Formulation of Solid Lipid Nanoparticles Loaded Thermo-reversible Nasal In-situ Gel Containing Hibiscus Rosa Sinensis (L.) Extract

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ABSTRACT

The present study was aimed to formulate Solid lipid nanoparticles loaded thermo-reversible nasal In-situ gel containing Hibiscus Rosa sinensis extract by cold technique to impart better anti-depressant activity. It can improve the penetration of drug to CNS and shows faster pharmacological action. Thermo-reversible nasal In-situ gel were prepared by Poloxamer188 (PluronicF68) with mucoadhesive polymer polymers Carbopol 940. Nasal drug delivery systems are better imparts the Anti-depressant activity. The pH of the formulations was found to be within the range of 6.4 to 7.4. Viscosity of solid lipid nanoparticles loaded thermo-reversible nasal in-situ gel was found to be (212 cps to 409.6) for the sol, where as for the gels it was upto (38969 cps). The Spreadability SLN loaded In-situ nasal gel was found to be 25.19 (gm.cm/sec).The optimized formulation showed a drug release of 72.17% in 5hrs.

Keywords: SLN loaded nasal in-situ gel, Poloxamer188, Carbopol 940.
INTRODUCTION

Hibiscus Rosa sinensis is a genus of flowering plants in the mallow family Malvaceae. It is known as Jaswandi or gudhal in Maharashtra, India. Hibiscus rosa sinensis flower used for treatment of many ailments including constipation stomach upset, hair fall, CNS disorder like depression. H.rosa-sinensis are reported to possess cardio-protective, hypertensive, anti-diabetic, anti-convulsant and antioxidant activity in constipation and diarrhea. The leaves and flowers are observed to be promoters of hair growth and aid in healing of ulcers. Solid lipid nanoparticles (SLNs) are an almost spherical biodegradable nano-dispersion system of an average diameter of 10–1000 nm. SLNs consist of a colloidal solid lipid core matrix that is emulsified and stabilized in an aqueous medium by a surfactant SLNs offer unique properties and several advantages over traditional dosage forms. They are characterized by a smaller particle size, a large surface area, and high drug entrapment efficiency (EE). The nano-sized property helps to cross the BBB easily. Nasal route is the preferred and noninvasive route for brain targeting. Because brain and nose compartments are connected with each other via olfactory, trigeminal nerves, the vasculatures, the cerebrospinal fluid, and lymphatic system. Nasal cavity consists of vascularized epithelium, large surface area, and lower enzymatic activity when compared to GIT. This pathway of a nose to brain deliver the drugs directly to CNS without first pass metabolism and provide faster and maximum therapeutic effect. Generally, the intravenous route is given for immediate relief from status of CNS disorder due to good bioavailability. But it produces pain, irritation, local systemic adverse effect of precipitation and tissue necrosis. For the Nasal route is an alternative route to parenteral since it has good bioavailability and less side effect.

The aim of this research was to study the formulation of solid lipid nanoparticles containing hibiscus Rosa sinensis extract for nasal delivery using cow ghee as lipid core. Mucoadhesive Solid lipid nanoparticle loaded in situ gel of Hibiscus Rosa sinensis extract for nasal delivery have been reported where researchers ensured longer retention time of Solid lipid nanoparticles at the site of deposition and avoidance of hepatic metabolism resulting in improved bioavailability. MATERIALS AND METHOD

Materials

Hibiscus rosa sinensis flower were obtained from the local market from solapur. Cow’s ghee as Lipid core. All other ingredients used i.e Polaxomer188 , polyethylene glycol 400, tween 80 , Carbopol 940 ,Propylene glycol, Triethanolamine were of pharmaceutical grade.
Table 1: Formulation

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>Equivalent to 100mg</td>
<td>Equivalent to 100mg</td>
<td>Equivalent to 100mg</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>0.5%</td>
<td>1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Carbopol 940</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>Distilled water</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

Preparation of Extracts of Hibiscus Rosa sinensis by maceration process

The methanolic extract was obtained by maceration of fresh sepal-less flowers of *H. rosa-sinensis* for 72 h, followed by filtration and concentrated to remove methanol. The extracted by a slight modification of method described earlier by Harborne. Fresh sepal-less flowers (200 g) of *H. rosa-sinensis* were macerated in 2 L methanol: 2M HCl (85:15 v/v) solution for 72 h. The extract was then concentrated to 500 ml and filtered. To the filtrate, 100 ml concentrated HCl was added. The mixture was then refrigerated until crystals were separated out. Were then filtered, air dried and then weight extract was recorded.

Preparation solid lipid nanoparticles loaded Nasal thermo-reversible In-situ gel

Preparations of temperature response mucoadhesive in-situ nasal gel were prepared by the cold method. Specified amount of poloxamer188 (P188) and carbopol 934 (C940) were stirred in the calculated amount of cold distilled water. The dispersion was cooled to 4°C by keeping it in refrigerator for overnight and then polymer solutions were mix properly with continuous stirring and then Equivalent to 10mg of Solid lipid Nanoparticles (optimized Formulation) was added slowly in polymeric solution with continuous stirring in (thermostatically magnetic stirrer). Dispersion was stored in refrigerator for overnight to get clear sol form. Eventually stored in a refrigerator so that it remains in sol form. Finally the solution pH was adjusted with triethanolamine.

Evaluation of Gel

Gelation temperature

The different formulations of in situ system combinations were evaluated for gelation temperature. The gelation temperature was determined by heating the solution (1-2 °C) min in a test tube with gentle stirring until gel was formed. The gel was formed when there was no flow after container has overturned.

Determination of Spreadability
For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000g weight for 5 min. weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of spreadability.

**Viscosity**

The rheological properties of gels were determined by the Brookfield Viscometer using spindle no LV-3 (63).

**Drug Content**

1 ml of formulation was added then sample was filtered in 100ml of distilled water to make 100 µg/ml stock solution and form that 1ml was taken and adjusted with 10ml distilled water to give 10µg/ml and at fixed wavelength the absorbance of the formulation was carried out.

**In-vitro drug release study**

In-vitro drug release study of the formulated thermo-reversible In-situ gel was carried out by using Franz diffusion cell the prepared nasal insitu gel was mounted on Franz diffusion cell to get permeation area of 3.14 cm$^2$ phosphate buffer pH 7.4 was added to the acceptor chamber maintained at 34°C formulation equivalent to 10mg of Solid lipid nanoparticles was placed in donor chamber at predetermined time points and 2.5 ml sample was withdrawn from the acceptor compartment and replaced with an equal volume of the phosphate buffer 7.4 then sample was filtered and drug release was determined by UV-Spectroscopy.

**Stability study**

Hibiscus Rosa sinensis Loaded SLN nasal Insitu gel formulation was performed under storage condition 4°C gel was stored in clear, dry, airtight, moisture proof glass vial sealed with rubber caps kept away from light for period of 3 months. Every month stability of optimized formulation was evaluated on the basis of measuring gelling temperature and release profile to detect does not any changes.

**RESULTS AND DISCUSSION**

The results of evaluation of the prepared gel are depicted in table 2.

**Measurement of pH**

pH of formulations was found to be 6.4 to 7.4 which can be suitable for the application to the nasal cavity without any irritation.

**Gelation temperature**
Formulations of in situ system combinations were evaluated for gelation temperature. The gelation temperature was determined by heating the solution (1-2°C) min in a test tube with gentle stirring until gel was formed. The gel was formed when there was no flow after container has overturned shown in table no.2. Batch F3 shows higher temperature for thermo-reversion hence it is not suitable for the nasal application as in situ gel. But other two batches show gelation temperature in the range of the body temperature.

**Determination of Spreadability**

For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000g weight for 5 min. weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of spreadability shown in table.2

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>pH</th>
<th>Viscosity of sol (cps)</th>
<th>Gelation Temp (°c)</th>
<th>Spreadability (gm/cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.4</td>
<td>212.4</td>
<td>36</td>
<td>21.13</td>
</tr>
<tr>
<td>F2</td>
<td>6.7</td>
<td>304.9</td>
<td>33</td>
<td>23.21</td>
</tr>
<tr>
<td>F3</td>
<td>7.4</td>
<td>409.6</td>
<td>40</td>
<td>25.19</td>
</tr>
</tbody>
</table>

**Viscosity**

The rheological properties of gels were determined by the Brookfield Viscometer using spindle no LV-3 (63). Formulations show good thixotropic behavior owing to the incorporation of carbopol. The rise in the viscosity can be correlated with the concentration of carbopol.

**In-vitro drug release study**

In-vitro drug release study of the formulated thermo-reversible In-situ gel was carried out by using Franz diffusion cell the prepared nasal in situ gel was mounted on Franz diffusion. It can be seen from the graph that the formulations showed extended release of the active medicament for the period of 4 hours. Although the physicochemical properties of three formulations are different, the drug release profiles show no significant differences. The characteristic should be studied further for the elaboration of the mechanism.
CONCLUSION

Various formulation (F1, F2 and F3) were developed by using a Carbopol 940. To Formulate Solid lipid nanoparticles Loaded Thermo-reversible nasal In-situ gel containing Hibiscus Rosa sinensis extract were evaluated for the physiochemical parameters such as drug content, pH, viscosity, spreadability, in vitro drug diffusion. Viscosity studies of various formulations revealed that formulation F2 was better to compare to others. From among all the developed formulation, F2 shows better drug diffusion, did good Rheological properties. pH of the F2 formulation is sufficient enough to improve the penetration of drug to CNS and show faster pharmacological action Thus, SLN Loaded In-situ gel can be successfully prepared using Carbopol-940 as mucoadhesive polymers suitable for Nasal application Hence formulation F2 should be further developed for scale-up to industrial production.

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REFERENCES


