Ethosomal gel: a novel choice for topical delivery of the antipsychotic drug Ziprasidone Hydrochloride

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Oral delivery of antipsychotic drugs like Ziprasidone HCl has a disadvantage of gastric disturbance and lack of adherence to the treatment. In the present study, Ziprasidone HCl loaded ethosomal gel was formulated to avoid the disadvantages of oral delivery. The ethosomes were prepared using Lipoid S 75 with Isopropyl alcohol and Propylene glycol as the solvents. The formulated ethosomes were evaluated for different parameters like particle size, poly dispersibility index and entrapment efficiency. Based on diffusion studies, optimized ethosomal formulation was incorporated in carbopol 934 gel base. The final dosage form of ethosomal gel was evaluated for physical characteristics, drug content and proceeded with ex vivo skin permeation studies. The maximum percentage of drug permeated after 24 hours was found to be 93.30±0.168. The flux was found to be 52.05± 0.564µg/hr/cm². From the kinetic model fitting results, it was concluded that the ethosomal gel followed the first order kinetics and the higher “R²” values of the Korsmeyer Peppas model (R²=0.934, n=0.54) indicate that the encapsulating polymer is the responsible factor in controlling the release of the drug. The ethosomal gel loaded with ziprasidone HCl improves the bioavailability of ziprasidone HCl as well as surpassing drawbacks with oral delivery.

Keywords: Ethosomes, Ziprasidone HCl, Ethosomal Gel, Lipoid S75, Carbopol 934.

1. INTRODUCTION

Ethosomes, the lipid vesicular carrier systems, also called as alcoholic liposomes are composed of phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are suitable carrier systems for both hydrophilic and lipophilic drugs. The small particle size of ethosomes (microns to nanometer) facilitates their potentiality in carrying the drug through the skin into systemic circulation. The ease of preparation, non-irritant nature, efficiency to encapsulate wide range of drug molecules and higher stability than any other vesicular systems makes the ethosomes the most opted carriers for topical delivery of drugs (Gangwar, Singh, Garg, 2010; Tarun et al., 2013; Leon, Herbert, Joseph, 2009).

Although, the actual phenomenon by which the ethosomes enhance permeability is not clear, it is believed to enhance by various pathways. They involved disruption of stratum corneum (Dinesh et al., 2010) or by getting themselves trapped in the follicles (i.e., pilosebaceous pathway). Ethosomes contains phospholipids entrapping alcoholic drug solutions. The phospho-lipids may vary from 0.5 to 10% in the formulations. The alcohols which can be a softener, vehicle and penetration enhancer along with glycol, constitute 22-70% of ethosomal formulations (Mamta, Anar, Rahul, 2013; Vaibhav, Dinesh, Jain, 2007; Manish, Lifeng, Sui, 2011). Through various studies, it was reported that varying the compositions of alcohol and water, the drug delivery can be modulated and thus the
bioavailability can be enhanced (Yi et al., 2009; Sheo, 2010; Subheet et al., 2007; Ravindra, Ajay, Sanjay, 2013; Zhen et al., 2012; Limsuwan, Amnuaikit et al., 2012).

Ziprasidone HCl is a new atypical antipsychotic agent affective in the treatment of schizophrenia and bipolar disorder. By several studies on patients treated with antipsychotic agents, it was concluded that the oral administration of antipsychotic agents brings complications like gastric or duodenal ulcer, ulcerative colitis, irritable colon syndrome or regional enteritis (www.rxlist.com; Samuel, 2006). These disturbances reduce patient compliance resulting in lack of adherence to therapy. These issues brought into light the importance of other routes of delivery of antipsychotics. Investigation from researchers revealed that delivering antipsychotic drug through oral dissolving tablets and intramuscular dosage form improved the adherence to therapy and provided rapid activity. It is even reported that sonophoresis improved the permeation of ziprasidone HCl (Stephen, 2008; Geetha, Sanju, 2010; Shalu, Kamal, Sanju, 2012). Objectives of the present study include formulation of ziprasidone HCl loaded ethosomes gel in order to improve the permeability and to overcome the problems associated with conventional oral drug delivery.

2. MATERIAL AND METHODS

2.1. Material

Ziprasidone Hydrochloride from Sun pharma Ltd, India and Lipoid S75 from Lipoid GMBH, Germany were obtained as a gift samples. Isopropyl alcohol (Sigma Aldrich, India), Propylene glycol (Universal laboratories, India), Carbopol 934P (Central drug house Pvt Ltd, India) and Triethanolamine (Fisher scientific, India) were procured. All other reagents and chemicals used were of analytical reagent grade.

2.2. Preliminary studies

2.2.1. Drug-excipients compatibility

Preformulation testing entailed an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It was the first step in the rational development of the dosage form. Drug excipient compatibility testing at an early stage helps in the selection of excipients that increase the probability of developing a stable dosage form. Incompatibility between drug and excipient can alter stability and bioavailability of drugs, affecting its safety and/or efficacy. Fourier transform infrared spectroscopy (FT-IR) is a simple technique for the detection of changes within excipient – drug mixture. The disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks give a clear evidence for interactions between drug and excipient. Ziprasidone HCl alone and mixtures with various excipients individually were prepared and kept at room temperature in a glass vial. The sample was grounded gently with anhydrous KBr and compressed to form pellet. The scanning range was 400 and 4000 cm⁻¹. Results of the IR spectrum, can be used to record the incompatibility such as the disappearance of a peak or peak intensity reduction or appearance of new peaks, if any., Finally, the excipients were selected for formulation based on the report of FTIR.

2.2.2. Construction of Calibration curve.

UV spectroscopic method was used for the estimation and analysis of ziprasidone HCl. Different concentrations of ziprasidone HCl were prepared using phosphate buffer saline pH 7.4 as a solvent. The prepared solutions were analyzed at 318nm using phosphate buffer saline pH 7.4 as blank. The calibration graph was constructed by plotting the absorbance versus the final concentration of the drug (μg/mL) and the corresponding regression equation was derived.

2.3. Preparation and evaluation of Ethosomes

2.3.1. Preparation of ethosomes

Required quantities of lipid (Lipoid S75) and ziprasidone HCl were taken in a closed vial containing isopropyl alcohol. Solubilized propylene glycol was added to the closed vial with stirring. This mixture was
heated to 30°C. Water was added dropwise to the prior mixture while stirring at 700rpm in a closed vial. The mixture was stirred for 5 minutes. The size of ethosomes formed was reduced by exposing the ethosomes to probe sonication for 4 minutes. Finally, the formulations (F1 to F6) were stored in the refrigerator for further use (Sujitha, Krishnamoorthy, Muthukumaran, 2014). The detailed formulation composition is represented in Table I.

2.3.2. Physical evaluation of ethosomes

2.3.2.1. Particle size and Poly dispersibility index:

The size of particles plays a major role in the movement of particles across the skin barrier apart from the characteristics of the excipients used. Poly dispersibility index (PDI) was used as a parameter to determine the size distribution of particles with a similar size range. The lower PDI value indicates that almost all the particles are of the same size. The increase in the PDI indicates that there are particles which vary much with respect to particle size. Particle size and poly dispersibility index of ethosomes were measured by Photon Correlation Spectroscopy (PCS) Delsa Nano C (Beckman Coulter Counter, USA) particle size analyzer. All ethosomal formulations (F1 to F6) were diluted appropriately with the aqueous phase for the measurements. The samples were kept in polystyrene cuvettes, and observations were made at a 165 degrees fixed angle every time.

2.3.2.2. Drug content

The drug content was determined by taking 1ml of ethosomes and dispersing in 100ml of phosphate buffer saline pH 7.4. Then it was stirred for 2hrs. Finally, the sample was collected, filtered and analyzed using UV visible spectrophotometer using phosphate buffer saline pH 7.4 at 318nm.

2.3.2.3. Entrapment efficiency

Entrapment efficiency (Donatella et al., 2012; Poonam, Kamla, 2012; Abdul et al., 2014; Mahmoud, Salma, Mahmoud, 2013) was determined to know the amount of Active pharmaceutical ingredient (API) entrapped in the ethosomes and to know the amount that could be delivered as intended. For determining the entrapment efficiency, 1ml of ethosomes was taken and centrifuged in high-speed cooling centrifuge at 10000 rpm for 45 min. The supernatant was collected and analyzed using UV-Visible spectrophotometer at 318nm after suitable dilutions. The drug entrapment efficiency (EE) was calculated using the following equation: percentage EE=(((Dt-DUE)/Dt) x100, Where EE is the entrapment efficiency; Dt is the total amount of drug; and DUE is the amount of drug unentrapped (Li et al., 2014).

Based on the results of above significant evaluation parameters, three of the six formulations were further taken up for in vitro diffusion studies.

2.3.3. In Vitro diffusion Studies

In vitro drug release of ziprasidone HCl from the ethosomes was determined by the diffusion technique using Franz-diffusion cell (Donatella et al., 2012). The dialysis membrane (Himedia, thickness 0.025 mm) was cut into equal pieces (6 cm x 2.5 cm) and soaked in distilled water for 12 hours before use. The drug release studies of the ziprasidone HCl loaded ethosomes are carried out in 10 ml of phosphate buffer pH 7.4 saline maintained at 37± 2°C. The Franz diffusion cell was placed on a magnetic stirrer with constant heating equipment (IKA Auto Temp Regulator, Germany). A sample of 2ml of ethosomes was placed in receptor compartment. Aliquot samples of 1ml were withdrawn at the regular intervals and replaced with the same volume of fresh buffer. The aliquots were diluted with fresh media, if necessary. Amount of drug diffused through the membrane was measured by using U.V. spectrophotometer at a wavelength of 318 nm against phosphate buffer (pH 7.4 saline) as the blank. The diffusion studies were conducted and compared with other ethosomal formulations. Depending on the diffusion studies report, one ethosomal formulation was considered as the final optimized formulation.
2.3.4. Scanning electron microscopical study (SEM)

Scanning electronic microscopical study (SEM) was also conducted to characterize the surface morphology of the ethosomes.

2.4. ETHOSOMAL GEL

2.4.1. Preparation of ethosomal gel:

Final optimized thatethosomal formulation based on diffusion study is incorporated into carbopol gel base. The gel base was prepared by dispersing carbopol 934 P in distilled water. The polymer was soaked in water for 2 hours and then dispersed in distilled water using a magnetic stirrer to obtain a homogeneous gel base of 2% w/w. The ziprasidone HCl ethosomal concentrate was obtained by centrifugation of the ethosomes at 10000 rpm for 45 minutes. The ethosomal concentrate (pellet) with drug equivalent to 1%w/w was incorporated into the priorly formed gel base. Triethanolamine was added to maintain the pH and for the spontaneous gel formation (Abdul et al., 2014).

2.4.2. Evaluation of ethosomal gel:

2.4.2.1. FTIR study

The ethosomal gel (GF3) was evaluated for any incompatibility using FTIR.

2.4.2.2. Visual inspection, Drug content and pH determination

Physical evaluation was done for the prepared gels kept at room temperature in a glass vial. This was carried out for a period of one month in open and closed glass vials. At two and four week intervals, the samples were examined for physical characteristics such as color change. Drug content (Sujitha, Krishnamoorthy, Muthukumaran, 2014) was estimated by dissolving one gram of gel in a 100 ml of phosphate buffer saline pH 7.4 by constant stirring using homogenizer for 2 hours. z. The resultant solution was filtered and drug content was analyzed at 318nm by U.V spectrophotometer. The pH of ethosomal gel formulation was determined by digital pH meter (Mahmoud, Salma, Mahmoud, 2013).

2.4.2.3. Skin permeation studies

The ex vivo skin permeation of ziprasidone HCl loaded ethosomal gel was carried out using transdermal Franz diffusion sampling system with an effective permeation area and receptor cell volume of 4.25cm² and 25 mL respectively. The temperature of the receiver vehicle (Phosphate Buffer Saline, pH 7.4) was maintained at 37±1ºC and was constantly stirred by a magnetic stirrer at 100 rpm. The pig skin was carefully checked through a magnifying glass to ensure that skin samples were free from any surface irregularity and free from adipose tissue. This was then used for transdermal permeation studies. The skin was mounted on a receptor compartment with the stratum corneum side facing towards the donor compartment. A measured weight of one gram of ethosomal gel was placed in the donor compartment. Samples were withdrawn from the receptor compartment via the sampling port at different time intervals for a total time of 24hrs and analyzed for drug content. The receptor phase was replenished with equal volume of fresh buffer immediately after sample withdrawal (Xingyan et al., 2011).

2.4.2.3.1. Calculation of flux:

Ex vivo percutaneous flux (µg/cm²h⁻¹) of Ziprasidone HCl from ethosomal gel was calculated by plotting time versus the cumulative amount of active compound permeated through the skin and dividing the slope of the linear portion of the curve (steady state) by the area of the skin surface through which diffusion took place (Paulo, Jose, 2001).

2.4.2.3.2. Kinetic model fitting:

The skin permeation study data was input into different kinetic models for finding the order of kinetics and path of diffusion (Paulo, Jose, 2001).
3. RESULTS AND DISCUSSION

3.1. Preliminary studies

3.1.1. Drug excipient compatibility study

The FTIR spectra wavenumbers of ziprasidone HCl, are 3421.3 cm\textsuperscript{-1} (for NH stretching), 3201.7 cm\textsuperscript{-1} (for Aromatic C-H stretch), 2928 cm\textsuperscript{-1} (for C-H stretch), 1714 cm\textsuperscript{-1} (for C=O stretch), 1631 cm\textsuperscript{-1} (for C=N stretch), 1493 cm\textsuperscript{-1} (for C-H bending), 972 cm\textsuperscript{-1} (for C-N ), 744 cm\textsuperscript{-1} (for C-H bending) and 651 cm\textsuperscript{-1} (for C-H bending). The wavenumbers of the drug were compared with the wavenumbers of physical mixture in IR spectrum. The wave numbers in FTIR Spectra of physical mixture, were 3301 cm\textsuperscript{-1} (for NH stretching), 2981 cm\textsuperscript{-1} (for C-H stretch), 1645 cm\textsuperscript{-1} (for C=N stretch), 1456 cm\textsuperscript{-1} (for C-H) and 876cm\textsuperscript{-1} (for C-N wagging). These results revealed that there was no disturbance in the principle peaks of pure drug ziprasidone HCl. This further confirms the integrity of pure drugs and their compatibility with the excipients. Figure 1 represents the overlap infrared spectrum of ziprasidone HCl, excipients and physical mixture.

![FIGURE 1 - The overlap infrared spectrum of ziprasidone HCl, excipients and physical mixture.](image)

3.1.2. Calibration curve for Ziprasidone HCl:

The regression equation for the method at 318nm was found to be \( y = 0.0101x+0.0509 \) (\( R^2=0.999 \)), where \( y \) is absorbance; \( x \) is concentration; slope is 0.0101, intercept is 0.0509. The coefficient of correlation defines the linearity over Beer’s range of 2–20 \( \mu \)g/mL. The correlation coefficient (\( R^2 \)) was used as an indicator of the best fit for each of the models considered. The linearity graph of ziprasidone HCl is presented as Figure 2.
3.2. Ethosomes

Totally six ethosomal formulations were prepared based on the formulae presented in Table I. All the formulations were evaluated through physical evaluation.

### TABLE I - Preparation of ethosomes of ziprasidone HCl

| Ingredients                  | F1  | F2  | F3  | F4  | F5  | F6  |
|------------------------------|-----|-----|-----|-----|-----|-----|
| Ziprasidone HCl (mg)         | 20  | 20  | 20  | 20  | 20  | 20  |
| Phospholipid (mg)            | 100 | 100 | 200 | 200 | 300 | 300 |
| Isopropyl Alcohol (mL)       | 3   | 4   | 3   | 4   | 3   | 4   |
| Propylene glycol (mL)        | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Water (mL) up to             | 10  | 10  | 10  | 10  | 10  | 10  |

#### 3.2.1. Physical Evaluation

The ethosomal formulations, F1 to F6 were evaluated for various physical properties individually, and values are presented in Table II. Ethosomes were evaluated for particle size, poly dispersibility index, drug content and entrapment efficiency. The range of poly dispersibility index was 0.335 to 1.000 and the range of particle size was 177 nm to 654.6 nm. The ethosomes formed were in nanometers to microns range and the poly dispersibility index for most of the formulations was greater than 0.5. The values indicate the non-uniform size distribution which may be due to insufficient sonication time. The size of the vesicles depends upon the alcohol concentration. PDI is the degree of heterogeneity of particles. The smaller PDI value or value close to zero indicates the lesser degree of heterogeneity in particle size (Samnani et al., 2012). The maximum
drug content and entrapment efficiency were found to be 99.513±0.456% and 87.54±1.19% respectively for F3 among the ethosomes formulated. The variations in the entrapment efficiency may be contributed to the varied concentration of alcohol and phospholipid. However, there were only minor differences in entrapment efficiency when the concentration of phospholipid is constant and alcohol is varied. It can be assumed from the entrapment efficiency values that the phospholipid concentration plays a vital role in deciding the amount of the drug to be entrapped. The concentration of phospholipid is directly proportional to the entrapment efficiency of the ethosomes. The drug ziprasidone HCl is highly soluble in isopropanol and hence the percentage of solvent could not show any major remarkable effect on the entrapment of ziprasidone HCl. It being lipophilic, when the concentration of phospholipid increases, ziprasidone HCl got a better chance of clinging and that may be the reason for the increased entrapment efficiency with increased phospholipid concentration. These results were further support by the results obtained by Jain et al., (2004) and Tauitou et al., (2000).

### TABLE II - Particle size, Polydispersibility Index, Drug content and Entrapment efficiency of formulated ethosomes

| Formulation | Average Particle size (nm) | Poly Dispersibility Index | Drug content (%) | Entrapment efficiency (%) |
|-------------|----------------------------|----------------------------|------------------|---------------------------|
| F1          | 628.9                      | 1.000                      | 98.877±0.766     | 58.18±3.36                |
| F2          | 543.6                      | 0.710                      | 97.691±1.041     | 74.23±4.37                |
| F3          | 177.0                      | 0.335                      | 99.513±0.456     | 87.54±1.19                |
| F4          | 654.6                      | 0.805                      | 93.351±0.202     | 80.10±0.621               |
| F5          | 311.2                      | 0.768                      | 85.011±1.192     | 69.83±2.45                |
| F6          | 237.8                      | 1.000                      | 88.715±0.618     | 68.27±2.33                |

n=3, mean±Standard deviation

3.2.2. *In vitro* diffusion studies

Based on the results of physical evaluation, three formulations (F2, F3 and F5) were selected for diffusion studies. The diffusion study results of selected formulations (F2, F3 and F5) are presented in Table III and the comparative data is represented graphically in the Figure 3. The maximum percentage of drug diffused after 24 hrs was found to be 45.47±0.754% and 65.42±1.24% for drug suspension and hydro-alcoholic solution respectively. The maximum percentage of drug diffused was found to be 96.75±0.99% for F3 after 24 hrs among the selected three ethosomal formulations. When compared with hydro alcoholic solution and drug suspension, the ethosomal preparations showed a greater diffusion rate, which can be attributed to the vesicular systems. In the ethosomal preparations, the correlation between entrapment efficiency and the rate of diffusion was observed. The formulations with greater entrapment efficiency have shown greater diffusion rate, indicating the prominence of the vesicular systems (the lipid outer membrane) in the diffusion of drug molecules. After the *in vitro* studies, the optimized final formulation (F3) was characterized for surface morphology.
TABLE III - *In vitro* diffusion studies data of selected F2, F3 and F5 ethosomes and its comparison

| Time (hrs) | F2 (Mean±Standard deviation) | F3 (Mean±Standard deviation) | F5 (Mean±Standard deviation) | Hydro-alcoholic solution (Mean±Standard deviation) | Drug suspension (Mean±Standard deviation) |
|-----------|------------------------------|------------------------------|------------------------------|---------------------------------------------|------------------------------------------|
|           | n=3                          | n=3                          | n=3                          | n=3                                         | n=3                                      |
| 0         | 0                            | 0                            | 0                            | 0                                           | 0                                        |
| 5         | 1.48±0.111                   | 11.56±0.610                  | 3.61±0.02                    | 4.99±0.22                                  | 0                                        |
| 10        | 10.82±0.125                  | 23.5±1.022                   | 8.87±0.10                    | 9.93±0.214                                 | 1.87±0.164                               |
| 15        | 19.2±0.134                   | 33.91±0.839                  | 13.39±0.08                   | 12.15±1.049                                | 3.23±0.129                               |
| 20        | 28.4±0.794                   | 36.26±1.55                   | 18.96±0.415                  | 23.74±1.518                                | 5.20±0.06                                |
| 30        | 32.03±2.012                  | 43.29±0.71                   | 21.21±0.185                  | 19.42±1.117                                | 4.38±0.219                               |
| 45        | 37.32±2.12                   | 51.85±0.349                  | 26.65±1.101                  | 37.92±1.43                                 | 16.71±1.83                               |
| 60        | 41.75±1.27                   | 58.63±0.33                   | 33.71±2.213                  | 41.37±2.11                                 | 21.89±0.860                              |
| 3         | 48.21±1.52                   | 62.96±0.787                  | 41.44±1.11                   | 34.72±0.96                                 | 11.16±0.22                               |
| 5         | 51.23±1.051                  | 70.85±0.558                  | 54.95±0.930                  | 37.92±1.43                                 | 16.71±1.83                               |
| 7         | 58.43±0.284                  | 78.2±3.721                   | 57.73±0.905                  | 41.37±2.11                                 | 21.89±0.860                              |
| 9         | 59.91±1.022                  | 79.15±0.527                  | 61.16±0.872                  | 46.82±0.91                                 | 25.75±1.646                              |
| 12        | 67.45±1.099                  | 84.61±2.076                  | 66.25±1.03                   | 49.51±0.97                                 | 32.37±2.45                               |
| 15        | 75.88±2.061                  | 88.18±0.87                   | 69.38±0.93                   | 56.78±1.33                                 | 35.22±1.726                              |
| 18        | 79.05±0.924                  | 90±0.279                     | 74.81±2.65                   | 60.62±1.55                                 | 38.13±0.801                              |
| 21        | 81.9±0.762                   | 94.8±0.22                    | 77.78±1.76                   | 63.95±0.718                                | 41.5±0.403                               |
| 24        | 85.06±1.43                   | **96.75±0.99**               | 82.21±0.68                   | 65.42±1.240                                | 45.47±0.754                              |

**FIGURE 3:** *In vitro* diffusion studies data of selected F2, F3 and F5 ethosomes and its comparison.
3.2.3. Scanning Electron Microscopical studies

The SEM studies were performed only for F3 ethosomes and the photographs of F3 ethosomes are represented in the Figure 4. The SEM results indicate the almost spherical nature of the formulations. The wall or the vesicular outer membrane was not definite. This even represents the importance of addition of cholesterol or edge activators to strengthen the vesicles formed. In the current work, we have not incorporated any of the two, which may be the reason for week vesicular membrane.

FIGURE 4 -: SEM image of F3 ethosomes.

3.3. Ethosomal gel

3.3.1. Preparation of ethosomal gel:

Based on the in vitro release studies, the best formulation (F3) was selected and incorporated into gel to increase the ease of application, stability and better dose appropriation than liquid formulations. The optimized ethosomes (F3) were incorporated into the gel. Ethosomal gel (GF3) was prepared and evaluated.

3.3.2. Evaluation of ethosomal gel

3.3.2.1. FT-IR Study

The ethosomal gel (GF3) was evaluated for any incompatibility using FTIR and the spectra obtained are presented in figure 5. FTIR Spectra wave numbers of the ethosomal gel (GF3), were 3400 cm⁻¹ (for NH stretching), 3288 cm⁻¹ (for Aromatic CH stretch), 1636 cm⁻¹ (for C=N stretch), 1412 cm⁻¹ (for C-H bending) and 1044 cm⁻¹ (for C-N wagging). These results revealed that there was no disturbance in the principle peaks of pure drug ziprasidone HCl indicating no interaction between drug and excipients.

FIGURE 5 -: FTIR spectra of the ethosomal gel (GF3).
3.3.2.2. Visual inspection, Drug content & pH.

In physical characteristic studies, the ethosomal gel (GF3) which was kept at room temperature, was evaluated for physical characteristics like color change and formation of lumps at different time intervals (days). The ethosomal gels were found to be transparent, uniform without any agglomerates or lumps. Hence, it can be concluded that all the compositions were stable. The amount of drug in ethosomal gel (GF3) was found to be 99.07±0.681%. The drug content value with low deviation indicates the uniform drug distribution (ethosomal distribution) in the gels, which was assured by the lump free transparent gels. The pH of the GF3 was determined using pH meter and was found to be 6.7±0.18. The pH of the gel indicates that they are non-irritating and will enhance the compatibility with the skin even on long-term application.

3.3.2.3. Skin permeation studies

The skin permeation studies were performed using pig skin and the maximum percentage of drug permeated in 24 hours was found to be 93.30±0.168 for GF3. The percentage of drug permeated from GF3 was given in the Table IV and figure 6. The increase in the lipid content showed enhanced skin permeation which was evident from the results of cumulative percentage drug permeated through the skin.

**TABLE IV:** Skin permeation studies for final ethosomal gel formulation

| Time (Min) | % Drug Permeated |
|------------|------------------|
| 0          | 0                |
| 5          | 7.25±0.167       |
| 10         | 13.14±0.218      |
| 15         | 22.79±0.792      |
| 30         | 30.38±0.112      |
| 60         | 38.67±0.183      |
| 120        | 51.32±0.176      |
| 180        | 60.29±0.172      |
| 300        | 62.68±0.185      |
| 420        | 75.19±0.152      |
| 720        | 77.79±0.129      |
| 1080       | 85.18±0.173      |
| 1440       | 93.30±0.168      |

**FIGURE 6**: Skin Permeation study report of GF3.
3.3.2.3.1. **Flux**

The flux was calculated based on skin permeation studies. The flux was found to be \(52.05 \pm 0.564 \mu g/hr/cm^2\) indicates a noticeable permeation of drug. In addition to the combined effect of ethanol as permeation enhancer and flexibility of ethosomal vesicles, encapsulation of drug in ethosomes renders more positive charge to its vesicle surface and favours higher invitro permeation. As earlier studies noted that lipophilic drugs like testosterone and minoxidil ethosomal formulation was shown enhanced skin permeation than its hydroethanolic solutions (Ainbinder, Touitou 2005; Jun et al., 2007).

3.3.2.3.2. **Kinetic model fitting**

The description of permeation profiles has been attempted using different release characterization models. The correlation coefficient \( (R^2) \) values of ethosomal gel were 0.966 & 0.915 for 0 to 30min & 30min to 24hrs respectively for zero order; 0.975 & 0.979 for 0 to 30min & 30min to 24hrs respectively for first order; 0.735 & 0.934 for Higuchi and Peppas model. The correlation coefficient \( (R^2) \) was used as an indicator of the best fit for each of the models considered. From the kinetic model fitting results, it was concluded that the ethosomal formulations followed the first order kinetics and the higher “\(R^2\)” values of the Korsmeyer Peppas model \( (R^2=0.934, n=0.54) \) indicate that the encapsulating polymer is the responsible factor in controlling the release of the drug. The value of the release exponent, \( n \) in Peppas model indicated the non-fickian diffusion.

4. **CONCLUSION:**

The Ziprasidone HCl loaded ethosomal gel (GF3) was prepared by incorporating the optimized ethosomes (F3) into the carbopol 934 P gel base. The ethosomal gel was evaluated for the incompatibility studies (FTIR), visual observation, drug content, pH and the *ex vivo* drug permeation and shown satisfactory results. During the storage the gels didn’t show any difference in the visual inspection exhibiting its stability. The importance of concentration of the polymer encapsulating the alcoholic drug solution is proved through the research. The skin permeation studies illustrate the promising potential of ziprasidone HCl loaded ethosomal gel as an alternative to conventional dosage form. Through the present study, it can be said that the ethosomal gels of ziprasidone HCl will be a useful strategy for the controlled release of entrapped molecule in to deeper layers of the skin, thus improving the bioavailability of Ziprasidone HCl. These formulations help in surpassing first pass metabolism and even the gastric disturbances caused by the oral intake of the drug can be reduced.

5. **ACKNOWLEDGEMENT**

The author is thankful to DST- INSPIRE, Government of India, India for their valuable support to complete this work successfully.

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Received for publication on 08th July 2019 Accepted for publication on 05th August 2020