Enhanced Transdermal Delivery of Diltiazem Hydrochloride Via Reverse Micellar Transformation Type Liquid Crystalline Gel

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Abstract:
Reverse micelle transformation based liquid crystalline (TLC) transdermal gel of diltiazem hydrochloride was prepared and evaluated. The gel was prepared using lecithin and isopropyl myristate and evaluated for anisotropy, vesicular size and size distribution, drug entrapment efficiency, viscosity and in vitro drug release study. Three formulation of TLC gel were prepared which differed in the ratio of soya lecithin and isopropyl myristate. Formulation TLC1 found to have better property in term of viscosity and in vitro drug release study. Handling of transdermal gel is important aspect which was good for TLC1 and also shown controlled drug delivery of diltiazem hydrochloride.

Keywords: Reverse micelle, liquid crystals, transdermal drug delivery, in vitro evaluation

Introduction

Transdermal drug delivery system is getting its fame day by day as it offers controlled drug delivery for over the period of time. In general it is two types i.e., gel and matrix patch preparations. Gel system offers better opportunity to pharmacist as it is easy to prepare, apply, economic, any time and any where. Liquid crystals are intermediate state of matter which exist between solid crystals and liquids. They possess both structural ordering and mobility; when viewed under polarized light in polarizing microscope intense color bands and birefringence are seen. This is also a proof for the presence of liquid crystals. Lyotropic liquid crystals are always strongly birefringent, although their physical nature may vary widely from that of a waxy substance to that of a clear gel. The liquid crystalline phase is thermodynamically stable and represents a condition of incomplete melting. Gel based topical formulations found to have local or systemic effect of the drug according to the therapeutic requirements. Different composition of drug, surfactant, solvent and procedure gives cubic, hexagonal lamellar micellar phases and reverse micellar, which differ from each other in their mechanical properties. Liquid crystals have enhanced physical stability due to their viscoelastic behaviour. The viscoelastic property of mesophases is valuable to examine them in their rheological ground where the technique of testing does not significantly alter the arrangement. Diltiazem hydrochloride (DH) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of mild to moderate hypertension. DH undergoes an extensive first-pass metabolism, which results in very less oral dose being excreted unchanged in urine. Bioavailability of DH is ~30% to 40% owing to an important biotransformation. It has an elimination half-life of 3.5 hours. DH requires multiple oral daily dosages in order to maintain adequate plasma concentrations. Therefore, it is a suitable candidate for transdermal formulation. Sustained action is likely with the application of transdermal gel and it would also lead to better patient compliance. The aim of our work was to develop and evaluate reverse micelle transformation based liquid crystalline transdermal gel.
of diltiazem hydrochloride that would enhance transdermal delivery of diltiazem hydrochloride.

MATERIALS AND METHODS:

Diltiazem hydrochloride was obtained from Modi Mundi Pharma Pvt. Ltd. Meerut, India. Soya lecithin from CDH India and isopropyl myristate was procured from E. Merck, Mumbai. All other ingredients unless otherwise specified were of analytical reagent grade. Double distilled water was used in the experiment.

Preparation and characterization of transformation type liquid crystals:

The reverse micelle lamellar transformation type liquid crystals (TLC) were prepared by the method reported by Goymann and Hamann with a slight modification. Weighed amount of soya lecithin was dissolved in isopropyl myristate at 60° C. A small amount of double distilled water was added to the oily solution of phospholipids with the help of syringe with constant stirring leading to the formation of reverse micelle. For the preparation of drug loaded reverse micellar solution 500 mg of diltiazem hydrochloride was mixed with 4 ml of double distilled water. Total volume of the gel kept 10 ml. The composition of different types of liquid crystalline formulations is given in Table 1. Formulation was kept in tightly closed container for evaluation.

Optical microscopy and size and size distribution:

Presence of liquid crystals was examined using the polarized light microscope (Nikon HFX Labohot, USA). The reverse micelle lamellar transformation type liquid crystals were examined immediately after preparation and at frequent intervals. The size and size distribution was determined with the help of polarized microscope.

Entrapment efficiency:

The reverse micelle lamellar transformation type liquid crystals were kept overnight at 4°C and centrifuged (Remi, India) for 2 hours at 4000 rpm. Unentrapped drug concentration was determined in the supernatant spectrophotometrically (Shimadzu, Japan) at \( \lambda_{max} 235 \) nm. The entrapment percentage was calculated from the following formula:

\[
EE = \left( \frac{(Qt - Qs)}{Qt} \right) \times 100
\]

Where EE is the entrapment efficiency, Qt is the theoretical amount of diltiazem HCL that was added, and Qs is the amount of diltiazem HCL detected only in the supernatant.

Determination of viscosity

Viscosity of reverse micelle lamellar transformation type liquid crystals was determined with the help of viscometer (Brookfield) using spindle number 2 at 30 rpm. The reverse micelle lamellar transformation type liquid crystals were filled up to the mark so as to dip spindle properly. The system was equilibrated and then viscosity directly taken from viscometer display.

In vitro drug release study:

The in vitro release study of diltiazem from reverse micelle lamellar transformation type liquid crystals was performed using locally fabricated Franz diffusion type cell. Semipermeable membrane was employed in the study as the permeation barrier. The semipermeable membrane (2.5 cm²) was mounted on the receptor compartment of the diffusion cell and a liquid crystal approximately equivalent to 5 mg of the drug was applied. The receptor compartment contained 30 ml of the phosphate buffer (pH-6) solution. Samples of 5 ml were withdrawn at a time interval of one hour and the same was replaced with 5 ml of the fresh media solution to maintain the sink condition. The withdrawn samples were diluted appropriately. The samples were analyzed spectrophotometrically for drug content at 235 nm using (Shimadzu, Japan) spectrophotometer.

RESULTS AND DISCUSSION

Reverse micelle transformation based liquid crystalline transdermal/topical gel of diltiazem hydrochloride was prepared for controlled delivery of drug. The gel was prepared using lecithin, isopropyl myristate, drug and distilled water and evaluated for anisotropy, vesicular size and size distribution, drug entrapment efficiency, viscosity and in vitro drug release study. Three formulation of TLC gel were prepared which differed in the ratio of soya lecithin and isopropyl myristate. The reverse micelle lamellar transformation type liquid crystals were prepared by the method reported by Goymann and Hamann with a slight modification. Weighed amount of soya lecithin was dissolved in isopropyl myristate at 60° C. solution was clear in step. A small amount of double distilled water was added to the oily solution of phospholipids with the help of syringe with constant stirring leading to the formation of reverse micelle. This can be understood as solubilisation. For the preparation of drug loaded reverse micellar solution 500 mg of diltiazem hydrochloride was mixed with 4 ml of double distilled water. Total volume of the gel kept 10 ml. The composition of different types of liquid crystalline formulations is given in Table 1. Formation of liquid crystals was confirmed by polarizing light microscope (Nikon HFX Labohot, USA). The reverse micelle lamellar transformation type liquid crystals were examined immediately after preparation.
and at frequent intervals. The presence of birefringence proves the presence of liquid crystals. Photomicrograph of developed formulation in polarized and plain light is given in Figure 1 showing birefringence in photomicrograph A in polarized light. The size and size distribution was calculated with the help of polarized microscope.

Entrapment efficiency was found from 81.93 to 86.38% higher efficiency may be due to presence of drug in inner part and aqueous solubility of drug. Formulation TLC1 had highest efficiency i.e. 86.38%.

Appropriate viscosity of a gel is important aspect which is useful for handling and application. Higher viscosity is also beneficial for making controlled drug delivery system. Viscosity of reverse micelle lamellar transformation type liquid crystals was determined with the help of viscometer (Brookfield) using spindle number 2 at 30 rpm. Viscosity was found from 1890 to 2140 cp which is good enough to handle as gel.

The in vitro release study of diltiazem from reverse micelle lamellar transformation type liquid crystals was performed using locally fabricated Franz diffusion type cell15-16. The samples were withdrawn in one hour interval and study was performed for 8 hour. Cumulative percentage drug released verses time represented in Figure 2. In vitro release data were used to determine release mechanism by calculating regression coefficient. All the formulation found to have zero order release mechanism, however formulation TLC1 found to be more prominent.

Formulation TLC1 found to have better property in term of viscosity and in vitro drug release study. Handling of transdermal gel is important aspect which was good for TLC1 and also shown controlled drug delivery of diltiazem hydrochloride. Therefore formulation TLC1 considered as developed formulation.

CONCLUSION

Reverse micelle transformation based liquid crystalline transdermal/topical gel of diltiazem hydrochloride was prepared using safe and economic ingredients. Method of preparation is also simple. Entrapment efficiency, viscosity and in vitro release study found to have satisfactory results. Developed formulation found to have controlled release of diltiazem for longer duration of time.

REFERENCES

TABLE 1: FORMULATION OF TRANSFORMATION TYPE LIQUID CRYSTALS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation Code</th>
<th>Lecithin: Isopropyl myristate ratio</th>
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<tbody>
<tr>
<td>1.</td>
<td>TLC1</td>
<td>1:1</td>
</tr>
<tr>
<td>2.</td>
<td>TLC2</td>
<td>1:2</td>
</tr>
<tr>
<td>3.</td>
<td>TLC3</td>
<td>2:1</td>
</tr>
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</table>

TABLE 2: EVALUATION OF TRANSFORMATION TYPE LIQUID CRYSTALS

<table>
<thead>
<tr>
<th>Film Code</th>
<th>Average vesicular size (µ)</th>
<th>Viscosity (cp)</th>
<th>Entrapment efficiency (%)</th>
<th>Anisotropy</th>
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</thead>
<tbody>
<tr>
<td>TLC1</td>
<td>54.48</td>
<td>2140</td>
<td>86.38</td>
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<tr>
<td>TLC2</td>
<td>62.19</td>
<td>1950</td>
<td>81.93</td>
<td>A</td>
</tr>
<tr>
<td>TLC3</td>
<td>58.42</td>
<td>1890</td>
<td>82.31</td>
<td>A</td>
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</table>

TABLE 3. THE REGRESSION COEFFICIENTS FOR IN VITRO RELEASE STUDY OF TRANSFORMATION TYPE LIQUID CRYSTALS

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero order</th>
<th>First order</th>
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<th>Peppas-Korsmeyer</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
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<tr>
<td>TLC1</td>
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<td>TLC2</td>
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<td>TLC3</td>
<td>0.9783</td>
<td>0.8782</td>
<td>0.9354</td>
<td>0.9156</td>
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</tbody>
</table>

Figure 1: Photomicrograph of TLC1 in polarized light (A) and plain light (B) at 40X

Figure 2: Cumulative percentage drug released vs time of diltiazem hydrochloride from transformation type liquid crystals