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FORMULATION, DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES OF ANTIPSYCHOTIC DRUG OLANZAPINE

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ABSTRACT

Olanzapine containing transdermal patch was prepared utilizing solvent casting method. Characterization of transdermal patches carried out by Thickness, Percent moisture content, Percent moisture uptake, Folding endurance, Tensile Strength, Drug Content and *In Vitro* skin permeation study. In all formulations formulation F4 contain minimum moisture contain 1.52±0.41% and minimum moisture uptake 2.11±0.74%. The maximum folding endurance was found 182±5 in formulation F4. Drug content of the all formulations was determined by dissolving the transdermal patches in methanol followed by centrifugation and then analyze on UV spectrophotometry. The drug content was found more than 90% in all the formulations with slight fluctuation. The drug content analysis of different formulations was done according to the procedure given in section. The drug content ranged between 96.65±0.52 and 99.85±0.41. The percentage drug content of all formulations. The maximum drug content was found in formulation F3, 99.85±0.41%. It was concluded here that the formulation F4 showed better permeability amongst the prepared transdermal matrix type patches for olanzapine.

Keywords: Olanzapine, Transdermal patch, Eudragit RSPO, HPMC, Evaluation, *In Vitro* skin permeation study.

INTRODUCTION

Transdermal drug delivery system is self-contained, discrete dosage form in which drug stick to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream[1]. Till now total 16 active ingredients and more than 35 Transdermal drug delivery products have been approved for use globally and for sale in the US market. By statistics analysis it has been found that there is an increase in transdermal market which was $ 21.5 billion in the year 2011 and will be $31.5 billion in the year 2015 as compared to $ 12.7 billion in year 2005[2]. Oxybutinin drug molecule patch is largest (359 Da) and

nicotine drug molecule patch is smallest (162Da) [3]. Transdermal drug delivery permits controlled release of the drug into the patient, it enables a steady blood level profile which causes reduced systemic side effects and improved efficacy over other dosage forms [4-5]. The main aim of transdermal drug delivery system is to administer drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation with user friendly, convenient, painless, and is multi day dosing, it offers improved patient compliance too1. Patch formulation is a complex process.

The rate and amount of transdermal absorption depend on factors like nature of the drug, the drug's concentration in the reservoir or matrix, area of skin covered by the patch.The formulations used are identical but the patches have different surface areas for different strengths of delivered drug when several dose strengths of a drug patch are marketed (e.g., estradiol patches). Drug is placed in large amount in the patches to keep the concentration gradient suitable for absorption because the active ingredients act at low dosage and are inexpensive, the cost of wasted excess drug is not economically significant [6-11]. New advanced technologies like chemical enhancers [12]iontophoresis, electroporation[13]. pressure waves generated by ultrasound or photoacoustic effects [14,15] have been developed to enhance transdermal drug delivery for therapeutic and diagnostic purposes [16].

Olanzapine (sold under the brand names Lanzek, Zypadhera and Zyprexa or in combination with fluoxetine, Symbyax) is an atypical antipsychotic, approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar disorder. The preparation of matrix type transdermal patch appears to be a most effective approach from the process development and scale-up point of view. In the present investigation, an attempt was made to formulate Olanzapine Patch using Eudragit RLPO, Eudragit RLSO, HPMC, Ethyl Cellulose, and Polyethylene glycol 600, Glycerol, Chloroform and Methanol. Characterization of prepared matrix transdermal patches.

MATERIALS AND METHODS

Materials:

Olanzapine was received as a generous gift sample from pharmaceutical company. HPMC and ethyl cellulose from Himedia Pvt. Ltd. Mumbai. Methanol was purchased from Himedia Laboratories India, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Methods:

Preparation of matrix type transdermal patches

Olanzapine containing transdermal patch was prepared utilizing method given by Touitou et al., 2001 with slight modification[17]. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg) and ethyl cellulose, Eudragit RSPO (50, 100 and 150mg) in 10 mL of methanol

and chloroform and water mixture in ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (10 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover.

Table 1: Different Formulation used for Optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	60	350	-	150	500	0.5	10
F2	60	400	-	100	500	0.5	10
F3	60	450	-	50	500	0.5	10
F4	60	350	150	-	500	0.5	10
F5	60	400	100	-	500	0.5	10
F6	60	450	50	-	500	0.5	10

Dose calculation

Dose calculations

- Width of the plate (mould) = 5 cm
- Length of the plate (mould) = 12 cm
- No. of 2.5 x 2.5 cm patch present whole(mould) = 12
- Each film contains 5 mg of drug.
- 12 no. of films contains mg of drug? = 5×12 = 60mg
- The amount of drug added in each plate was approximately equal to 60 mg.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated[18].

Percent moisture content

Weighed individually the films (1cm^2) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content [19].

$$\%\ Moisture\ content = \frac{Intial\ weight - final\ weight}{\text{Intial weight}} \times 100$$

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity (Rh) using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved [20].

$$\%\ Moisture\ uptake\ = \frac{final\ weight - Intial\ weight}{\text{final weight}} \times 100$$

Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance[21].

Tensile Strength.

The tensile strength of the patch was evaluated by using the tensiometer (Erection and instrumentation, Ahmedabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg[22].

$$Tensile\ Strength\ (s) = \frac{Applied\ force\ (m * g)}{Cross\ sectional\ area(b * t)}$$

Where, S = tensile stress in 980 dynes/cm2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm2)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

Drug Content

The patches (2.5*2.5 cm (Equivalent to 6.25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. The solution was centrifuged to separate out any particulate matter. 1mL of sample was withdrawn and transferred in volumetric flask (10 mL of capacity). The sample was dilute upto the mark with distilled water and analyzed by UV spectrophotometer at 226.0 nm[23].

In Vitro skin permeation study

The *in vitro* skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 5 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. 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. The temperature of receptor compartment was maintained at 32±0.5ºC. The samples were withdrawn at different time intervals and analyzed for drug content. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval[23].

RESULTS AND DISCUSSION

Olanzapine containing transdermal patch was prepared utilizing solvent casting method. Characterization of transdermal patches carried out by Thickness, Percent moisture content, Percent moisture uptake, Folding endurance, Tensile Strength, Drug Content and *In Vitro* skin permeation study. All the formulation show lowest moisture content and moisture uptake i.e. less than 4%. Moisture in this value is required to provide strength and flexibility to the patches. In all formulations formulation F4 contain minimum moisture contain 1.52±0.41% and minimum moisture uptake 2.11±0.74%. The maximum folding endurance was found 182±5 in formulation F4. Drug content of the all formulations was determined by dissolving the transdermal patches in methanol followed by centrifugation and then analyze on UV spectrophotometry. The drug content was found more than 90% in all the formulations with slight fluctuation. The drug content analysis of different formulations was done according to the procedure given in section. The drug content ranged between 96.65±0.52 and 99.85±0.41 Table 2. The percentage drug content of all formulations. The maximum drug content was found in formulation F4, 99.85±0.41% Table 2.

Table 2: Results of characterization of transdermal patches

Formulation Code	Thickness (mm)	% Moisture Content	% Moisture Uptake	Folding Endurance	Tensile Strength (kg/cm)	% Drug Content
F1	85±4	2.25±0.45	3.69±0.52	145±4	0.82±0.05	97.45±0.85
F2	89±6	2.32±0.62	3.85±0.32	158±3	0.94±0.08	96.56±0.65
F3	92±3	2.15±0.32	2.98±0.14	182±5	0.89±0.06	98.85±0.23
F4	85±4	1.52±0.41	2.11±0.74	172±6	1.15±0.04	99.85±0.41
F5	89±2	2.35±0.85	3.52±0.21	165±4	0.97±0.07	97.89±0.54
F6	93±3	2.45±0.62	3.14±0.21	165±5	0.89±0.06	96.65±0.52

Values are represented as mean ±SD (n=3)

Table 3: *In Vitro* cumulative % drug release from optimized batch of transdermal patches F4

Time (Hrs.)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
0.5	0.707	-0.301	22.25	1.347	77.75	1.891
1	1	0	33.36	1.523	66.64	1.824
2	1.414	0.301	45.56	1.659	54.44	1.736
4	2	0.602	56.78	1.754	43.22	1.636
6	2.449	0.778	62.23	1.794	37.77	1.577
8	2.828	0.903	74.45	1.872	25.55	1.407
10	3.162	1	88.85	1.949	11.15	1.047
12	3.464	1.079	98.89	1.995	1.11	0.045

Values are represented as mean ±SD (n=3)

Conclusion

Flexible, smooth and transparent films were obtained with HPMC and Eudragit RSPO polymers. It was found that the transdermal patch containing polymers HPMC and Eudragit RSPO (350:150); 60 mg olanzapine for 12 patches; Propylene glycol 0.5% and 10% Permeation enhancer showed best release and permeation. Again, it was concluded here that the formulation F4 showed better permeability amongst the prepared transdermal matrix type patches for olanzapine.

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