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Study on the formulation of transdermal patches of zolpidem tartrate therapy

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Abstract
Getting a controlled and sustained dose of Zolpidem tartrate therapy for the treatment of anxiety disorders was the purpose of the current study. The technique of film casting was utilised in the preparation of the matrix type of transdermal drug delivery. In order to characterise and evaluate the formulations, various parameters such as *in vitro* drug release and skin permeation studies were conducted. The effect of varying ratios of matrix-forming polymer, specifically Eudragit RL 100 and Eudragit RS100, combined with PVP K 30 was investigated in terms of its influence on *in vitro* drug release. According to the findings, the percentage of cumulative drug release after 48 hours for each of the different formulations ranged anywhere from 66 to 81 percent. The values that corresponded to the cumulative amount of drug permeation ranged anywhere from sixty to eighty percent. This innovative method of administering the drug via the skin results in a greater amount of the drug's effects being maintained over time.

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

Introduction
The fundamental incapability of conventional dosage forms to achieve spatial placement was the main motivation for the creation of controlled release drug delivery systems, one of which being transdermal delivery systems (TDS). The transdermal route of administration is an attractive alternative delivery system for medications since it has various advantages over the oral route of administration as well as the injection route using hypodermic needles. TDS maintain a constant plasma level within the therapeutic range for an extended period of time and are an effective route of delivery for treatments with a long duration, such as those for anxiety.
Anxiety is a phenomenon that affects everyone, and if its symptoms continue to manifest in a severe form, mental performance may suffer as a result. The treatment of anxiety can involve the use of both benzodiazepines and other types of sedatives.
Zolpidem is a member of the imino pyridines class of drugs and has a short half life of only two to three hours. It is necessary to administer it in divided dosages, which may cause patients to not comply with the instructions. It has a low molecular weight of 764 and a high partition coefficient of 3.85, and it travels through the first pass of metabolism in the liver. The fact that it possesses all of these qualities suggests that it would make an excellent candidate for TDS. The purpose of the current research was to create and assess a transdermal therapeutic system for zolpidem tartrate that was capable of maintaining the desired therapeutic concentration of the drug for a period of forty-eight hours.

Materials and Methods
Anglo French Pharmaceuticals was kind enough to provide us with a sample of their Zolpidem tartrate medication. Both Eudragit RL& RS and PVP-K30 were provided free of charge by their respective companies, Rohm Pharma (Germany) and La Grade (P) Ltd. The following items were acquired from SD Chemicals: dimethyl sulfoxide (DMSO), polyethylene glycol 400 (PEG400), dimethyl formamide (DMF), sodium lauryl sulphate (SLS), dimethyl acetamide, menthol, thymol, and silica gel. Rankem was the supplier for the HPLC-grade methanol and acetonitrile that was needed. M/s Blosoom Kosher was the vendor who supplied the Ylang ylang oil and the basil oil that was acquired.

Solubility studies
The drug's soluble potential was tested in a variety of different solvents. To do this, an excessive quantity of the drug was mixed into 10 millilitres of the solvent, and the mixture

was stirred continuously at room temperature for twenty-four hours. Once that, it was filtered, and after it dried, the weight of the filter, as well as the extra drug that hadn't dissolved, was measured.

***In Vitro* skin permeation studies of the pure drug**

Franz Diffusion Cell was utilised for the drug permeation test that was performed *in vitro*. It was necessary to remove the skin from the abdomen region of the albino wistar rats so that it could be installed between the two halves of the cell. The phosphate buffer with a pH of 7.4 was injected into the receptor compartment. The receiver fluid was stirred with a magnetic rotor at a speed of 50 rpm and the temperature was maintained at 37º± 0.5 ºC. After every 15 minutes, the entire buffer solution was discarded and replaced with a brand-new buffer. After the skin had been stabilised, the receptor compartment was loaded with a drug solution at a concentration of 10 mg/ml in each of the several vehicles that were being investigated, with or without permeation enhancers. In order to quantify the amount of the drug that was absorbed via the skin, samples were taken (1 ml each) at various intervals of time over the course of 24 hours and analysed using an ultraviolet spectrophotometer set to 243 nm.

Preparation of Transdermal patches

Using the technique of solvent evaporation, a monolithic matrix system was designed in order to facilitate the transdermal distribution of zolpidem tartrate. Several different placebo transdermal films were created in an effort to identify the polymer, plasticizer, and solvent system configuration that produced the best results. The formula for an optimised placebo film was used in the production of medicated films instead of developing a new formula. A homogenous mixture of the polymer (Eudragit RL 100 + PVP K-30 and Eudragit RS 100 + PVP K-30), plasticizer (dibutyl phthalate), and penetration enhancer (ylang ylang oil), along with the drug (14 percent w/w), was dissolved in a solvent mixture (methanol and dichloromethane; 50:50 w/v), and then it was poured carefully in the aluminium pocket of the casting assembly. The assembly was placed in hot air oven maintained at 32 ºC ± 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. The backing film was then laminated with an adhesive tape on top of it. At long last, a piece of lightweight aluminium foil served as the release liner that was applied to the reverse side. After that, the patches were kept for a period of seven days in sealed containers at room temperature until they were used.

Evaluation of the prepared Transdermal patches

The prepared patches were evaluated for the following properties:

Thickness of the patch

The screw gauge was utilised to determine the thickness of the patches. The patch was handled carefully while being held in the instrument's jaws, and the readings were recorded.

Weight uniformity

Utilizing digital balancing, we were able to determine the mass of the film (at one patch size). The individual weights were used to calculate the mean and standard deviation of the values.

Folding endurance

The number of times that a particular portion of the film may be folded without tearing is what is meant by the term "folding endurance." The film was edited to an even size throughout (2X3 cm^2). It was folded in half lengthwise at the centre of the longer side in between the thumb and the finger, and then it was opened back up. This was referred to as the First fold. This was maintained until cracks started to develop on the fold, and the number of folds determined how durable the fold would be.

***In Vitro* drug release studies**

In order to evaluate the rate at which the medicine is released from patches, a USP XXIII paddle over disc assembly that had been modified was utilised. The releasing surfaces of the patches were oriented so that they were mounted on the disc so that they faced upwards. The media for dissolution was 900 millilitres of an isotonic phosphate buffer (IPB) with a pH of 7.4. The apparatus was equilibrated to 37 ºC ± 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±0.5 ºC with the help of water bath. Before using the skin, it was allowed to come to room temperature and then mounted in such a way that the stratum corneum would be facing the donor cell and the dermis would be put in such a way that it would be facing the receiver cell. The phosphate buffer with a pH of 7.4 was added to the receptor chamber, and it was agitated using a Teflon-coated magnetic rotor at a speed of 500 revolutions per minute. Aliquots of five millilitres each were removed from the receiver chamber at regular intervals of time throughout the course of forty-eight hours, and the volume was maintained by adding an equivalent quantity of previously warmed receiver solution. The UV spectrophotometric method was used at 243 nm in order to conduct the drug content analysis. (Made in the USA, Beckman DU-64 Spectrophotometer)

Results and Discussions

Polymers such as Eudragit RL 100, Eudragit RS 100, and PVP K 30 were utilised in the process of developing a transdermal drug delivery system for the administration of zolpidem tartrate as part of the present work.

Dibutyl phthalate was discovered to be an appropriate plasticizer, and the oil of ylang ylang was utilised as a

penetration enhancer in the process. On the basis of solubility investigations, a solvent solution consisting of dichloro methane and methane in a ratio of 1 to 1 was chosen as the most favourable. It was determined that the change in weight, the folding endurance, and the thickness of the placebo films were the most important factors in optimising the concentration of polymers. (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 recast into medicated films by adding Zolpidem tartrate to the formulation and employing the same method, with or without the inclusion of a penetration enhancer. This was done in order to create the medicated films.

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 release rate constants of the substance are increased by the addition of hydrophilic components like PVP, which cause the soluble components to be leached out. In the pursuit of a system that is as efficient as possible, the formula for F3 and F5 was further altered by changing the ratio of polymer to penetration enhancer and the concentration of the enhancer. In order to improve the drug's ability to penetrate the skin, the amount of oil of ylang ylang used in the formulation was increased from 5 percent to 10 percent by weight of polymers. In a study that lasted for 48 hours, the transdermal system F7 that contained Eudragit RL100 and PVP K30 (in a ratio of 50:50) demonstrated a drug release rate of 74.75 percent and a drug permeation rate of 71.30 percent. While formulation F8, which contained Eudragit RL100 and PVP K30 in a ratio of 40:60, demonstrated 81.53 percent of drug release and 82.29 percent of drug permeation, formulation F7 did not show any significant difference. In comparison, the formulations F9 and F10, which were made up of various ratios of Eudragit RS100 and PVP K30, had a lower rate of release. The fact that Eudragit RL100 is more water permeable than Eudragit RS100 can help to explain such a pattern.

Because it included a greater concentration of PVP K30, F8 displayed a more favourable drug release and permeation pattern.

As a result, it was determined to be the optimal 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

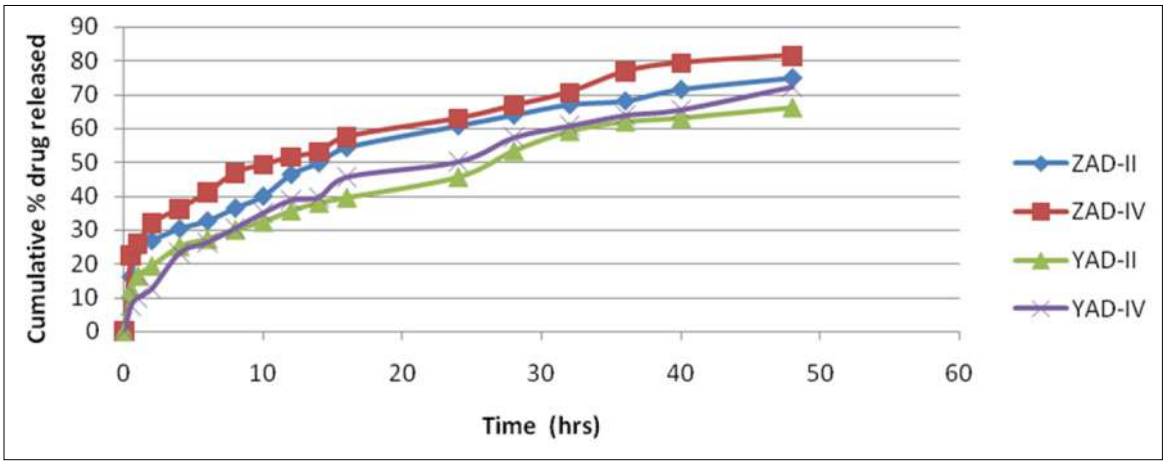

Fig 1: *In-vitro* drug release studies

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

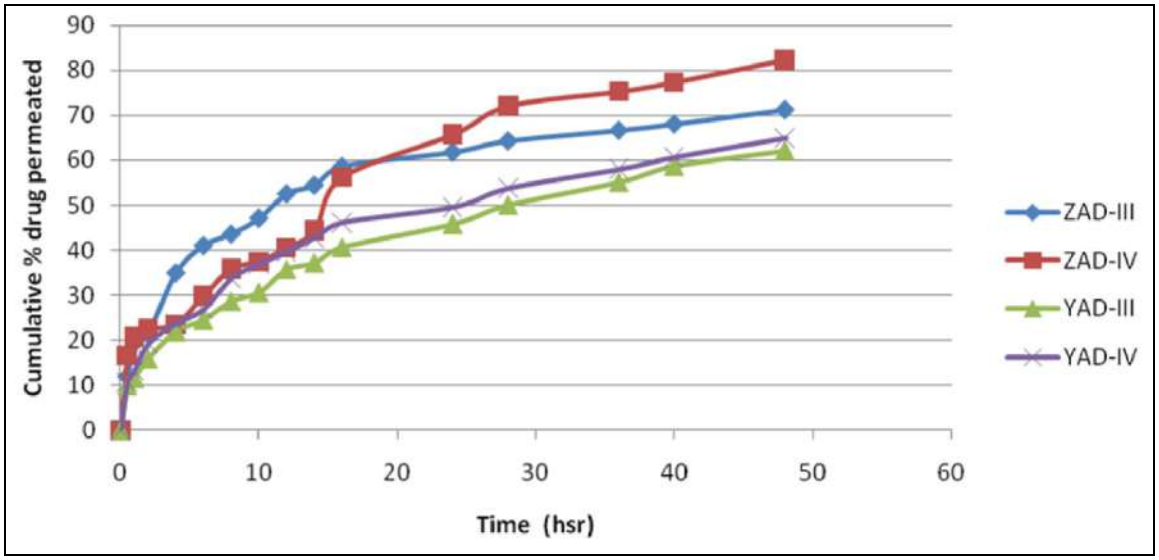

Fig 2: *In-vitro* drug permeation studies

Conclusion

In the current research, the F7 transdermal treatment system demonstrated successful outcomes in terms of *in vitro* release and penetration investigations.

This formulation included the polymers Eudragit RL 100 and PVP K30, as well as the platicizers PEG 400 and dibutyl phthalate. The penetration enhancers were a ten percent concentration of oil of ylang ylang.

The completed formulation has the potential to be studied further in living organisms.

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