



TRANSDERMAL DRUG DELIVERY OF ZIPRASIDONE HYDROCHLORIDE MONOHYDRATE BY PHYSICAL PENETRATION ENHANCER

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ABSTRACT

The aim of this work was to study the permeation of ziprasidone hydrochloride monohydrate across the skin. The effect of physical technique sonophoresis was investigated. Permeation experiments were performed by using rat abdominal skin as barrier. The formulated gel containing tulsi oil at different concentrations (5%, 10%, 15%, 20% & 25%) was investigated by sonophoresis. Stratum corneum acts as a barrier that limits the penetration of substances through the skin. Application of ultrasound to the skin increases its permeability and enables the delivery of various substances in to and through the skin. Sonophoresis creates holes in the skin and allowed fluid to travel in to and out of the body. The mechanism of action of sonophoresis was that it disrupts the lipid bilayers of the skin.

Keywords: Skin, Permeation enhancer, Sonophoresis, Permeability, Transdermal.

INTRODUCTION

Ziprasidone hydrochloride monohydrate is a typical antipsychotic agent used in the treatment of schizophrenia, bipolar disorders etc is currently administered by the oral and intramuscular route.¹ The oral bioavailability of the drug is 50% so to overcome the oral bioavailability we have explored the possibility of administering the ziprasidone hydrochloride monohydrate via transdermal route.^{2,3} The physicochemical properties of ziprasidone hydrochloride monohydrate are not favourable for its permeation across the skin because the drug has more protein binding and have out of range partition coefficient. Thus the study the effect of physical permeation enhancers on skin permeation of ziprasidone hydrochloride monohydrate will help in the creation of effective topical formulation.

Among the techniques described in the literature to improve the skin permeation of hydrophilic molecules, chemical penetration enhancers and sonophoresis can be useful for ziprasidone hydrochloride monohydrate transdermal administration.^{4,5}

The aim of this work was to study the permeation of ziprasidone hydrochloride monohydrate across the skin. The permeation of ziprasidone hydrochloride monohydrate was investigated from a carbopol gel containing tulsi oil as a chemical penetration enhancer.

MATERIALS AND METHODS

Materials

Ziprasidone hydrochloride monohydrate was received as a gift sample from New Delhi, India. Carbopol, liquid paraffin, triethanolamine, and other chemicals were of analytical grade and used without further purification. For

high- performance liquid chromatography (HPLC) solvent preparation phosphate buffer and HPLC grade methanol was used.

Drug Analysis

The concentrations of ziprasidone were measured in serum samples using HPLC technique. The mobile phase consisted of phosphate buffer (pH 3.5) and methanol in the ratio of 55:45v/v. The buffer was prepared by dissolving 3.4 g of monobasic potassium phosphate in water, adjusting the pH to 3.5 with phosphoric acid. The flow rate was 1ml/min.⁶ UV detection was carried out at 318 nm. The chromatographic system consisted of an Agilent 1200 Series G1311A solvent delivery quaternary pump equipped with a 20 µl loop and rheodyne sample injector. Eclipsex DB-C₁₈ (5µm; 4.6 x 150 mm) analytical column was used. The mobile phase was freshly prepared before each experiment. The data was recorded using Empower Software.

Method of Preparations

1 Carbopol Gel: Carbopol gel was prepared by mixing carbopol 940 with distilled water, ethanol and drug (mixture I). Mixture II was prepared by mixing triethanolamine, ethanol distilled water and enhancer. Then add mixture II drop by drop to mixture I and the gel was prepared. Compositions were provided in table 1.

2 Skin Sample

Anaesthetized the rats weighing 250- 300 gms by giving i.p injection of Ketamine and hairs from abdominal region was removed by means of surgical and razor carefully.

Permeation Experiment

Hold the rat on the cage and tied in such a way that their shaved abdomen is on the upper side. After that apply



the ultrasound gel and give sonophoretic treatment with intensity of 2.5 watts/sq.sec for 30 minutes using frequency 1MHZ. After the sonophoretic treatment, jelly is wiped and the abdominal skin washed with distilled water and dried. Now the formulated gel is applied over the skin and the sample is taken after some interval of time from first animal, after particular interval of time samples are taken from all the animals, the samples is taken from the eye of the rat by retro-ocular method. The capillary used to take sample is heparin – coated. The blood samples were centrifuged at 5000 rpm for 30 min. Supernatant serum was collected and drug concentration was analysed using HPLC method.

Table 1: Compositions of gels

Ingredients	Formulation code					
	G1	G2	G3	G4	G5	G6
Ziprasidone	0.07	0.07	0.07	0.07	0.07	0.07
Carbopol 940	0.3	0.3	0.3	0.3	0.3	0.3
Distilled water	25	25	25	25	25	25
Ethanol	18.75	18.75	18.75	18.75	18.75	18.75
Triethanolamine	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol	6.25	6.25	6.25	6.25	6.25	6.25
Distilled water	49.3	49.3	49.3	49.3	49.3	49.3
Tulsi oil	-	5%	10%	15%	20%	25%

RESULTS AND DISCUSSIONS

A solution of ziprasidone HCl gel was prepared by dissolving the gel in mobile phase. Aliquot volumes from Ziprasidone HCl stock solution were taken and further diluted to give concentrations of 10, 15, 20, 25, 30, 35, 40 and 45µg/ml. Filtered through a 0.45µm Millex-HV membrane filter paper and assayed. Calibration curve was constructed in rat serum (10- 45 µg/ml) by spiking the blank serum samples with standard amount of ziprasidone HCl. The data were acquired and processed using Empower software.

Under these conditions the retention time of Ziprasidone HCl was about 4.48 minutes. The calibration curve was linear over the range of 10 – 45 µg/ml. The data for standard curve was shown in table 2 and the curve was shown in fig 1.

Table 2: Data of standard curve of ziprasidone hydrochloride monohydrate

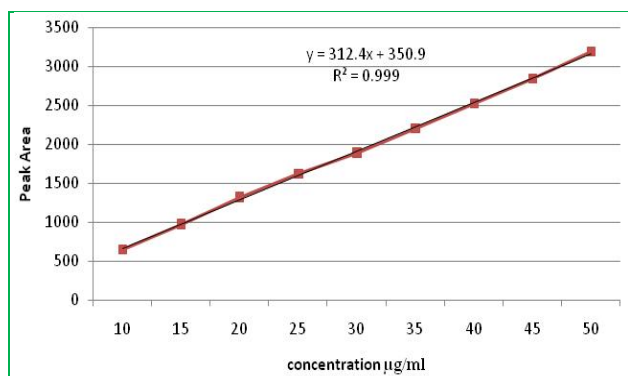
Conc. (µg/ml)	Peak Area (mAU x s)
10	651
15	973
20	1321
25	1623
30	1891
35	2204
40	2527
45	2841

Table 3: Mean Plasma Concentration (ng/ml) of Ziprasidone HCl applied topically over the skin

Time (h)	G1 (without P.E. and S.T.)	G2 (with 5% P.E. and S.T.)	G3 (with 10% P.E. and S.T.)	G4 (with 15% P.E. and S.T.)	G5 (with 20% P.E. and S.T.)	G6 (with 25% P.E. and S.T.)
0.5	56.56±5.01	65.84±2.03	78.34±4.03	86.76±3.89	98.37±4.1	112.67±3.1
1	69.45±3.26	84.45±4.46	89.07±2.34	113.56±3.78	128.64±4.05	135.45±2.9
2	90.34±2.45	102.63±5.73	115.45±2.78	148.74±4.01	157.26±3.90	167.89±3.43
3	110.29±3.34	126.48±3.34	139.23±4.65	175.54±4.11	189.45±4.12	198.78±3.37
4	118.56±4.56	115.45±2.76	126.47±2.78	154.23±3.98	172.56±3.88	182.89±3.85
5	93.67±4.78	95.78±3.45	114.56±3.65	120.48±4.11	153.89±4.19	164.23±2.95
6	77.18±5.56	83.34±4.67	92.74±4.01	105.28±3.87	126.34±4.21	137.65±3.18

P.E: penetration enhancer, S.T: Sonophoresis treatment

Figure 1: Standard curve of ziprasidone hydrochloride monohydrate



The pharmacokinetic parameters were calculated and expressed as the mean± SD as shown in table 3. From this study we conclude that the formulation G1 that containing tulsi oil as a chemical penetration enhancer is applied on the rat abdominal skin and no sonophoresis treatment was given to that rat showed less drug release in plasma as compared to the other formulations in which both physical and chemical techniques are applied. Moreover we also conclude that as we increase the concentration of chemical enhancer and applied constant sonophoretic treatment to the formulations G2-G6 showed increase in the drug release.

CONCLUSION

From the results obtained, it can be concluded that the permeation of ziprasidone hydrochloride monohydrate across the skin can be enhanced using chemical and/or physical penetration enhancer. The mechanism of action of sonophoresis was to disrupt the lipid bilayer structure of stratum corneum.

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