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DEVELOPMENT AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF ZALEPLON

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ABSTRACT

At present scenario transdermal drug delivery systems has gained a lot of interest due to many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass effect, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance. Zaleplon is a pyrazolopyrimidine derivative having sedative and hypnotic properties. It's properties like low molecular weight, favorable logarithmic partition coefficient, smaller dose (1mg to 10mg), short elimination half-life and poor oral bioavailability (30.6±10.2%), indicates need to develop a novel drug delivery systems. Different transdermal patches were prepared using different polymers and evaluated on many parameters. Accelerated stability studies for 12 weeks revealed that the transdermal patches formulations were stable at up to 45^0C. The stability study of the optimized formulation showed satisfactory characteristics without being drastically influenced. Locally fabricated Franz diffusion cell was used for the in-vitro release study.

KEYWORDS: Zaleplon, transdermal patches, HPMC, in-vitro release, stability studies, TDDS.

INTRODUCTION

At present scenario, humans are using a lot of substances to their skin as cosmetics and therapeutic agents. About two third of drugs available in market are taken orally, but these are not so effective[1]. An ideal dosage form maintains the drug concentration in the blood at a constant level nearly coinciding with the minimum effective concentration of drug throughout the treatment period. This leads to the concept of the controlled drug delivery.[2]

Transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations associated with conventional as well as parenteral route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both.[3] A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream.[4]

Zaleplon is a pyrazolopyrimidine hypnotic drug indicated for the treatment of insomnia. Zaleplon interacts with GABA A receptor. Zaleplon is a new non-benzodiazepine hypnotic agent indicated for the short-term treatment of insomnia. It also possess some pharmacological properties of benzodiazepines.[5] Zaleplon is well absorbed, but its absolute bioavailability is approximately 30% because it undergoes significant presystemic metabolism.[6]

Zaleplon was selected as a candidate for the drug delivery because[7, 8]

a. It has a low molecular weight 305.54 g/mol.
b. Poor oral bioavailability (30.6±10.2%)
c. It has melting point i.e. 158ºC that is suitable to develop a transdermal drug delivery system
d. Smaller dose (1mg to 10mg).
e. It has short elimination half-life (1.05±0.13h).
f. Favorable logarithmic partition coefficient (log octanol/water: 1.23).

So, all these properties makes Zaleplon a suitable candidate for transdermal dosage form.

MATERIALS AND METHODS

Zaleplon and HPMC K100 was received as gift sample from Cipla, Ltd., Mumbai, HPMC K100. Ethyl cellulose, Eudragit RS 100 was received as gift sample from Asia private ltd.Goa and Chitosan from Central Institute of Fisheries, Cochin. All other chemicals were of analytical grade.

General procedure for fabricating the drug free films

A fixed volume of polymer solution with plasticizer was poured onto a glass petri dish of area 56.77 cm^2 (inner diameter 8.5 cm and height 2 cm). The Petri dish was placed on an even and smooth surface to ensure uniform spreading of the polymer solution. It was then placed in an oven. An inverted funnel was placed on the Petri dish to facilitate the evaporation of the solvent at the controlled rate over the drying periods of 12 hrs at 40 °C. The film thus formed was retrieved by cutting along the edges with a sharp razor blade.[9]

General Procedure for fabricating the Zaleplon loaded polymeric films

The drug loaded polymeric films were prepared in a similar manner described above except that a weighed quantity of the drug Zaleplon was dissolved to the polymer solution containing the plasticizer. This solution was poured into a glass petri dish. An inverted funnel was placed on it to control the rate of evaporation. The whole assembly was maintained at 40°C in hot air oven.

At the end of the 12 hrs the film was lifted from the surface of Petridish after the cutting the edges with a sharp razor. The film thus formed was neutralized with 2 % NaOH and dried. After that the film was isolated and wrapped in an aluminium foil and stored at 79.5 % relative humidity chamber (desiccator) containing solution of ammonium chloride until further use.

Table-1: Compositions of the Zaleplon transdermal patches

Batch Code	Polymer Ratio	Solvent	Plasticizer
TP1	Chitosan :Ethyl cellulose:: 20:80	Acetic acid (1 % w/v)	Castor oil (20%)
TP2	HPMC:PVP K30::20:80	Dichloromethane (2% w/v)	Glycerine (20%)
TP3	Eudragit RS 100: PVP K30::20:80	Acetic acid (1% w/v)	Glycerine (20%)
TP4	Ethyl cellulose: PVP K30::20:80	Dichloromethane (2% w/v)	Castor oil (20%)

200 mg drug was incorporated in each batch

Evaluation

Physical Properties

1. Thickness[10]

The thickness of each film was measured at five different places by means of a screw gauge.

2. Weight Uniformity[11]

Five patches (area = 2.009 cm^2) of each film were weighed accurately and the average weight of the patch was found out.

3. Content Uniformity[12]

To determine the amount of Zaleplon in the patches, the patch of 2.009 cm^2 area was dissolved in 10ml of phosphate buffer solution (pH 7.4) and then after dilution the amount was measured spectrophotometrically at 232 nm.

4. Folding Endurance[13]

The folding endurance of the patch was determined by repeatedly folding one patch at the same place up to 290 times, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

5. Percentage moisture loss[14]

The films were weighted accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula.

$$\% \text{ Moisture loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

6. Percentage moisture content[15]

The prepared films were weighed individually and kept in a dessicator containing silica at room temperature and the films were weighed again and again until they showed a constant weight. The percentage moisture content was calculated using the following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

7. Percentage moisture absorption[16]

The films were weighed accurately and placed in the desiccator containing 100 ml of saturated solution of aluminium chloride which maintains 79.50% RH. After 3 days the films were taken out and weighed. The percentage moisture absorption was calculated using the formula.

$$\% \text{ Moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} X100$$

8. Water vapour transmission rate (WVTR)[17]

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly an dried in an oven. About 1.0 g of fused calcium chloride was taken in the cells and the polymeric films

measuring 2.009 cm^2 area were fixed over the brim with the help of an adhesive.

The cells were weighed accurately and initial weight is recorded and then kept in a closed desiccator containing saturated solution of potassium chloride (200ml), containing humidity between 80-90% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6, and 7^{th} day of storage. From increase in the weights the amount of water vapour transmitted and rate at which water vapour transmitted were calculated as shown below.

$$WVTR = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time x Area}} X100$$

9. Flatness[18]

Longitudinal strips of 1.6 cm in length were cut out from the prepared medicated film and than variation in the lengths due to the non-uniformity in flatness was measured.

Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{l1 - l2}{l2} X100$$

Where, l_1 = final length of each strip, and l_2 = initial length

10. In-vitro release studies[19]

A modified Franz-diffusion cell which is also called Keshary – Chein cell was fabricated to study the *in-vitro* release profile from the films of diffusion cell with an improved efficiency in fluid mixing. The diffusion cell consists of two cylindrical compartments in vertical arrangement, a donor compartment which was exposed to ambient temperature and a receptor compartment, which was maintained at 37^0C.

For the *in-vitro* study the patches were stuck to an aluminum foil which was previously cut to have a diameter of 2 cm and a slightly larger patch was fixed using an water-impermeable adhesive to ensure that the receptor fluid does not come in contact with the sides of the films.

Before placing the patch fixed on to the diffusion cell, the mouth of the cell was coated with a thin layer of silicone grease to prevent leakage of the receptor fluid 1 ml of the receptor fluid was withdrawn at periodic interval for 10 hrs. It was immediately replaced with 1 ml of fresh drug free buffer (pH 5.0) solution to maintain constant volume. The fluid removed, after suitable dilution with phosphate buffer was analyzed spectrophotometrically at 232 nm and the concentration were noted from the calibration curve.

12: Stability study[20]

Stability studies carried out by storing the prepared transdermal patches of batch TP1, at various temperature conditions like refrigeration on (2-8^0C) room temperature (25±0.5^0C) and elevated temperature (45±0.5^0C) for a period of 12 weeks. Drug content and variation in the average vesicle diameter were periodically monitored. ICH (International Conference on Harmonisation) guidelines were followed.

RESULTS AND DISCUSSION

Four transdermal patches formulations of Zaleplon were prepared by using different polymers i.e. HPMC, chitosan, PVP K30, EC, Eudragit RS 100 in different ratio. Thickness lies in the range of 0.031 to 0.039 mm. Though the average thickness was almost uniform within same formulation a small variation in thickness was observed with different formulations. The variations in thickness may be attributed to viscosity of polymer solutions of different formulations. The other reasons may be due to lack of temperature control which have affected the controlled evaporation of solvent from the wet film surface. An increase or decrease in thickness had a direct relationship with weight of the patch and drug content. The weight of patches lies in the range of 42.3 to 47.2 mg. The % drug content analysis of prepared formulations has shown that the process employed to prepare the study of the patches, was capable of giving uniform drug content and minimum batch variability.

The % drug content lies in the range of 96.41 to 98.31. Content uniformity studies proved that the amount of Zaleplon in each patch of 2.009 cm^2 was found to be fairly uniform containing 13-15 mg of Zaleplon. Percent moisture absorption was found to be in the range of 4.328 to -6.342, largest in formulations of batch code TP1 and least in the batch code TP2.

Percent moisture content was found to be in the range of 2.45 to 3.25.

The values of the % MA, % ML, % MC, WVTR in the patches containing Eudragit RS 100 can be explained on the basis of hydrophilicity, which is least in Eudragit RS 100 whereas PVPK30 is the hydrophilic polymer.

The folding endurance was measured manually; films were folded 290 times and if the films shows any cracks it was taken as the end point The folding endurance represents the elasticity of the patches.

Table-2: Physical Characterization of transdermal patches.

	TP1	TP2	TP3	TP4
Physical Appearance	**Hard and tough**	**Smooth tough**	**Smooth flexible but wrinkled**	**Smooth tough**
Thickness (mm) ± SD	0.031 ± 0.01	0.033 ± 0.17	0.035 ± 0.21	0.039 ± 0.08
Mass uniformity (mg)	45.2 ± 0.24	44.7 ± 0.02	42.3 ± 0.08	47.2 ± 0.11
% Drug content	98.31± 0.12	98.31± 0.31	96.42± 0.09	96.41± 0.21
% Moisture Content	3.25 ± 0.18	2.45 ± 0.15	2.69 ± 0.16	2.65 ± 0.13
% Moisture absorption	6.342 ± 0.07	4.328 ± 0.89	5.355 ± 0.54	4.482 ± 0.34
% Moisture loss	3.881± 0.14	2.552 ± 0.15	3.224 ± 0.08	3.532 ± 0.04
WVTR (g/cm^2/hrs	1.427X10^{-4}± 0.09	1.528 X10^{-4}± 0.24	1.531X10^{-4}±0.08	1.147X10^{-4}± 0.12
Folding endurance	> 244	> 255	> 263	> 288
Flatness	100%	100%	100%	100%

mean ± SD, N=3

The in-vitro permeation of Zaleplon transdermal patches formulation was studied using locally fabricated Franz diffusion cell. The cumulative percent drug release after 10 hrs in between 34.28 to 86.42. Largest in batch code TP1 and least in formulations of batch code TP3.

Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used.

These results indicates hydrophilic nature of polymer PVP K30. Chitosan are more hydrophilic as compared to Eudragit RS 100. Hydrophobic polymer have less affinity for water this results in decrease in thermodynamic activity of the drug in the film and decreased drug release. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the facts that dissolution of the aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to a decrease in the mean diffusional path length of the drug molecules to release into the diffusion medium and hence to higher release rates.

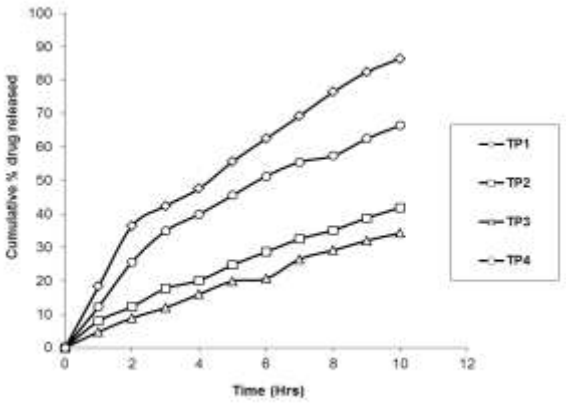

Figure-1: Percentage of drug released from Zaleplon transdermal patches.

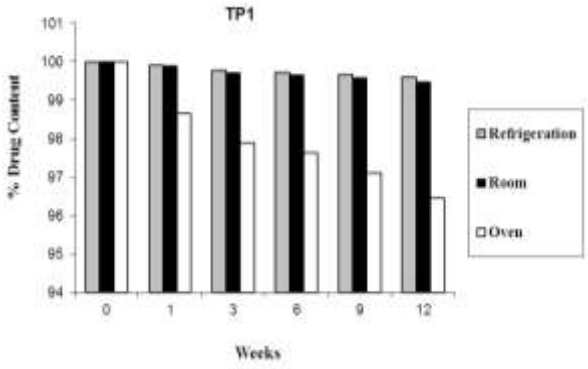

Figure-2: Stability study of Zaleplon transdermal patches of batch TP1 at different temperature.

Accelerated stability studies for 12 weeks revealed that the transdermal patches formulations were stable at up to 45^{0}C. The results showed that transdermal patches formulation was quite stable at refrigeration and room temperatures as not much leakage of drug was found at these temperatures.

Therefore, the selected transdermal patches formulations can be stored at either refrigeration or room temperature. The pure drug shows sensitivity to light and moisture.

CONCLUSION

Four Zaleplon transdermal patches formulations were successfully developed by using different polymers i.e. HPMC, PVP K30, Chitosan, EC with a view of improving its oral bioavailability and giving a prolonged release of drug. Accelerated stability studies for 12 weeks revealed that the transdermal patches formulations were stable at up to 45^{0}C. The stability study of the optimized formulation showed satisfactory characteristics without being drastically influenced.

On basis of different physical properties of patches, in-vitro release and stability studies, it can be concluded that formulation TP1 was an optimum formulation.

Therefore it may be concluded that the transdermal patches are suitable system for the controlled release of Zaleplon.

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REFERENCES

1. Shivakumar HN, Jamakandi VG, Mulla JS, Vinay BL, Formulation, characterization and evaluation of matrixtype transdermal patches of a model antihypertensive drug. Asian J Pharm, 2009; 3: 59-64.
2. Rao V, Mamatha T, Mukkanti K, Ramesh. Transdermal drug delivery system for atomoxetine hydrochloride- in vitro and ex vivo evaluation. Current Trends in Biotechnology and Pharmacy, 2009; 3(2): 188-96.
3. Ubaidulla U, Reddy MVS, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPS Pharm Sci Tech, 2007; 8(1): E13-20.
4. Okabe H, Obata Y, Takayama, K, Nagai T. Percutaneous absorption enhancing effect and skin irritation of monocyclic monoterpenes. Drug Des Deliv., 1990; 6: 229-238.
5. Kristin Wiisanen Weikel, Julie M. Wickman, Sara Grimsley Augustin, and J. Grady Strom, New Drugs Zaleplon: A Pyrazolopyrimidine Sedative-Hypnotic Agent for the Treatment of Insomnia, Clinical Therapeutics, 2000; 22(11): 16-22.
6. B Beer, DE Clody, R Mangano, M. Levner,P. Mayer. A Review of the preclinical developmentof zaleplon, a novel non-benzodiazepine hypnotic for the treatment of insomnia, CNS drug reviews, 1997; 3(3): 207-224.
7. C F P George, The Lancet, 2001; 358(10): 1623-1625.
8. Venkata Ramana Reddy, Sathyanarayana Dondeti, Manavalan R, Sreekanth J. Development and Characterization of compressed ODT formulation of insoluble low bitter drug, International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(2): 102-106.
9. De P, Damodharan N, Mallick S, Mukherjee B. Development and evaluation of nefopam transdermal matrix patch system in human volunteers. PDA J Pharm Sci Technol., 2009; 63(6): 537–46.
10. Rao PR, Diwan PV. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Dev Ind Pharm., 1998; 24: 327–336.
11. Jain NK, Thomas NS, Panchagnula R. Transdermal drug delivery of imipramine hydrochloride I Effect of terpenes, J Control Release., 2002; 79: 93-101.
12. Panchagnula R, Bokalial R, Sharma P, Khandavilli S. Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies, Int J Pharm 2005, 293, 213-223.
13. Tymes NW, Shah VP, Skelly JP. In vitro release profile of estradiol transdermal therapeutic systems, J Pharm Sci 2006, 79, 601-602.
14. Siewert M, Dressman J, Brown CK, Shah VP. FIP/AAPS guidelines to dissolution / in vitro release testing of novel/ special dosage forms, AAPS Pharm Sci Tech. 2003; 4: 7.
15. Fox LT, Gerber M, Plassis J Du, Hanman JH, Transdermal drug delivery enhancement by compounds of natural origin; Molecules, 2011; 10507-10540.
16. Sood A, Panchagnula R. Role of dissolution studies in controlled release drug delivery system, STP Pharma Sci, 1999; 9: 157-168.
17. Higuchi T. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J Pharm Sci, 1963; 52: 1145-1149.
18. Sankar V, Sivanand V. Design and Evaluation of Nifedipine Transdermal Patches, Indian J Pharm Sci, 2003; 65(5): 510 – 515.
19. Priyanka Arora, Biswajit Mukherjee. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethyl ammonium salt. Journal of pharmaceutical sciences, 2002; 91(9): 80-84.
20. Jain, S. K. Sabitha, M., Jain, R., Development and Characterization of Transdermal Drug Delivery Systems for Diltiazem Hydrochloride, Drug Delivery, 2003; 10: 169-177.