.11	3.3539	38.06	1.2808	53.56	2.9262	49.84	1.4951
8	47.51	1.5484	51.47	1.2808	60.54	3.1573	58.06	1.3223
12	59.30	3.0232	63.56	2.4427	72.40	2.7744	69.76	1.0136
24	70.30	1.2808	77.20	1.0136	83.40	1.8797	80.61	1.3626

Mean ± SD (n=3)

Fig 2 : In vitro permeation of Diltiazem Hcl through exised hairless mouse skin.



SKIN IRRITATION TEST:

A primary skin irritation test of patch F3A on rabbit was studied. No signs of erythema, oedema or ulceration were observed on the skin of albino rabbits after 7days.

SCANNING ELECTRON MICROSCOPY:

The SEM of the drug loaded patch (F3) clearly indicates that Diltiazem Hcl is molecularly dissolved in the patch. After permeation experiment the film showed that the presence of pores/channels indicating the drug permeation is diffusion controlled. The SEM photographs of related transdermal patch were presented in fig (11,12, 13,)

Fig 3: SEM photograph of blank film

Fig 4: SEM photograph of Diltiazem Hcl loaded film before perm

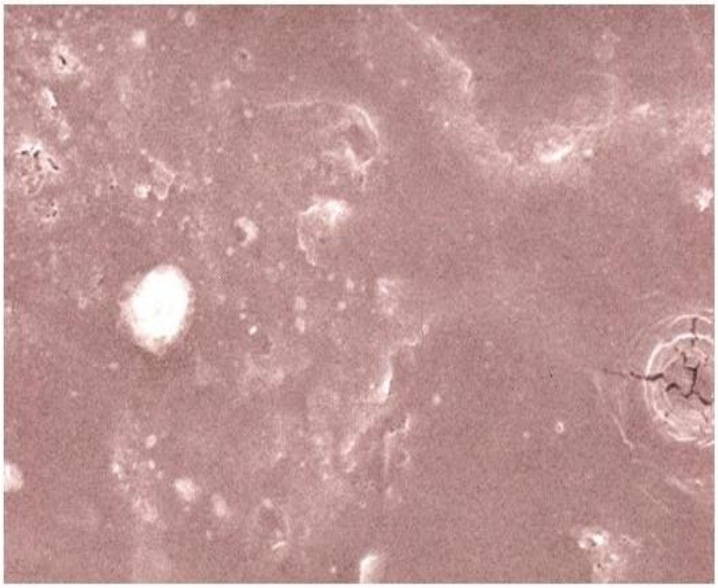
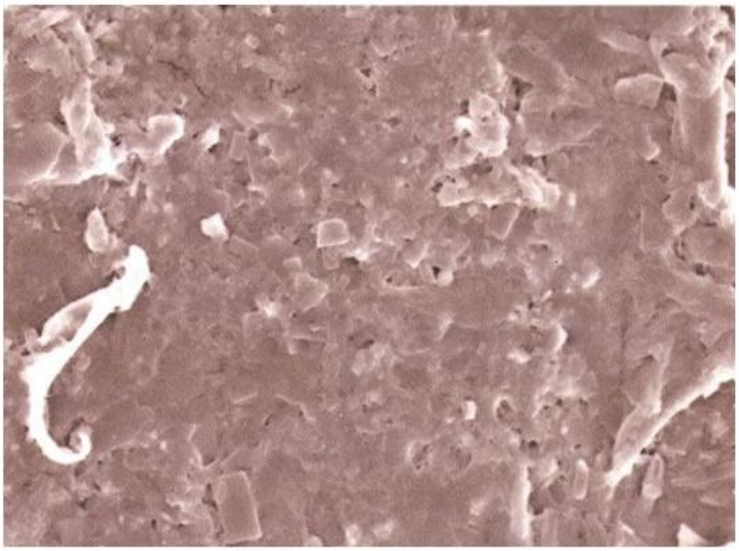


Fig5 : SEM photograph of Diltiazem Hcl load film after permeation



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