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DEVELOPMENT OF ZIPRASIDONE HYDROCHLORIDE MATRIX TYPE TRANSDERMAL DRUG DELIVERY SYSTEM: *IN VITRO* AND *EX VIVO* CHARACTERIZATION

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ABSTRACT
Ziprasidone HCL is an Anti-Psychotic drug having efficacy in schizophrenia whose mechanism of action is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonisms. The matrix type transdermal patches of Ziprasidone HCL were prepared using HPMC E 15 and ERL 100 by solvent evaporation technique. All formulations carried 15% v/w of propylene glycol as plasticizer. The prepared patches were characterized for various physicochemical parameters like weight, thickness, folding endurance, drug content, percent moisture content, percent moisture absorption, in vitro drug release and ex vivo permeation.. The drug permeation kinetics followed zero order profile with diffusion mechanism. The mechanical properties, tensile strength, elastic modulus reveal that the formulations were found to be strong but not brittle. The FTIR studies showed drug polymer compatibility. The results indicate that Ziprasidone HCL matrix type transdermal therapeutic systems could be prepared with the required flux having suitable mechanical properties.

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KEYWORDS : *Transdemal, Ziprasidone, schizophrenia, plasticizer, permeation.*

INTRODUCTION

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.Antagonism at receptors other

than dopamine and 5HT2 with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Transdermal drug delivery offers many advantages such as reduced side effects, improved patient compliance, elimination of first-pass effect, sustained drug delivery and interruption or termination of treatment when necessary (Chien, 1987; Kanikkannan et al., 2004; Lopes et al., 2005). In order to enhance the in vivo effectiveness of Ziprasidone a suitable candidate for transdermal delivery, we have formulated the matrix transdermal systems of Ziprasidone using HPMC E 15(Hydroxypropile methyl cellulose) and Eudragit RL-100 (hydrophilic) and evaluated with respect to various in vitro and preclinical in vivo parameters.

MATERIALS AND METHODS

Materials

HPMC E15 was purchased from SD Fine Chemicals Ltd., India. Polyvinylpyrrolidone-K30 (PVP) was procured from Loba Chemie, India. Eudragit RL-100 (ERL) and Eudragit RS-100 (ERS) were obtained from Degussa,Ziprasidone was a gift sample from Hetero Drugs Ltd., Hyderabad, Andrhapradesh, India. Dialysis membrane and D-limonene purchased from Himedia Laboratories Pvt. Ltd., Mumbai. All the other chemicals used were of analytical grade.

Preparation of Ziprasidone HCl Transdermal Patches

Matrix type transdermal patches containing Ziprasidone HCl were prepared by solvent evaporation technique, using different ratios of HPMC E 15, ERL100 (F1 to F5) and HPMC E 15, ERS100 (F6 to F10) A series. The polymers were weighed in requisite ratios by keeping the total polymer weight 1350mg and allowed for swelling for about 6 hrs in solvent mixture (1:1 ratio of di- chloromethane, methanol). 15%v/w Propylene glycol was incorporated as plasticizer. Then the drug solution was added to the polymeric solution, casted on to anumbra petriplate of surface area about 69.42sq.cm, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 6.15cm^2 i.e. with a diameter of 2.8cm. About 8 patches were obtained from each sheet. Six formulations (C1 to C3 and D1 to D3) composed of HPMC E15 and ERL 100 in 5:1 ratio with two penetration enhancers D-Limonene, Oleic acid in three different concentrations 4%, 8% and 12% v/w were prepared. All formulations carried 15% v/w propylene glycol as plasticizer.

Table 1. Composition of Ziprasidone HCl transdermal patches

Formulation code	Drug (mg)	HPMC E15 (mg)	ERL 100 (mg)	ERS 100 (mg)
F1	225	225	1125	-
F2	225	900	450	-
F3	225	675	675	-
F4	225	450	900	-
F5	225	1125	225	-
F6	225	450	-	900
F7	225	900	-	450
F8	225	675	-	675
F9	225	1125	-	225
F10	225	225	-	1125

15% propylene glycol was used as plasticizer.Each patch (6.15 cm^2) contains 20mg of Ziprasidone HCl

Table 2. Composition of transdermal patches with penetration enhancers

Formulation code	D-limonene (%)	Oleic acid (%)
C1	4	-
C2	8	-
C3	12	-
D1	-	4
D2	-	8
D3	-	12

Characterization of Ziprasidone HCl Transdermal Patches

Physicochemical properties the Patches prepared by general procedure were evaluated for the following properties

Thickness: The thickness of the film was measured at ten different points on one film using screw gauge. For each formulation three selected Patches were used and average thickness was recorded.

Weight variation: Six Patches from each batch of an area of 6.15cm^2 were weighed individually and the average weight was calculated.

Folding endurance: Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number

Estimation of drug content in polymeric Patches: The formulated polymeric Patches were assayed for drug content in each case. Three polymeric Patches from each formulation were assayed for content of drug. Patches from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 312 nm against methanol dichloromethane mixture (1:1) as blank.

Moisture Absorption Studies:The patches were weighed accurately and placed in the desicator containing 100ml of saturated solution of aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the following formula

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Content Determination

The patches were weighed accurately and placed in a desicator containing calcium chloride at 40^{o}C for 24hr. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Measurement of Mechanical Properties

Mechanical properties of the Patches were evaluated using a microprocessor based advanced force gauze (Ultra Test, Mecmesin, UK) equipped with a 25 kg load cell. Film strip with dimensions 60 x 10 mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2mm/s pulled the strips to a distance till the film broke. The force and elongation were measured when the film broke. The mechanical properties were calculated according to the following formulae. Measurements were run in four replicates for each formulation (Das et.al 2006).

$$\text{Tensile strength (kg. mm}^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2)}$$

$$\text{Elongation at break (\% mm}^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \times \frac{100}{\text{Cross sectional area}}$$

$$\text{Elastic Modulus} = \frac{\text{Force at corresponding strain (kg)}}{\text{Cross-sectional area (mm}^2)} \times \frac{1}{\text{Corresponding Strain}}$$

$$\text{Strain} = \frac{\text{Tensile strength}}{\text{Elastic modulus}}$$

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength (TS) and elastic modulus (EM) and elongation at break (E/B). A soft and weak polymer is characterized by a low TS, EM and E/B; a hard and brittle polymer is defined by a moderate TS, high EM and low E/B; a soft and tough polymer is characterized by a moderate TS, low EM and high E/B; where as a hard and tough polymer is characterized by a high TS, EM and E/B. Another parameter strain has been used as an indicator of the overall mechanical quality of the film. A high strain value indicates that the film is strong and elastic. Hence, it is suggested that a suitable transdermal film should have a relatively high TS, E/B and strain but low EM (Ramesh et.al 2007).

***In vitro* Release Studies**

Preparation of Rat Abdominal Skin

The male albino rats weighing 150-200gm were sacrificed using anaesthetic ether. The hair of test animals was carefully trimmed short (<2mm) with a trimmer taking extreme precaution not to damage the skin and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique, which involved soaking the entire abdominal skin in water at $60^{o}C$ for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water, dried in a desiccator, wrapped in aluminium foil and stored at $4\pm1^{o}C$. At the time of use, the epidermis was rehydrated by immersion in water for 1hr at room temperature (Panigraha et al,2005)

***Ex vivo* Permeation Studies**

Franz diffusion cell with a surface area of $4.15cm^2$ was used for *ex vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS under test. A dialysis membrane was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receiptor phase is 24ml of phosphate buffer saline (PBS) pH 7.4 stirred at 500rpm on a magnetic stirrer. The amount of drug permeated was determined by removing 5ml of sample at appropriate time intervals upto 24 hr, the volume was replenished with an equal volume of pH 7.4 buffer. The absorbance was measured at 312nm spectrophotometrically. Cumulative amounts of drug permeated in $\mu g/cm^2$ were calculated and plotted against time. Drug flux ($\mu g/hr/cm^2$) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface ($6.15cm^2$). The target flux is calculated using the following equation(35).

$$J_{Target} = \frac{C_{SS}\ Cl_T\ BW}{A}$$

'A' represents the surface area of the transdermal patch (i.e. $6.15cm^2$), 'BW' the standard human body weight of 60 kg, 'C_{SS}' the Ziprasidone HCl concentration at the therapeutic level (26.6 nanogram/ml) and the 'Cl_T' the total clearance (7.5 ml/hr), the calculated target flux value for Ziprasidone HCl was $116.78\mu g/hr/cm^2$.

Drug-Excipient Compatibility study

This was carried out by FTIR analysis of pure drug (Ziprasidone HCl), pure polymers (HPMC E 15, ERL 100 and ERS 100) and their physical mixtures as used in formulations to study the possible interaction between drug and polymers.

RESULTS AND DISCUSSION

Characterization of Ziprasidone HCl Transdermal Patches

The results of weight variation test for various transdermal Patches were shown in Table 3 & 4. Results of weight variation test indicated uniformity in weight of patches. In formulations F1 to F10 the weight of the patches decreased with decrease in HPMC E15 concentration and in C1 to C3 and D1 to D3 the weights of the patches were

same.In thickness variation test, the thickness was found to be uniform. The thickness increased with increase in HPMC E15 concentration. The results of thickness variation test for various transdermal Patches were shown in Table 3& 4.

Folding endurance number The folding endurance numbers of ERS 100 containing patches has in the range of 40 to 90, ERL 100 containing patches has in the range of 18 to 85and for the formulations prepared with penetration enhancers has in the range of 70 to 105. It gives mechanical strength to patches The folding endurance number was increased with increasing HPMC E15 content.

Table 3. Weights, thickness and folding endurance of Ziprasidone HCl transdermal patches

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
F1	210.2±0.17	0.28±0.25	85±7.64
F2	208.2±0.61	0.29±2.05	62.5±1.05
F3	225.1±1.23	0.32±0.45	56.31±3.83
F4	235.2±0.27	0.33±0.42	26.16±5.04
F5	233.2±0.84	0.32±0.29	28.33±2.58
F6	224.2±0.82	0.38±0.14	90±8.91
F7	233.3±0.96	0.35±2.17	70.83±2.15
F8	241.1±0.54	0.29±0.19	83.5±5.95
F9	234.3±1.67	0.36±1.63	44.5±3.90
F10	237.3±0.28	0.32±1.23	49.67±3.46

Table 4. Weight, thickness and folding endurance of Ziprasidone HCl transdermal patches with penetration enhancers

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance
C1	240.15±0.15	0.34±0.71	105.1±1.20
C2	242.5±1.53	0.36±0.42	88.21±0.78
C3	238.06±0.84	0.33±0.41	75.25±2.92
D1	245.43±0.94	0.36±0.70	85.25±0.56
D2	232.65±0.69	0.34±1.35	92.05±1.38
D3	243.25±0.44	0.37±0.24	78.75±1.6

Estimation of drug content in polymeric Patches:

Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged from 16.72 to 19.3mg per 6.15 cm^2. The results of drug content for various transdermal Patches were shown in Table 5 and 6.

Moisture Absorption and moisture Content study

The results of moisture content and moisture absorption studies were shown in Table 7 &and 8 and Fig 1 and 2. The moisture content in the patches was ranged from 3.21 to 5.3% and 3.3 to 5.63% (for formulation A series and B series respectively). The moisture absorption in the formulations is ranged from 3.18 to 9.63% and 5.85 to 10.1% (for formulation A series and B series respectively). The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The results of moisture content and moisture absorption studies for the formulations C1to C3 and D1 to D3 ranged from 3.85 to 7.55% and 6.6 to 13.5% respectively.

Table 7. Drug content, %Moisture absorbed and %Moisture content of Ziprasidone HCl transdermal patches, mean ± S.D (n=3)

Formulation	Drug content (mg)	% Moisture absorbed	% Moisture content
F1	16.35±0.64	9.63±1.52	5.3±0.24
F2	18.08±0.56	8.3±0.19	4.38±0.46
F3	16.72±0.55	6.6±1.34	4.03±0.88
F4	17.1±0.95	4.35±1.40	3.21±0.80
F5	19.3±0.07	3.18±1.26	3.98±0.60
F6	17.3±0.86	10.1±0.57	3.3±0.52
F7	18.17±0.29	7.91±2.45	4.88±0.57
F8	17.6±0.03	9.23±1.26	5.63±0.45
F9	19.01±0.06	6.38±1.95	4.9±0.66
F10	18.93±0.64	5.85±1.66	3.95±0.05

Fig 1. % Moisture absorbed and Moisture content of Ziprasidone HCl transdermal patches, mean ± S.D (n=3)

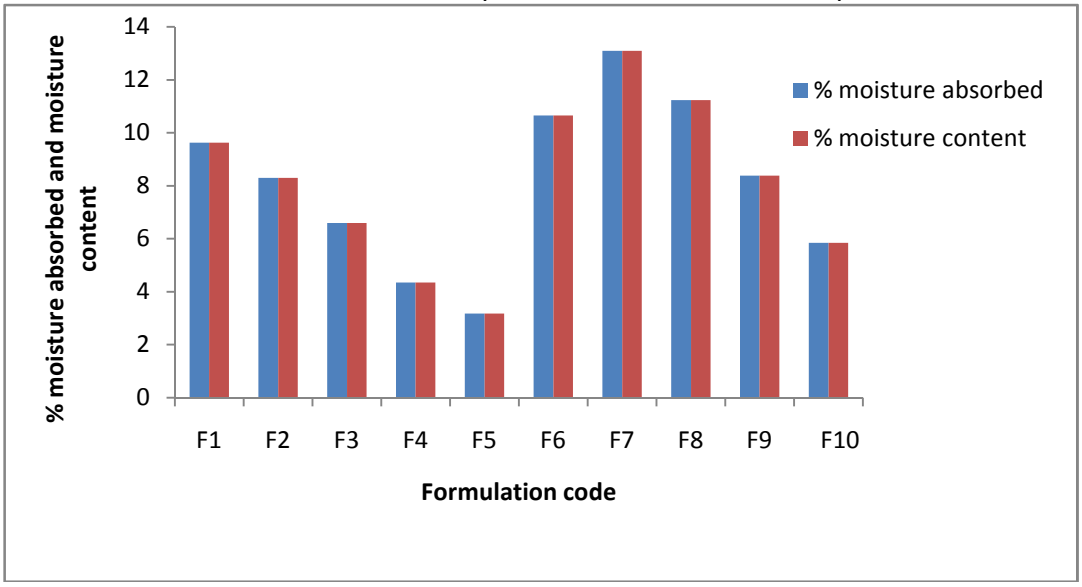
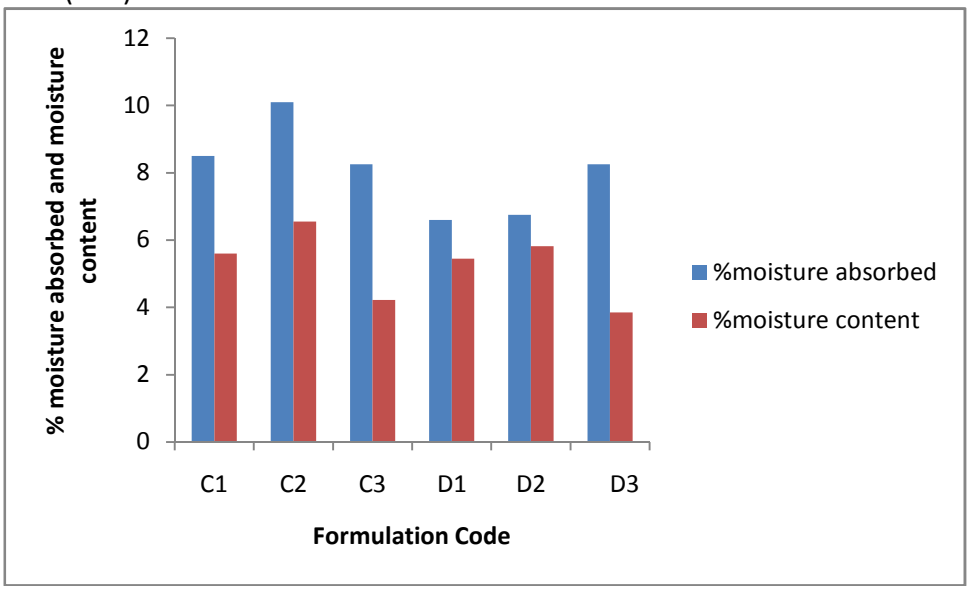


Table 8. Drug content, %Moisture absorbed and %Moisture content of Ziprasidone HCl transdermal patches with penetration enhancers, mean ± S.D (n=3)

Formulation code	Drug content (mg)	% moisture absorbed	% moisture content
C1	18.28±0.82	8.5±0.16	5.6±0.75
C2	19.05±1.05	13.5±1.95	7.55±0.22
C3	18.5±0.84	8.25±1.47	4.22±1.22
D1	17.25±0.68	6.6±2.85	5.45±1.08
D2	18.7±1.07	6.75±3.36	5.82±0.68
D3	19.25±0.88	8.25±1.25	3.85±1.22

Fig 2. % Moisture absorbed and Moisture content of Ziprasidone HCL transdermal patches with penetration enhancers, mean ± S.D (n=3)



***Ex vivo* permeation studies through rat abdominal skin from transdermal patches**

The results of *ex vivo* skin permeation of Ziprasidone HCl from patches were shown in Fig 3 and 4. The formulations (area of 6.15cm^2) F5 and F9 exhibited the greatest (1360.35±1.70 and 1170.35±1.70µg/cm^2 respectively) cumulative amounts of drug permeation, which were significantly different compared to the lowest values observed with the formulations containing ERL100 (F1) and ERS100 (F7) (653.6±1.20 and 682.38±1.12 µg/cm^2 respectively) in 24hr.

As the proportion of HPMC increased in all the formulations, increased drug release and permeation in both series were observed. But with these formulations the required flux was not obtained. The results of *ex vivo* skin permeation of Ziprasidone HCl from patches prepared with penetration enhancers were shown in Fig 5and 6 . The formulations C3 (containing 12% D-Limonene), D3 (containing 12% oleic acid) exhibited greatest (2373.86±1.10, 2273.38±0.08 µg/cm^2 respectively) cumulative amounts of drug permeation and these formulations exhibited the required flux.

Figure 3 :cumulative percentage of Ziprasidone HCl Permeated from transdermal patch

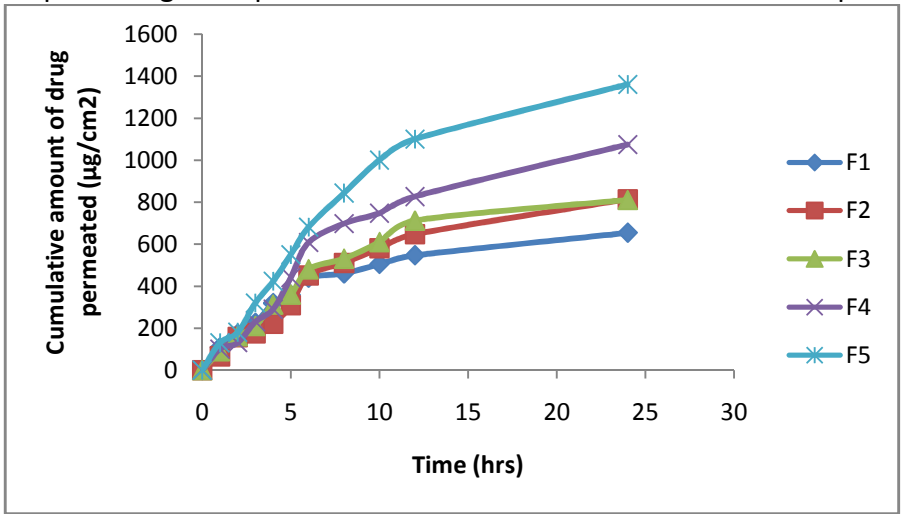


Fig 4. Permeation of Ziprasidone HCl from transdermal patches (B series)

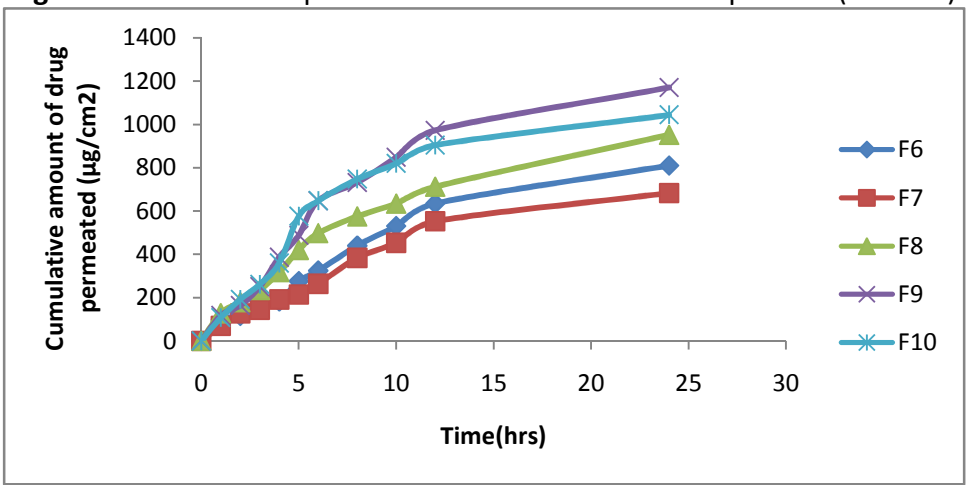


Fig 5. Permeation of Ziprasidone HCl from transdermal patches (C1 to C3)

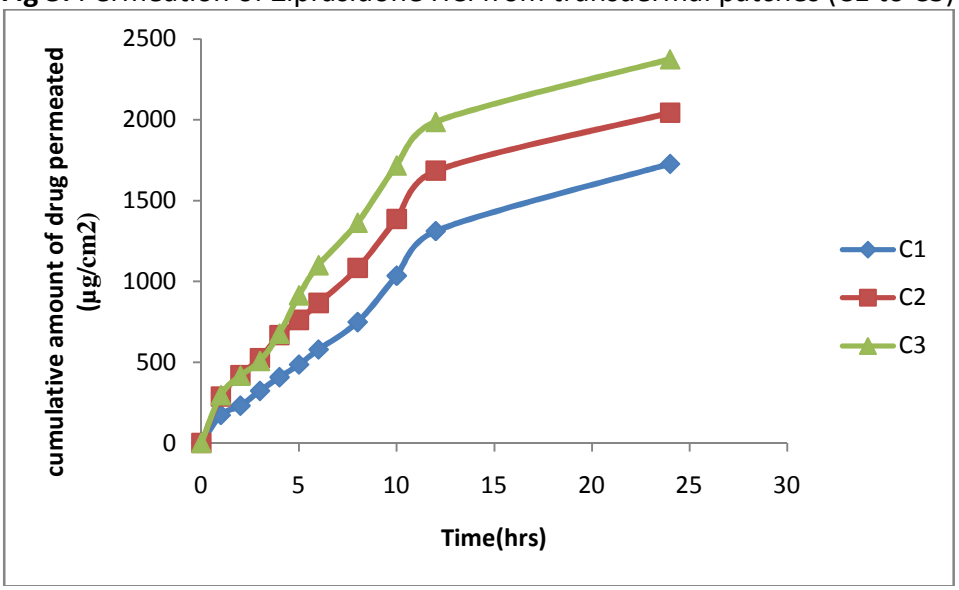
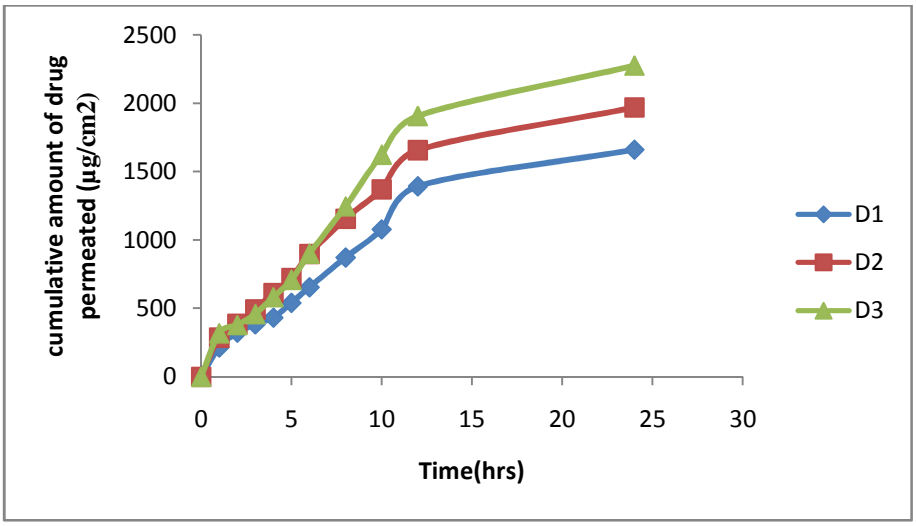


Fig 6.Permeation of Ziprasidone HCl from transdermal patches (D1 to D3)



The *ex vivo* permeation results of optimized formulations C3 and D3 were fitted into various kinetic models (zero order, first order and higuchi square root model). The R^2 values of zero order plots(0.845, 0.873 and 0.884 figures 7,8,9) were greater than the R^2 values of first order plots (0.559, 0.512 and 0.541) and the R^2 values of higuchi plots were greater than 0.90 (0.939, 0.945 and 0.9926). The R^2 values reveal that the permeation of Ziprasidone HCl from the transdermal Patches followed zero order mechanism and through diffusion process. The results of drug permeation from transdermal patches of Ziprasidone HCl through the rat abdominal skin confirmed that Ziprasidone HCl was released from the formulation and permeated through the rat skin and hence could possibly permeate through the human skin.

Figure 7. Zero order model (cumulative percent of drug permeated vs time)

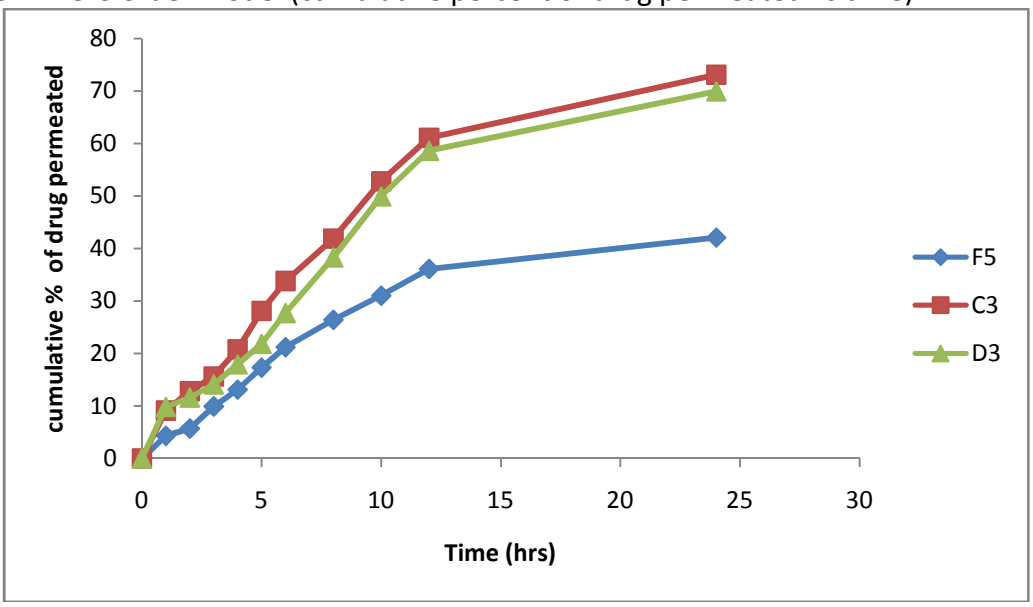


Figure 8. First order model (log cumulative percent of drug permeated vs time)

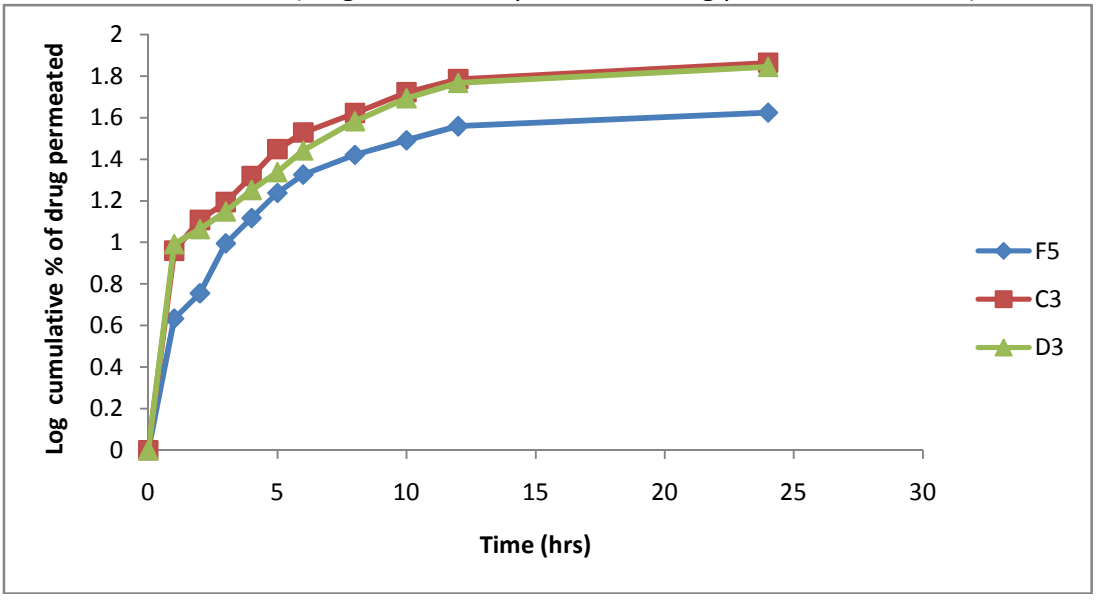


Figure 9. Higuchi model (cumulative percent of drug permeated vs square root of time)

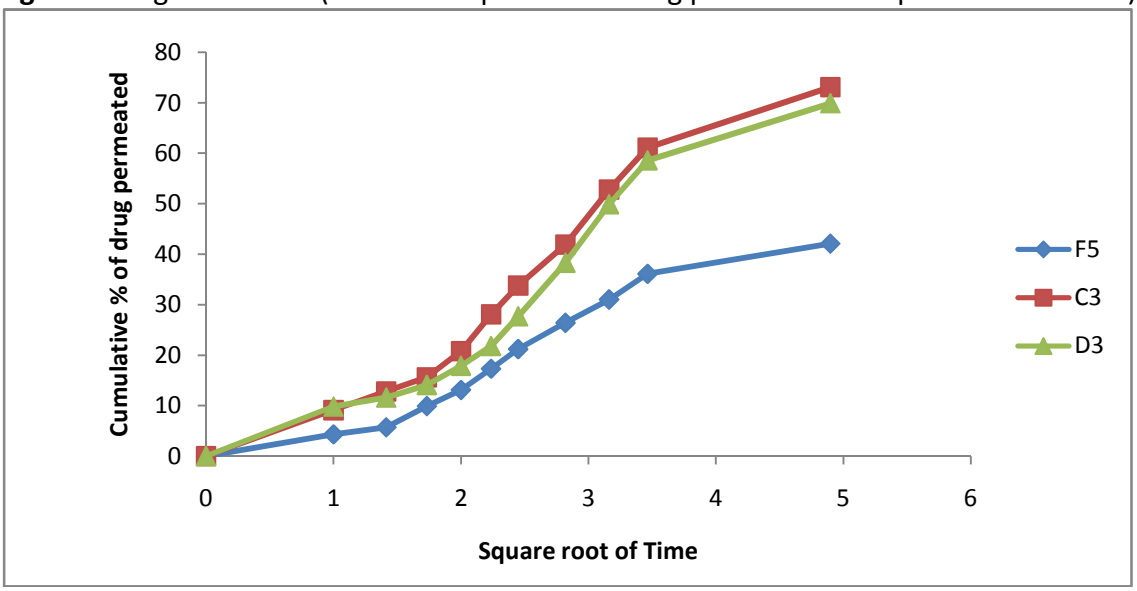


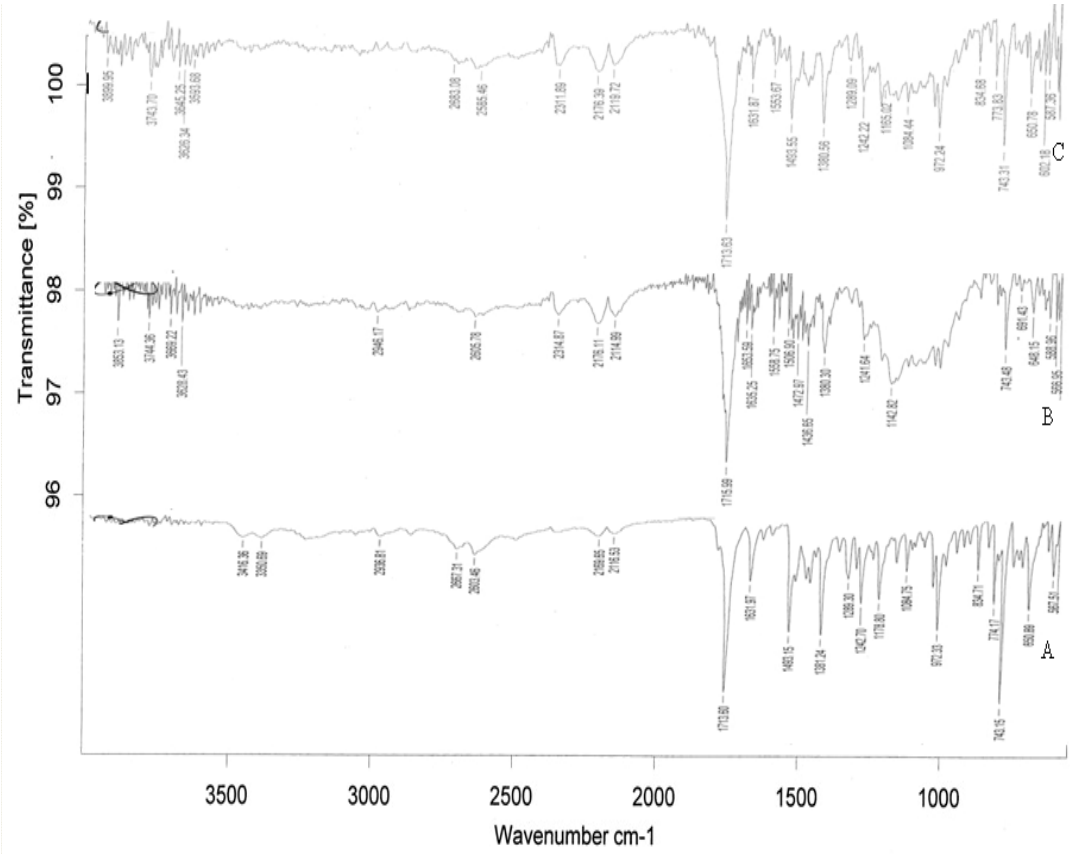
Table 11 . Correlation coefficients of kinetic models of optimized formulations

Formulation code	Zero order	First order	Higuchi model
F5	0.845	0.559	0.939
C3	0.873	0.512	0.945
D3	0.884	0.54	0.926

Mechanical Properties :The results of mechanical properties (tensile strength, elongation at break, elastic modulus and strin) were shown in Table12. These observations indicate that the optimized formulations were found to be strong and flexible but not brittle.Drug - Excipient Compatibility: FTIR of optimized formulations shows no interaction between polymers and drug.

Table 12 . Mechanical properties of optimized formulations

Formulation code	Tensile strength(kg/m^2)	Elongation at break (%mm^{-2})	Elastic modulus (kg/mm^2)	Strain
F5	1.02±0.26	65.92±2.02	2.68±0.38	0.46±0.023
C3	1.09±0.31	69.7±1.06	2.09±0.41	0.52±0.018
D3	1.06±0.11	72.16±1.89	2.84±0.50	0.49±0.037



CONCLUSION

Different polymeric films containing Ziprasidone HCl were prepared and evaluated for physicochemical, in vitro drug release and permeation characteristics.Ziprasidone HCl transdermal films with penetration enhancers D-limonene, Oleic acid in 4%, 8% and 12% v/w concentrations were prepared and evaluated for physicochemical and permeation characteristics.The formulations containing D-limonene (12%), Oleic acid (12%) were found to meet the required flux. The transdermal patches of Ziprasidone HCl with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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