Design and development of zolmitriptan niosomal in situ nasal gel for the treatment of migraine

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ABSTRACT

The objective of the present study was to development of Zolmitriptan (ZMT) niosomal in situ nasal gel formulation for migraine treatment. By intranasal route delivered drug to the central nervous system (CNS) through the olfactory lobes, which bypasses the first-pass metabolism and consequently enhances the bioavailability. Noisome of ZMT were prepared by using the lipid film hydration method. Optimized niosomal formulation was used to prepare in situ gel. The developed Noisomal formulations were characterized for vesicle size, shape, zeta potential, entrapment efficiency, drug content and in-vitro diffusion study, mucoadhesive strength, permeation study, FTIR, DSC and XRD studies. The FTIR and DSC studies predicted that there was no any interaction in drug and excipients. ZMT niosomes were showed particle size, Polydispersity index (PDI), Zeta potential, % entrapment efficiency and drug content, 149nm, 0.223, -28.9, 88.16±0.8 % and 96.23±1.2% respectively. In-vitro diffusion study of niosomes shows 96.23±0.7% at 8h. The permeation rate of in situ niosomes gel and the pure drug was about 98.56% and 79.46%, respectively. XRD & DSC studies were showed that reduce crystalinity in the formulations. The SEM images of niosomes were found spherical in shape to some extent showing particle size distribution. Thus, it can be concluded that developed ZMT niosomal in situ gel formulation can be considered as a promising system for which may reduce dose requirement, improve patient acceptability and efficient targeting drug delivery to the brain through the olfactory lobe for migraine treatment.

INTRODUCTION

Migraine disease is a chronic neurological disorders characterized by recurrent to moderate to severe headache. Typically migraine headache is unilateral, throbbing or pulsating, which remains for 2 to 72 h. The migraine disease having severe symptoms includes nausea, vomiting, photophobia and phonophobia. The oral route is sometimes inefficient due to the low bioavailability, low solubility and absorption, and but the parental route, like the subcutaneous route, is one of the option but patient fewer acceptances. (Indira et al., 2015)
To overcome these problems intranasal route is preferred because this route provides beneficial of improving bioavailability and permeability mainly for lipophilic type of drugs, easy for self-administration and administered drugs to patients in vomiting and unconscious state also. (Patil et al., 2015) In situ forming polymeric formulations were before administration in solution form, then it undergoes gelation to form a gel. (Inayat et al., 2013) In situ gelling systems, formulations were in liquid form at room temperature but undergo gelation when in contact with body fluids or change in pH used as mucoadhesives drug delivery. (Khairnar et al., 2011)

Nasal gels were highly viscous in nature, thickened solution or suspension. The advantages of nasal gel includes the reduction of postnasal drip due to high viscosity, anterior leakage, irritancy except by using emollient and targeted to mucosa for high absorption of drugs. (Parmar and Lumbhani, 2012; Türker et al., 2004).

The niosome function was to form drug depots that release the drug in a controlled manner. (Madhavi et al., 2013). Moreover, recent advancement in an intranasal route that the nasal mucosa can act as the site for directly delivering the drugs to the CNS through the olfactory lobes, it helps to circumvent the BBB. (Namdev et al., 1999)

In recent decades different drugs like antihistaminics and anti-epileptic has been investigated to delivered the drugs through intranasal route; for this purpose, the drug should be formulated in the form of nasal gel and so as to give sustained release of drug by adhering the gel into the local tissues and releasing the drug through the olfactory lobe to the brain. (Qian et al., 2011)

ZMT is a selective agonist of serotonin (5- hydroxtriptan:5HT) TYPE 1B and 1D receptor. Oral administration of ZMT shows poor bioavailability due to its low permeability through the epithelium of cells BBB. ZMT after oral administration leads to gastric irritations, first-pass effect. To overcome all problems of ZMT was selected as a model drug to improved its nasal residence time by using mucoadhesive polymer and sustaining the drug release action with using controlled release polymer, HPMC K100. (Agarwal et al., 2001)

The present work was to formulate the ZMT niosomal in-situ nasal gel, which will increase the nasal residence time and thus sustained the drug release. Hence, ultimately enhance the bioavailability of the drug by using ion-dependent polymer gellan gum and control release polymer HPMC K100 respectively. (Lavanya et al., 2014) Niosomal in-situ nasal gel formulation, which may reduce dose requirement, improve patient acceptability and will be useful for efficient targeting the drug through the olfactory lobe, delivery to the brain.

**MATERIALS AND METHODS**

Zolmitriptan pure drug was procured from Emcure Pharmaceuticals Ltd. Pune, India. Gellan gum was purchased from CP KELCO. Mumbai, India. Cholesterol, Tween 40 were purchased from Molychem Mumbai. Benzalkonium Chloride was purchased from E. Merck (India) Ltd., Mumbai, India.

**Preformulation studies**

The sample of ZMT was visually evaluated for physical state colour, odour and taste. The melting point of ZMT was determined using the capillary tube method. Fourier transform-infrared (FTIR) of pure ZMT, gellan gum and niosomes samples were obtained on Jasco-4100 FTIR.

**Preparation of ZMT niosomes**

The batches for the experiment were design such that every formulation should contain ZMT, tween 40, cholesterol, a mixture of methanol as solvent and hydrating solvent as SNES. The surfactant ratio was increased; drug and cholesterol ratios were kept constant. Trail batches were conducted to decide the final ratios and method of preparation of niosomes by using parameters like particle size, entrapment efficiency shown in Table 1. (Bini et al., 2012)

**Niosomes preparation**

ZMT niosomes were prepared by using the lipid film hydration method. ZMT, surfactant and cholesterol in different ratios were dissolved in 15mL of methanol. The contents were processed in a rotary evaporator at 60°C for 30 min. at 100 rpm under reduced pressure of 25mmHg. At the edge of the round bottom flask, a thin film was formed. The resulting film was hydrated with 10 mL simulated nasal electrolyte solution (SNES). The obtained niosomes was sonicated in an ice bath sonicator for 20 min. The niosomes was kept overnight to mature and stable the niosomes. (Pardakhty et al., 2007)

**Characterization of niosomes**

Various batches of niosomes were formulated with lipid film hydration technique and subjected to evaluation of vesicle size by Dynamic light scattering technique.

**Determination of zeta potential**

The zeta potential of the niosomes was determined by using the Malvern Zeta sizer (Malvern Instruments, UK). The measurements were performed at
25°C using a constant cell drive of 150mV.

**% Entrapment efficiency**

The % entrapment efficiency of niosomes were determined by the ultracentrifugation method, where the niosomal dispersion was centrifuged at 14000 rpm for 90 min. The clear supernatant from the resulting solution was diluted with SNES pH 6.4 and observed by using a spectrophotometer. The % of encapsulation efficiency was calculated by using Equation (1).

\[
\text{% Entrapment efficiency} = \frac{T_p - T_I}{T_p} \times 100
\]  

(1)

**Drug content**

The 10 mg of lyophilized niosomes was dissolve in 1 mL methanol and volume adjusted with SNES pH 6.4. 0.1 mL of solution was further diluted with 10 mL SNES pH 6.4 and observed by using an analyzed spectrophotometer at 282 nm. The ZMT content in niosomes was (% w/v) was calculated using a calibration curve.

**In vitro diffusion studies**

In vitro release studies were carried out Franz diffusion cell, using dialysis membrane (molecular weight 10000-12000KDA), which was previously soaked into SNF phosphates pH6.4. The temperature was maintained at 37°C. 1ml sample of each formulation was transferred into a diffusion cell. Samples were withdrawn from the receptor cell at time intervals of 0.5,1,2,3,4,5,6,7,8 h. The samples were analyzed for drug content using UV Spectrophotometer.

**Formulation of niosomal nasal in situ gel**

Niosomal in situ nasal gel formulations were prepared by using ion-dependent polymer gellan gum at different concentration and HPMC K100 as controlled release polymer. Gellan gum solutions of different concentrations were prepared by adding the gum to deionised water and heating up to 90°C by continuous stirring on a magnetic stirrer. After cooling up to 40°C, HPMC K100, niosomal dispersion, mannitol, and benzalkonium chloride were added and mix well. (Singh et al., 2013) preparation of in situ gel formulation given Table 2.

**Characterization of in situ gel**

The niosomal gel prepared where subjected to their physical appearance to categorize the gel according to transparent, translucent, and opaque by its appearance. The viscosity study was performed by Brookfield synochoelectric viscometer fitted with spindle S-63 was subjected with rpm 10, 30, 50 and viscosity was observed. The gelling capacity of the formulation is dependent on the concentration of gelling agent and its concentration. More viscous gel leads to the formation of gel immediately but may or may not remain for an extended period of time, and some gel remains in gel state for an extended period of time due to more viscosity of the formulation. (Jyotivardhan et al., 2012)

**Mucoadhesive Strength/Gel strength**

A section of the nasal mucosa was cut from the sheep nasal cavity and instantly secured with mucosal out onto each glass vial using a rubber band. The vials with mucosa were stored at 37°C for 6 min and connected to the balance, and the other vials were placed on a height-adjustable pan. The weight was kept raised until two vials were detached. Mucoadhesive force, the detachment stress, was determined from the minimum weight that detached two vials. The mucoadhesive force expressed as the detachment stress in dyne/cm² was determined from the minimal weight that detached the mucosal tissue from the surface of each formulation. (Chaudhari et al., 2013) Mucoadhesive strength of in situ gel was determined using Equation (2).

\[
\text{Mucoadhesive strength (dynes/cm}^2) = m/A
\]  

(2)

Where,

- \(m\) = weight required for detachment in grams,
- \(g\) = Acceleration due to gravity (980 cm/s²).
- \(A\) = Area of mucosa exposed

**In vitro diffusion study**

In-vitro diffusion study of the in situ gel formulation was carried out in Franz diffusion cell. The Procedure was the same, which was used for In vitro diffusion study of the niosomes, aliquots of 3mL was withdrawn from the receiver compartment initially after 15, 30 min and 1 h interval. Aliquots withdrawn were suitably diluted with media and observed by using a spectrophotometer at 282 nm.

**Ex-vivo permeation study**

A fresh nasal tissues sample was inserted in the Franz diffusion cell. 7 mL of SNF phosphates pH 6.4 was added to the acceptor chamber and agitated with a magnetic stirrer at 37°C. Pure drug solution and the optimized batch formulation was placed in the donor chamber. 0.2 mL sample aliquots were withdrawn at time interval up to 8 h, filtered and observed by using a spectrophotometer at 282 nm. (Dattatraya et al., 2012) Permeability coefficient \(P\) was calculated from the slope graph of % of drug transported v/s time by using Equation (3).

\[
P = \text{slope} \times \frac{V d}{S}
\]  

(3)
<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Ratios (%)</th>
<th>Particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50:1:1</td>
<td>487</td>
</tr>
<tr>
<td>2</td>
<td>0.75:1:1</td>
<td>347</td>
</tr>
<tr>
<td>3</td>
<td>1:1:1</td>
<td>325</td>
</tr>
<tr>
<td>4</td>
<td>1.25:1:1</td>
<td>251</td>
</tr>
<tr>
<td>5</td>
<td>1.5:1:1</td>
<td>320</td>
</tr>
<tr>
<td>6</td>
<td>1.75:1:1</td>
<td>421</td>
</tr>
</tbody>
</table>

*S:D:C ratios

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Gellan gum (%w/v)</th>
<th>HPMC K 100 (%w/v)</th>
<th>Niosomal Dispersion (ml)</th>
<th>Benzalkonium Chloride (%v/v)</th>
<th>Mannitol (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G4.1</td>
<td>0.3</td>
<td>0.13</td>
<td>10</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>G4.2</td>
<td>0.6</td>
<td>0.13</td>
<td>10</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>G4.3</td>
<td>0.9</td>
<td>0.13</td>
<td>10</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>G4.4</td>
<td>1.2</td>
<td>0.13</td>
<td>10</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>G4.5</td>
<td>1.5</td>
<td>0.13</td>
<td>10</td>
<td>0.02</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Particle size (nm)</th>
<th>PDI</th>
<th>Mean zeta potential (mV)</th>
<th>% EE *</th>
<th>% Drug content *</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>353</td>
<td>0.528</td>
<td>-4.59</td>
<td>62.50±0.7</td>
<td>67.26±0.4</td>
</tr>
<tr>
<td>F2</td>
<td>327</td>
<td>0.421</td>
<td>-5.40</td>
<td>58.20±0.5</td>
<td>70.56±0.7</td>
</tr>
<tr>
<td>F3</td>
<td>217</td>
<td>0.152</td>
<td>-13.3</td>
<td>76.12±1.2</td>
<td>84.26±0.4</td>
</tr>
<tr>
<td>F4</td>
<td>149</td>
<td>0.223</td>
<td>-19.56</td>
<td>88.16±0.8</td>
<td>96.23±1.2</td>
</tr>
<tr>
<td>F5</td>
<td>247</td>
<td>0.112</td>
<td>-12.5</td>
<td>82.14±1.2</td>
<td>85.45±0.8</td>
</tr>
<tr>
<td>F6</td>
<td>450</td>
<td>1.012</td>
<td>-3.5</td>
<td>79.08±1.4</td>
<td>81.54±0.7</td>
</tr>
</tbody>
</table>

*Indicates average triplicate ±SD

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Gelling capacity</th>
<th>Appearance</th>
<th>Gellan gum concentration (%)</th>
<th>Viscosity (cps)</th>
<th>Mucoadhesive strength (dynes/cm²)</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>G4.1</td>
<td>+</td>
<td>Translucent</td>
<td>0.3</td>
<td>30</td>
<td>2018±0.4</td>
<td>89.23±0.5</td>
</tr>
<tr>
<td>G4.2</td>
<td>++</td>
<td>Translucent</td>
<td>0.6</td>
<td>38</td>
<td>2132±0.9</td>
<td>89.23±0.5</td>
</tr>
<tr>
<td>G4.3</td>
<td>++</td>
<td>Translucent</td>
<td>0.9</td>
<td>56</td>
<td>2386±1.5</td>
<td>92.45±0.8</td>
</tr>
<tr>
<td>G4.4</td>
<td>+++</td>
<td>Translucent</td>
<td>1.2</td>
<td>72</td>
<td>2643±1.2</td>
<td>88.26±1.2</td>
</tr>
<tr>
<td>G4.5</td>
<td>+++</td>
<td>Translucent</td>
<td>1.5</td>
<td>98</td>
<td>2934±0.4</td>
<td>91.56±0.9</td>
</tr>
</tbody>
</table>

*Indicates average triplicate ±SD

- : No gelation, +: slowly gels and dissolves, ++: gels immediately and remains for hours
+++ : gels immediately and remains for an extended period of time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pure drug</th>
<th>Optimized batch G4.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeability coefficient (cm/hr²)</td>
<td>59.12</td>
<td>78.12</td>
</tr>
<tr>
<td>Flux (µg/cm²/hr)</td>
<td>458.04</td>
<td>635.32</td>
</tr>
</tbody>
</table>
Table 6: Stability study data of Niosomal gel

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Drug Content (%) (2-8°C) *</th>
<th>Drug Content (%) (RT) *</th>
<th>Viscosity (cps) (2-8°C)</th>
<th>Viscosity (cps) (RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>89.18±0.12</td>
<td>86.02±0.4</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>88.02±0.4</td>
<td>85.25±0.6</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>88.12±0.8</td>
<td>85.09±1.2</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>87.42±0.5</td>
<td>84.26±0.2</td>
<td>38</td>
<td>37</td>
</tr>
</tbody>
</table>

*Indicates average triplicate ±SD

Where,

\[ V_d = \text{Volume of donor solution}, \]
\[ S = \text{Surface area of tissue}. \]

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by using Equation (4).

\[ \text{Flux (} J \text{)} = P X C D \]  

Where, \( CD = \text{Concentration} \)
\( P = \text{Permeability} \)
\( J = \text{Flux} \)

**Fourier transform infrared spectroscopy studies**

FTIR absorption spectrum of ZMT was determined by Fourier transform infrared spectrophotometer (Jasco-V-530 model). Spectra were recorded over the wave number 400-4000 cm\(^{-1}\).

**Differential scanning calorimetry studies**

Differential scanning calorimetry studies were carried out using the Mettler-Toledo DSC821 instrument. The nasal in situ gel of optimized batch and pure drug ZMT were hermetically sealed in aluminum crucibles and heated at a constant rate of 10°C/min over a temperature range of 25-300°C. The inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50mL/min.

**X-Ray diffraction studies**

XRD patterns were determined by using an X-ray diffractometer (PW1729, Philips, Netherlands) instrument. Samples were irradiated with monochromatized Cu-K\(\alpha\) radiation (1.542A°) and analyzed from 50 to 500 2\(\theta\). The voltage and current used were 30kV and 30mA, respectively.

**Scanning electron microscopy studies**

Morphology of niosomes was determined by using the JSM-6360 microscope (JEOL, Tokyo, Japan) instrument. Samples were scattered on a thin film of a two-component epoxy resin, coated with a platinum layer and acceleration during the observation was 25kV.

**Stability studies**

The stability studies of optimized niosomal in situ nasal gel was conducted for a short term accelerated stability studies for 3 months at 25°C±2°C/60%±5% RH as modified as per ICH guidelines. Samples were analyzed every 30 days for the appearance, entrapment efficiency and drug content parameters.

**RESULTS AND DISCUSSION**

**Preformulation studies**

The sample of ZMT was found to be white in color, odorless crystalline solid. The melting point of ZMT was found to be 138-140°C, which complies with the IP monograph.

**Fourier transform infrared spectroscopy studies**

A characteristic peak of carbonyl group C-O stretching observed at 1232, A band of N-H stretching at 3346 owing amino group, Peak observed at C-N stretching, characteristic peak at 1278 showing C=C stretching confirms aromatic group present and of the carbonyl group at 1731 confirms, presence of ZMT, depicted in Figure 1.

**Figure 1: FTIR spectrum of pure drug Zolmitriptan**

**Formulation & characterization of niosomes**

**Particle size analysis**

Particle size and the PDI of all the formulations were found that the smallest particle size and batch F4
Figure 2: Particle size distribution of optimized batch F4

Figure 3: Zeta Potential of optimized batch F4

Figure 4: *In vitro* diffusion of Niosomes

Figure 5: *In-vitro* diffusion profile of niosomal gel

Figure 6: *Ex vivo* drug permeation study of niosomal gel

Figure 7: FTIR Spectra of A) pure drug, B) polymer C) optimized batch

Figure 8: DSC of pure drug Zolmitriptan

Figure 9: DSC of niosomal Zolmitriptan Gel
smaller particle size as compared to other batch formulations. Particle sizes and PDI of pure ZMT and all the formulation batches was shown in Table 3 and Figure 2.

As the concentration of surfactant and stirring time were increased, reducing in particle size, but at an optimum concentration of surfactant beyond the surfactant has a negative impact on particle size.

**Zeta potential analysis**

The zeta potential of batches were found in between -3.5 to -19.56, and the optimized batch showed -19.56 mV, its indicated that the optimized batch have more stability than other batches. The Zeta potential analysis of niosomes of batches were shown in Table 3 and Figure 3.

**Percentage entrapment efficiency**

The percentage entrapment efficiency of batches were observed in between 58.20±0.5 to 88.16±0.8, and batch F4 showed entrapment efficiency 88.16±0.4%. Whereas, F2 batch shows low entrapment efficiency 58.20±0.5%. As the concentration of surfactant was increased, the more the drug gets entrapped into the niosomes. The percent entrapment efficiency and drug content of all batches of niosomes were shown in Table 3. In vitro diffusion studies of niosomes were observed and optimized F4 batch showed release 96.23% release after 8 h. In vitro diffusion studies data shown in Figure 4.

**Characterization of niosomal gel**

Niosomes were prepared by using an optimized batch was incorporated into a gel with gellan gum ion-dependent polymer and HPMC K100 using different concentration. The viscosity of all formulation batches were found that as the concentration of gellan gum increased, viscosity gradually increased, as viscosity increased, the stiffness of gel was increased. The viscosity of all niosomal gel formulation shown in Table 4.

**Mucoadhesive strength**

The mucoadhesive strength of in situ gel, results were revealed that polymer concentration increase, mucoadhesive strength also increases, mucoadhesion increased with polymer concentration due to extensive bonding with glycoprotein. So the prepared formulation possesses sufficient mucoadhesive property and may have desired residence time in the nasal cavity. Mucoadhesive strength results are shown in Table 4.

**In- vitro diffusion studies of in situ gel**

The in-vitro diffusion studies of in situ gel of all baths results were showed that the G4.1 batch showed 96.15%, and pure drug 82.46% at 8 h. So, the optimized G4.1 batch was used for further permeation studies. As the concentration of gellan gum was increased, the release of the drug was decreased. % Cumulative release profile of niosomal in situ gel shown in Figure 5.

**Ex vivo permeation studies**

Optimized batch G4.1 gel was used for studies of permeation rate of gel comparing with pure drug. The results showed that the optimized batch G4.1 gel and pure drug were permeation about 98.23% and 79.46% at 8 h, respectively. So, increase in permeation rate of an optimized batch as compared with pure drug. Ex-vivo permeation studies of niosomal in situ gel results shown in Figure 6 and Table 5.

**Fourier transforms infrared spectroscopy Studies.**

FTIR studies revealed that the fundamental peaks of ZMT was retained in the optimized formulation and indicating an absence of any chemical interaction between ZMT and excipients used. From the FTIR studies, it can be shown that the principle peaks of the pure drug of ZMT were retained in the optimized batch are almost identical and when compared with pure drug. Overlaid FTIR spectrum of (A) Pure drug, (B) polymer (C) optimized batch was shown in Figure 7.
Differential scanning calorimetry Studies

DSC studies results of the ZMT pure drug and the optimized batch G4.1 gel formulations were reveals that the pure drug exhibited, sharp endothermic peak at 141°C, indicating the melting point of the drug. DSC thermogram of nasal in situ gel formulation showed an endothermic peak at the melting of ZMT, indicated the slight change in the crystalline nature of the drug. However, the endothermic peak of ZMT shifted about to the left due to a reduction in the crystallinity at 82.20°C of the optimized formulation. Besides this, no additional peaks were found to demonstrate the significant changes in the melting characteristics of ZMT. The peaks were found with a calculated enthalpy (ΔH) of pure drug and gel were about 82.23 J/g, -121.40 J/g, respectively. DSC of thermogram of pure drug and niosomal ZMT gel shown in Figures 8 and 9 respectively.

X-Ray diffraction studies

The diffraction spectrum of pure drug ZMT showed that crystalline in nature as indicated by numerous, relative sharp and distinct peaks. The niosomes of optimized batch F4 was characterized by less intensity of the diffraction peak, which demonstrates that the chemical structure of the drug was not changed after the batch process. It was confirmed that ZMT existed in an amorphous state in the ZMT niosomes because of the disappeared sharp peak of ZMT in the diffraction pattern. Overlain spectra of XRD of A) pure drug B) Polymer c) Optimized batch shown in Figure 10.

Scanning electron microscopy

The surface morphology of the niosomal optimized batch formulation was found that crystalline in nature. The niosomes were found to be some extent spherical in shape with a narrow particle size distribution. Scanning electron microscopy of niosomes were shown in Figure 11.

Stability Studies

The stability studies of ZMT niosomes in situ gel optimized batch G4.1 showed physical stability for a period of 3 months at refrigerated conditions. The drug content of the niosomes gel formulation at different intervals, at room temperature, found to be decreased. It was found that no significant difference was observed drug content of niosomes gel formulation after 3 months at refrigerated condition. Stability studies data of niosomal gel shown in Table 6.

CONCLUSIONS

The present study was an attempt to formulate niosomal in situ gel of ZMT drug, having poor bioavailability. The niosomal in situ gel formulations was successfully prepared owing to an increased nasal residence time of the drug and gradually increase the permeation rate, which revealed that there was an increased in nasal residence time and increase the bioavailability of a drug. Niosomal in situ nasal gel can bypass the BBB to target the migraine disorders in the brain and decrease the intensity of migraine attacks.

ACKNOWLEDGEMENTS

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Author contributions

The author designed and performed the experiment, analyzed data, and prepared the manuscript. All authors played an equal role in completing this research work.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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