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FORMULATION AND EVALUATION OF DARIFENACIN HYDROBROMIDE TRANSDERMAL PATCH

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ABSTRACT The aim of present study is to formulate and characterize darifenacin hydrobromide transdermal patch and the effects of non-ionic surfactants span 20 and tween 20 on drug permeation were studied. Transdermal patches were prepared by solvent casting method using PVA, PVP, HPMC E5, HPMC E15 polymers. Propylene glycol and Glycerol were used as plasticizers and Span 20 and Tween 20 were used as permeation enhancers. The prepared patches were evaluated for physicochemical properties like drug content, thickness, weight variation, folding endurance, moisture uptake, watervapour transmission studies. Physicochemical properties have shown better. Drug release studies by *in-vitro* diffusion, *ex-vivo* permeation as well as skin irritation. Formulations DPAT2, DPLT3 showed better drug release rate, flux and Q_{24} when compared to DPAS2, DPLS2. From the results it was concluded that darifenacin hydrobromide transdermal patch (DPAT2) formulation would reduce the administration frequency, side effects and may avoid fluctuations of drug level in the blood in comparison to immediate release formulations which might enhance the patient compliance.

KEYWORDS : Transdermal patch; Non-ionic surfactants; Solvent casting method; Plasticizers; Permeation enhancers;

INTRODUCTION

There are a most of drugs for every disease or condition known to human and a variety these drugs are delivered to the human body for treatment such as tablets, capsules injections, creams, ointment, liquids etc., referred as conventional drug formulations. After administration of one dose, the drug concentration rises to high levels, as time goes on the concentration diminishes owing to natural metabolic processes and a second dose must be administrated to prevent the dropping of concentration below the minimum level to maintenance of drug concentrations in body within therapeutically effective range [1, 2]. Therapy with such formulations involves by introduction of fixed doses of drug, at regular intervals in to the body.

Recently, it is becoming evident that the benefits of i.v drug infusion can be closely duplicated, without piercing, by using the skin as the port for drug administration [3]. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms in which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation [5]. Transdermal route has advantages over conventional modes of drug administration as it avoids hepatic first pass metabolism and improves patient compliance [6]. The main goal of transdermal products dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin.

Darifenacin hydrobromide is used to treat overactive bladder syndrome which is characterized by high frequency of urination. It works by blocking the M3 muscarinic acetylcholine receptor, which is primarily responsible for bladder muscle contractions. It thereby decreases the urgency to urinate. It undergoes extensive first pass metabolism with 15% and 19% bioavailability following oral administration of 7.5 and 15 mg doses respectively. It requires repeated dosing because of its short half-life (3 hrs). This creates the need for an alternative route of administration of drug, which can bypass the hepatic first-pass metabolism. Transdermal route is an alternative choice for the route of administration of the drug [7]. In the present study darifenacin hydrobromide is formulated as transdermal patch.

EXPERIMENTAL METHODOLOGY

Solvent Casting of placebo films: Specified quantities of the polymers (PVA, PVP, HPMC E15, HPMC E5) were dissolved in the solvents by soaking them for 8-12 hrs and then plasticizers like glycerol, propylene glycol were added. The solution was sonicated for few seconds. The solution was poured in to Teflon petridishes. The plates were kept in oven for 24 hrs.

Casting of drug loaded films: Specified quantity of drug was dissolved and subjected to vortex mixing for few minutes. To the polymeric solution drug solution was added. plasticizer was incorporated into Teflon petridishes. The plates were kept in oven for 24hrs.

The prepared patches were evaluated for physicochemical properties like drug content, thickness, weight variation, folding endurance, moisture uptake, water vapour transmission studies. Drug release studies by *in-vitro* diffusion, *ex-vivo* permeation as well as skin irritation.

Table 1: Formulation of transdermal patches using Tween 20

S.No	Form. code	PVA (%)	PVP K30 (%)	HPMC E5 (%)	HPMC E15LV (%)	Propylene glycol (%)	Glycerol (ml)	Tween 20 (%)
1	DPAT1	4	1	-	-	-	0.26	0.2
2	DPAT2	3	2	-	-	-	0.26	0.2
3	DPAT3	2	3	-	-	-	0.26	0.2
4	DPAT4	1	4	-	-	-	0.26	0.2
5	DPHT1	-	4	1	-	0.23	-	0.2
6	DPHT2	-	3	2	-	0.23	-	0.2
7	DPHT3	-	2	3	-	0.23	-	0.2
8	DPHT4	-	1	4	-	0.23	-	0.2
9	DPLT1	-	1	-	4	0.23	-	0.2
10	DPLT2	-	2	-	3	0.23	-	0.2
11	DPLT3	-	3	-	2	0.23	-	0.2
12	DPLT4	-	4	-	1	0.23	-	0.2

Table 2: Formulation of transdermal patches using Span 20

S.No	Form. code	PVA (%)	PVP K30 (%)	HPMC E5 (%)	HPMC E15LV (%)	Propylene glycol (%)	Glycerol (ml)	Span 20 (%)
13	DPAS1	4	1	-	-	-	0.26	0.2
14	DPAS2	3	2	-	-	-	0.26	0.2
15	DPAS3	2	3	-	-	-	0.26	0.2
16	DPAS4	1	4	-	-	-	0.26	0.2
17	DPHS1	-	4	1	-	0.23	-	0.2

18	DPHS2	-	3	2	-	0.23	-	0.2
19	DPHS3	-	2	3	-	0.23	-	0.2
20	DPHS4	-	1	4	-	0.23	-	0.2
21	DPLS1	-	4	-	1	0.23	-	0.2
22	DPLS2	-	3	-	2	0.23	-	0.2
23	DPLS3	-	2	-	3	0.23	-	0.2
24	DPLS4	-	1	-	4	0.23	-	0.2

Evaluation of prepared transdermal patches

The prepared patches were evaluated for physicochemical properties like drug content, thickness, weight variation, folding endurance, moisture uptake, water vapour transmission studies. Drug release studies by *in-vitro* diffusion, *ex-vivo* permeation as well as skin irritation.

1. Compatibility studies by Fourier Transforms Infrared Spectroscopy (FTIR)

To ensure the compatibility between drug and excipient, this study was performed. Fourier transform infrared spectra were obtained for pure drug darifenacin hydrobromide and liquid FTIR studies were carried out to the prepared formulations with various excipients and their compatibility was checked. Potassium bromide disc method used to obtain the FTIR spectrum. The dry samples were obtained by applying 10 tons/inch^2 pressure for 10 min to prepare the pellet.

2. Physicochemical Evaluation of transdermal patch [5, 8, 9,10]

A) Thickness of the patch

The thickness of the prepared patch is measured by using a digital micrometer at different regions of the patch and the average thickness is determined, to ensure the thickness of the prepared patch.

B) Folding Endurance

Folding endurance were measured, and will be expressed by number of times the patch is folded at the same place to check either to develop visible cracks or to break the patch. This is essential to check the withstand of sample ability to folding. This also referred to brittleness.

C) Weight variation

For this randomly selected patches were used for weight variation test, 3 films from each batch were weighed individually and then average weight was considered.

D) Water vapour transmission (WVT)

The quantity of moisture transmitted through unit area of a patch in unit time is called as water vapour transmission. The WVT data for transdermal patches to know the permeation characteristics of patch. As transmission cells glass vials of equal diameter were used. These transmission cells were washed and dried thoroughly, then about 1 gm of fused calcium chloride as a desiccant was taken in the vials and then polymeric patches were fixed over the brim with the help of glue tape. These preweighed vials were stored in a humidity chamber at an RH of 80% with the temperature set to 30 ºC for a period of 24 hours. After 24 hours, the weight gain will be determined for every hour up to 24 hours. The water vapour transmission rate was calculated using the following 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;

E) Moisture Uptake

Preweighed films are placed in a desiccator chamber, where a humidity condition of 75%RH was maintained by using saturated solution of sodium chloride. After three days the films were reweighed. The percentage of moisture uptake was calculated by using the formula.

$$\%\ Moisture\ Uptake = \frac{Final\ Weight - Initial\ Weight}{Initial\ Weight}\ X\ 100$$

3. *In-vitro* diffusion studies

For diffusion study, the dialysis membrane was mounted between the donor and receptor compartments was performed using fradnz diffusion cell. Patch formulation (2cm x 2cm) was applied uniformly on the dialysis membrane and the compartment clamped together. The receptor compartment was filled with phosphate buffer pH 7.4 and magnetic bead was used to in the receptor compartment for stirring. At pre-determined time intervals, 1ml of samples were withdrawn and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 285.6 nm.

4. *Ex-vivo* studies

For *ex-vivo* studies, the cell will be taken, which consists of two chambers, the donor and the receptor. The donor compartment is open and exposed to the atmosphere. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37°C ± 2°C and is provided with a sampling port. The abdomen rat skin containing patch was mounted between the two compartments. The diffusion medium was phosphate buffer of pH 7.4, which was stirred with magnetic bead (operated by a magnetic stirrer). Diffusion media was stirred to prevent the formation of concentrated drug solution just beneath the membrane. 1 ml sample from the receptor compartment were taken at various intervals of time over a period of 24 hours and an equal volume of buffer was replaced, then samples were analyzed spectrophotometrically.

Drug release kinetics [11, 12]

The results obtained from ex-vivo release studies of the optimized formulation was attempted to fit into various mathematical models. The regression coefficient (r2) values of zero order, first order, Higuchi and Korsmeyer-Peppas are tabulated.

5. Skin irritation studies [11, 12]

A protocol for the study was prepared. After approval from Institutional Ethics Committee the study was conducted as per protocol. Skin irritation test was conducted to test the different formulations of patch upon the rabbit skin. Test was performed on two healthy rabbits weighing between 1.5-2 kg. The hair on the ventral surface of animal was removed using the depilator. The test formulations were applied on the depilated area of the animal and kept under observation for 3days. Symptoms of flushing (redness of skin), papules, wheals and erythema, vesciles and marked edema were observed.

RESULTS AND DISCUSSIONS

1. Compatibility studies by Fourier Transforms Infrared Spectroscopy (FTIR)

The IR spectral analysis of Darifenacin hydrobromide showed principal peaks at 1577.6, 1490.8, 1440.73, 1359.7 as shown in **Figure 1 (a)** in the IR spectra of the physical mixture of Darifenacin hydrobromide, PVA, HPMC E15 peaks were observed at similar wavenumbers. Characteristic drug peak was retained as such even in the physical mixture of drug and polymer which is evident from **Figure 1 (d & e)**. These results show that there is no interaction between the drug and polymer.

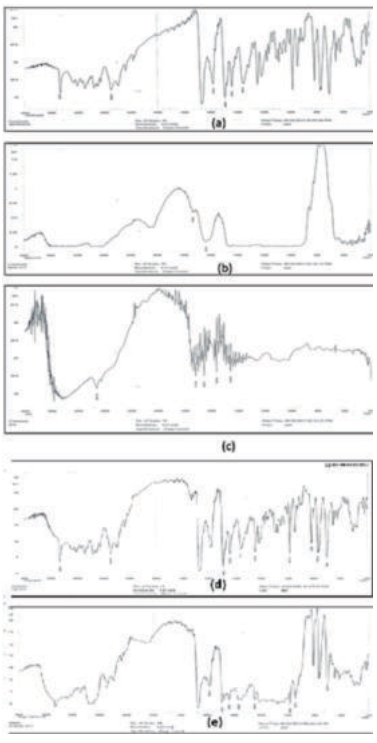

Figure 1: Ftir Spectra Of A) Pure Drug B) Pva C) Hpmc E15 D) Drug + Pva E) Drug+hpmc E15

2. Physicochemical evaluation of transdermal patches

The prepared patches were evaluated for physicochemical properties like drug content, thickness, weight variation, folding endurance, moisture uptake, water vapour transmission studies and, the observations are given in **Table 3.**

Table 3: Physicochemical evaluation of prepared patches

Formulation Code	Thickness (µm)±SD	Weight uniformity (mg) ±SD	Folding endurance	Percent moisture uptake ±SD	WVTR (gm/cm^2/hr)
DPAT2	110±1.16	40±1.15	>200	1.27±1.02	0.028±1.09
DPAT4	120±1.27	43±2.11	<150	1.41±1.03	0.031±1.05
DPHT1	150±1.18	51±1.9	<150	6.8±1.19	0.061±1.09
DPHT2	120±1.58	53±1.7	>200	0.91±1.19	0.059±1.02
DPLT2	140±1.45	46±1.22	>200	6.8±1.17	0.078±1.06
DPLT1	130±1.92	52±1.39	<200	1.7±1.366	0.076±1.02
DPAS2	115±1.29	49±1.3	>200	5.9±1.14	0.078±0.06
DPAS4	120±1.92	45±1.62	<200	0.56±1.64	0.059±0.02
DPHS1	125±1.32	53±1.36	<200	10.3±0.02	0.027±1.04
DPHS2	150±1.18	48±1.33	>200	8.6±0.6	0.049±1.05
DPLS2	120±1.58	55±1.62	>200	6.3±1.53	0.031±1.05
DPLS1	140±1.45	50±1.39	<200	9.8±1.3	0.061±1.09

Note: All the values expressed as mean±SD; n=3;

All the films were found to be uniform in their weight and thickness with low SD values. The weight variation was found to be in the range of 120-150 mg. The thickness was found to be in the range of 110-140 µm as shown in **Table 3**. The highest folding endurance was found to be greater than 200. DPAT4, DPHT1, DPLT2, DPAS4, DPHS1, DPLS2, were eliminated from the *in vitro* diffusion studies due to the folding endurance of these patches were found to be <200, all other formulations were selected for *in vitro* studies.

3. *In-vitro* diffusion studies

In-vitro diffusion studies of the prepared transdermal patches were carried using the Franz-diffusion cell. The diffusion profile is shown in **Figure 2.** From the *in-vitro* diffusion profiles, it is evident that DPAT2 prepared using Tween 20 and DPAS2 prepared using Span 20 as permeation showed maximum release of drug as shown in **Figure 2** were studied further for the *ex-vivo* studies.

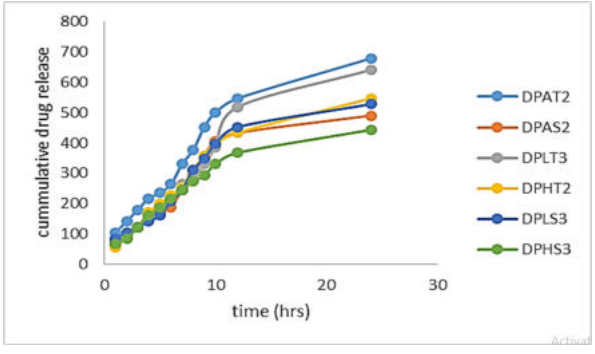

Figure 2. *In-vitro* diffusion profiles of patches prepared using Tween 20 and Span 20

4. *Ex-vivo* studies

Ex-vivo studies of the prepared patch were carried using rat skin. *Ex-vivo* profiles were shown in **Figure 3.** From the *ex-vivo* diffusion profiles, it is evident that DPAT2 prepared using Tween 20 and DPAS2 prepared using Span 20 as permeation showed maximum release of drug as shown in **Figure 3.**

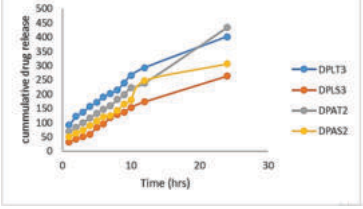

Figure 3. *Ex-vivo* profiles of patches prepared using Tween 20 and Span 20

Drug release kinetics

From the kinetic studies, it was observed that all the formulations as well as the optimized, DPAT2 followed zero-order kinetics from R^2 value 0.998 and the mechanism was found to be non-fickian from the n value 0.6 as shown in **Table 4.**

Table 4: Model dependent kinetics of patches

Form. Code	Zero order	First order	Higuchi	Korsmeyer- Peppas	n	Diffusion mechanism	Q24	Flux
	R^2	R^2	R^2	R^2				
DPAT2	0.9984	0.9013	0.947	0.96	0.5	Non-Fickian diffusion	433.9	15.9
DPAS2	0.9282	0.816	0.946	0.958	0.6	Non-Fickian diffusion	306.6	11.9
DPLT3	0.958	0.834	0.987	0.98	0.5	Non-Fickian diffusion	401.8	13.5
DPLS3	0.958	0.77	0.981	0.971	0.7	Non-Fickian diffusion	263.2	10.54

5. Skin irritation studies

The Skin irritation test was conducted to test the different formulations of patches upon the rabbit skin. There were no symptoms of flushing (redness of the skin), papules, wheals and erythema, vesciles and marked edema were observed. Skin irritation studies proved that the formulation was non-toxic and non-irritant.

CONCLUSION

Darifenacin hydrobromide transdermal patches were prepared successfully by solvent casting method. Among all the formulations, formulation with PVP K30 and PVA using tween20 as permeation enhancer showed better drug release rate, flux. Hence DPAT2 is considered as optimized formulation. The prepared transdermal formulation would reduce the administration frequency, side effects and may avoid fluctuations of drug level in the blood in comparison to immediate release formulations which might enhance the patient compliance.

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