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Formulation and Evaluation of Transdermal Patches of an Anti anxiety Drug

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ABSTRACT

The objective of the present investigation was to achieve controlled and long term Zolpidem tartrate therapy for managing anxiety disorders. The matrix type transdermal drug delivery was prepared by film casting technique. The formulations were characterized and evaluated for various parameters including *in vitro* drug release & skin permeation studies.. The impact of different ratio of matrix forming polymer namely Eudragit RL 100 and Eudragit RS100 with PVP K 30 on the *in vitro* drug release was assessed. The results showed that cumulative drug release for 48 hrs of different formulations ranged between 66-81 %.The corresponding values for cumulative amount of drug permeation varied between 60-80%.. A greater amount of the sustained effect of the drug was achieved by this novel transdermal delivery.

Keywords: Transdermal drug delivery, skin permeation, zolpidem tartrate, anxiety.

1. INTRODUCTION

The intrinsic inability of the conventional dosage forms to achieve spatial placement is the compelling motive for the development of controlled release drug delivery systems, one of which is Transdermal delivery systems (TDS)[1-2]. The Transdermal route of administration is an attractive alternative delivery system for the drugs with numerous advantages over the oral as well as hypodermic injections. TDS provide a steady plasma level in the therapeutic range for long time period and are useful mode of delivery in long duration therapy like anxiety[11-12].

Anxiety is a universal phenomenon and if its symptoms persist in a severe form mental impaired performance can occur. Benzodiazepines and non benzodiazepines are used for the treatment of anxiety.
Zolpidem belongs to the class of imino pyridines and has a short half life of 2-3 hours[3-5]. It has to administered in divided doses which may lead to patient non compliance. It undergoes hepatic first pass metabolism , has low molecular weight of 764 and has high partition coefficient of 3.85.All these characteristics indicate it to be an appropriate candidate for TDS[6-7].

The rationale of the present study was to develop and evaluate a Transdermal therapeutic system for Zolpidem tartrate which could maintain the desired therapeutic concentration of the drug for 48 hours.

2. MATERIALS AND METHODS

Zolpidem tartrate was obtained as a kind gift sample from Anglo French Pharmaceuticals. Eudragit RL& RS were gifted by Rohm Pharma(Germany) and PVP-K30 by La Grade(P) Ltd. Dimethyl sulfoxide (DMSO),PEG400, Dimethyl formamide(DMF), sodium lauryl sulphate(SLS) dimethyl acetamide , menthol, sodium hydroxide, thymol, silica gel were purchased from SD Chemicals. Methanol & acetonitrile (H.P.L.C.) grade were procured from Rankem. Oil of Ylang ylang and Basil oil was purchased from M/s Blosoom Kosher.

Solubility studies

Solubility of the drug was evaluated in different solvents. This was done by adding excessive amount of the drug in 10 ml of the solvent and stirring for 24 hrs at the room temperature. It was then filtered and the weight of filter along with excess undissolved drug was weighed after drying.

In Vitro skin permeation studies of the pure drug

The *in vitro* drug permeation was carried out using Franz Diffusion Cell. The skin from the abdominal region of the albino wistar rats was excised and mounted between two half cells of the cell. The receptor compartment was filled with phosphate buffer of pH 7.4. The receiver fluid was stirred with a magnetic rotor at a speed of 50 rpm and the temperature was maintained at 37º$\pm$ 0.5 ºC. The whole buffer solution was replaced with the fresh buffer after every 15 mins. After the stabilization of the skin, the receptor compartment was filled with drug solution (10mg/ml) in various vehicles under study, with or without permeation enhancers. The samples were withdrawn (1ml) at various intervals of time for 24hours and analysed by UV spectrophotometer at 243 nm to determine the amount of the drug permeated through the skin.

Preparation of Transdermal patches

A monolithic matrix system was developed for the transdermal delivery of Zolpidem tartrate using solvent evaporation technique. A number of placebo transdermal films were developed to find an optimum combination of polymer, plasticizer and solvent system. The formula for optimized placebo film was utilized for the formation of medicated films. A homogenous mixture of the polymer (Eudragit RL 100 + PVP K-30 and Eudragit RS 100+ PVP K30), plasticizer (dibutyl phthalate) and penetration enhancer (ylang ylang oil) along with the drug(14%w/w) was dissolved in solvent mixture (methanol and dichloromethane; 50:50 w/v) and poured carefully in the aluminium pocket of the casting assembly. The assembly was placed in hot air oven maintained at 32 ºC $\pm$ 0.5 ºC. An inverted funnel was placed over the petridish to prevent the rapid evaporation of the solvent and also to prevent cracking of the films. The open end of the funnel was plugged with cotton wool to allow the uniform evaporation of the solvent. After 12 hours all the dried films were cut with the help of die and stored in desiccators. The

solvent was allowed to evaporate at ambient conditions (32 ºC RH 45%) for 24 hours. The dried films including the aluminum foil laminate were cut into patches with a circular metallic die to give patches of 6.74 cm^2 area. An adhesive tape was then laminated on the backing film. Finally, a thin aluminium foil was placed on the other side as the release liner. The patches were then stored in airtight containers in ambient conditions for 7 days prior to use.

Evaluation of the prepared Transdermal patches

The prepared patches were evaluated for the following properties:

Thickness of the patch

The thickness of the patches was measured by Screw gauge. The patch was gently held between the jaw of the instrument and readings were noted.

Weight uniformity

The mass of the film (one patch size) was determined using digital balance. The average values were calculated from the individual weight.

Folding endurance

The folding endurance is defined as the number of times the film can be folded at the same area without breaking. The film was cut of uniform size (2X3 cm^2). It was folded end to end on the longer side along the centre in between the thumb and the finger and it was open again This was called First fold. This was continued until cracks began to appear on the fold and the number of folds gave folding endurance.

***In Vitro* drug release studies**

A modified paddle over disc assembly (USP XXIII) was used for the assessment of the release of the drug from patches. The patches were mounted on the disc with the release surface facing upwards. The dissolution medium was 900 ml isotonic phosphate buffer (IPB) of pH 7.4. The apparatus was equilibrated to 37 ºC $\pm$ 0.5 ºC and operated at 50 rpm. The 5 ml sample was withdrawn at different intervals of time up to 48 hours and analyzed at 243nm (Beckman DU-64 spectrophotometer,USA) The readings were taken in triplicate.

***In Vitro* skin permeation studies**

The *In vitro* skin permeation study was carried out with the abdominal rat skin using Franz Diffusion cell. The cell consisted of two half cells with an area of 9 cm^2 and the capacity of 40 ml. The temperature of the receiver chamber was maintained at 37$\pm$0.5 ºC with the help of water bath. The skin was thawed to room temperature prior to use and it was mounted such that the stratum corneum faced the donor cell and the dermis was placed such that it faced the receiver cell. The receptor chamber was filled with Phospahte buffer 7.4 and was stirred with a Teflon coated magnetic rotor at 500 rpm. The aliquots (5 ml) were withdrawn from the receiver chamber at predetermined intervals of time for 48 hours and volume was replenished by equal

quantity of pre warmed receiver solution. The drug content was analyzed by UV spectrophotometeric method at 243 nm.(Beckman DU-64 Spectrophotometer,USA)

3. RESULTS AND DISCUSSIONS

The present work was carried out to formulate a transdermal drug delivery system of Zolpidem tartrate using polymers like Eudragit RL 100, Eudragit RS 100 and PVP K 30.

The oil of ylang ylang was used as penetration enhancer and dibutyl phthalate was found to be suitable plasticizer. On the basis of solubility studies 1:1 ratio of dichloro methane and methane was selected as favourable solvent system. The concentration of polymers was optimized on the basis of weight variation, folding endurance and thickness of the placebo films. (Table 1)

Table 1: Evaluation tests of Placebo transdermal films

Placebo Films	**Thickness(µm)±S.D.**	**Weight(mg)±S.D.**	**Folding Endurance± S.D.**
P1	263±1.69	103±1.76	100±2.76
P2	215±1.55	244±2.39	144±4.33
P3	245±0.72	218±2.33	110±3.22

The selected placebo films were re-casted to form medicated films, by adding Zolpidem tartrate to the formula using the same technique with or without the addition of penetration enhancer.

Table 2: Composition of Zolpidem tartrate transdermal patches

Ingredients	**Formulation Code**									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Eudragit RL100(mg)	630	630	504	504	-	-	400	300	-	-
Eudragit RS100(mg)	210	210	-	-	504	504	-	-	400	294
PVP K30(mg)	-	-	336	336	336	336	400	500	400	546
Zolpidem tartrate(mg)	136	136	136	136	136	136	136	136	136	136
Methanol(ml)	3	3	3	3	3	3	3	3	3	3
Dichlromethane(ml)	3	3	3	3	3	3	3	3	3	3
Oil of ylang ylang(ml)	42	-	42	-	42	-	84	84	84	84
Dibutyl phthalate(mg)	168	168	168	168	168	168	168	168	168	168

Initially six medicated films were made(F1-F6) with the composition shown in (Table 2**)** The Formulations F1 & F2 showed the drug release of 56.585% and 32.774% in 48 hours while their *in-vitro skin* permeation was found to be 53.0121% and 33.862%.These formulations were rejected at this stage only. This outcome can be attributed to the water insoluble nature of acrylate polymers and the drug. The Transdermal systems in which the penetration enhancer was incorporated showed better result as compared to the systems without penetration enhancers in the order F3>F5>F4>F6 for *in-vitro* % cumulative drug release and % drug permeated. The addition of hydrophilic components like PVP enhances its release rate constants by leaching out

the soluble components. The formula for F3 & F5 was further modified in search of an optimized system by varying the polymer ratio and concentration of the penetration enhancer. The amount of oil of ylang ylang was increased from 5% -10%w/w of polymers to enhance the skin permeation of the drug. The transdermal system F7 containing Eudragit RL100 and PVP K30 (50:50) showed 74.75% of drug release and 71.30% of drug permeation in 48 hours. While the formulation F8 which had Eudragit RL100 and PVP K30 in the ratio of 40:60 showed 81.53% of drug release and 82.29% of drug permeation. In comparison the formulations F9 and F10 which consisted of different compositions of Eudragit RS100 and PVP K30 had less release. Such pattern can be explained by the fact that Eudragit RL100 is more water permeable than Eudragit RS100.

F8 depicted better drug release and permeation pattern as it had higher concentration of PVP K30.Hence it was found to be optimized formulation.

Table 3 : *In-vitro* drug release studies

Time (hrs)	ZAD-II	ZAD-IV	YAD-II	YAD-IV
0	0	0	0	0
0.5	16.12	22.49	12.3	7.58
1	24.48	25.99	16.44	10.02
2	26.79	32.02	19.35	12.7
4	30.31	36.31	25.15	23.19
6	32.6	41.15	27.26	26.34
8	36.38	46.95	30.03	30.53
10	39.9	49.24	32.38	35.02
12	46.27	51.55	35.62	38.75
14	49.7	53.07	37.98	39.64
16	54.22	57.53	39.49	45.59
24	60.62	62.93	45.56	50.1
28	**63.79**	**66.73**	**53.3**	**57.26**
32	**66.86**	**70.69**	**59.11**	**60.67**
36	**67.95**	**76.78**	**61.9**	**63.81**
40	**71.34**	**79.33**	**63.04**	**65.48**
48	**74.75**	**81.53**	**66.08**	**72.23**

Fig 1: *In-vitro* drug release studies

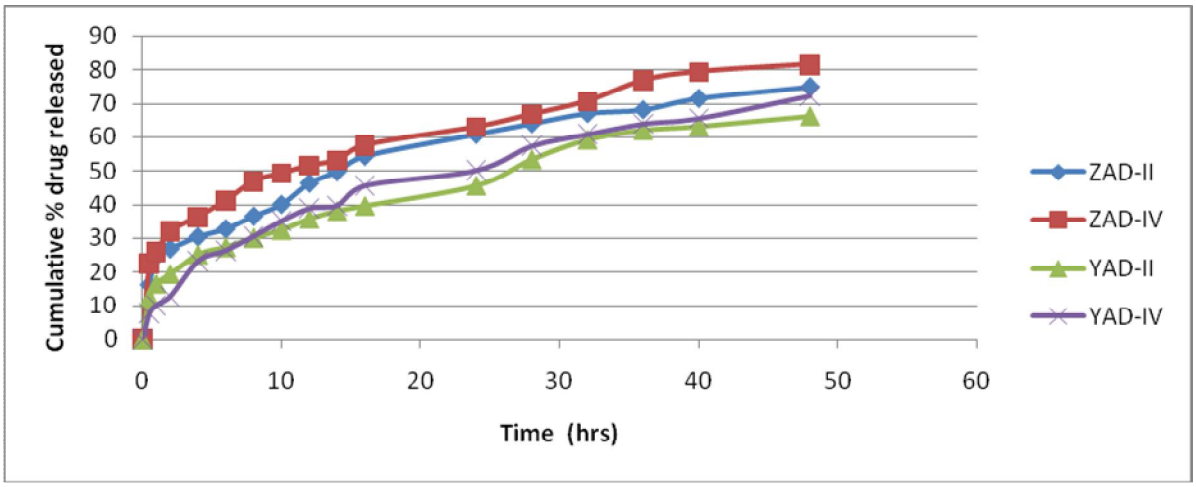
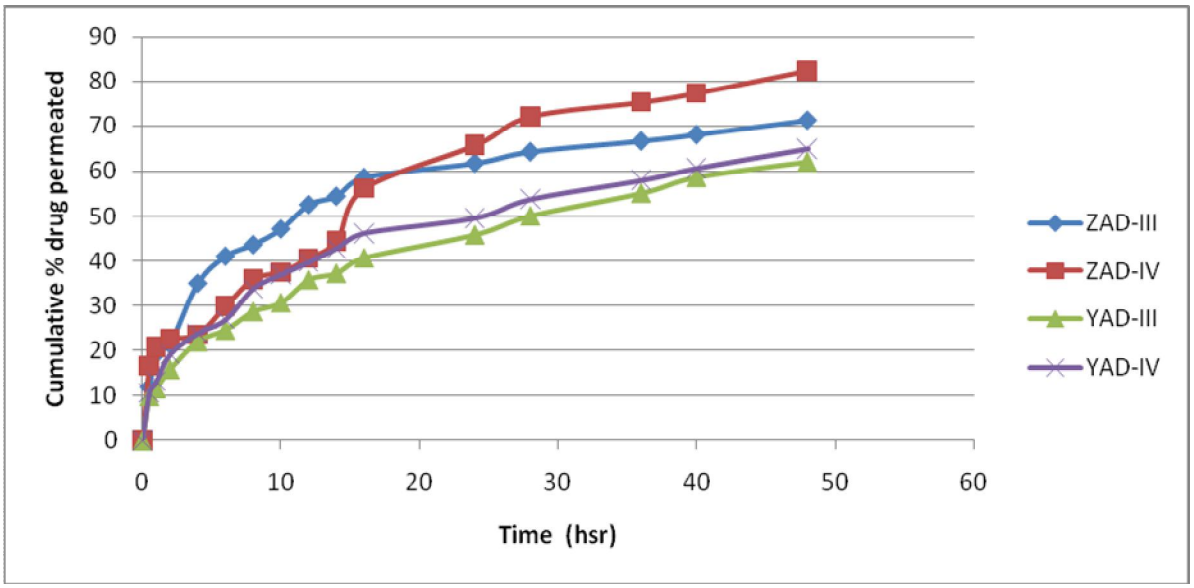


Table 4: *In-vitro* drug permeation studies

Time (hrs)	ZAD-III	ZAD-IV	YAD-III	YAD-IV
0	0	0	0	0
0.5	12.03	16.65	9.98	10.7
1	19.32	20.78	11.72	13.26
2	21.58	22.56	15.96	19.22
4	35.06	23.56	22.07	23.78
6	41.1	29.86	24.63	26.91
8	43.69	35.93	28.72	33.84
10	47.2	37.5	30.7	36.99
12	52.63	40.55	35.82	39.73
14	54.52	44.41	37.27	42.84
16	58.73	56.19	40.75	46.24
24	61.87	65.7	45.93	49.64
28	64.36	72.02	50.15	53.83
36	66.72	75.22	55.25	58.07
40	68.13	77.3	58.81	60.74
48	71.3	82.29	62.21	65.02

Fig2 : *In-vitro* drug permeation studies



4. CONCLUSION

In the present study F7 transdermal therapeutic system showed satisfactory results with respect to *in vitro* release and permeation studies .

This formulation contained Eudragit RL 100 and PVP K30 as polymers and PEG 400 and dibutyl phthalate as platicizers 10% oil of ylang ylang was the penetration enhancers.

The final formulation has potential for further *in vivo* studies.

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