Formulation and evaluation of microemulsion containing ketoprofen

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Abstract---Ketoprofen microemulsion is presently considered as the novel drug delivery system. It shows prolonged action. Ketoprofen is a BCS II class drug. It is a highly lipophilic poorly soluble drug with low oral bioavailability. The present aim was to increase the solubility by a microemulsion system for topical delivery. Microemulsions are clear, stable and isotropic liquid. They show advantages such as spontaneous preparation, scale up, ease of preparation, improving drug solubility of hydrophobic drugs. It is also used to increase the bioavailability of drug. These also aim at controlling the bioavailability of various drug molecules. The review put forward the development in a microemulsion-containing system. They improve solubility, chemical stability and oral bioavailability of poorly water-soluble drugs. There is a formulation of four different batches. The batches differ in the quantity of surfactant and co-surfactants.

Keywords---ketoprofen, microemulsion, particle size, zeta potential, scanning electron microscopy.
Introduction

The formulation and development of novel drug delivery system with the nature of enhancing the effectiveness of the existing of drug is an ongoing process in pharmaceutical research. The microemulsion concept was introduced in 1940s by Hoar and Schulman who generated a clear single-phase solution by triturating milky emulsion with hexanol. Microemulsions are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant. Alternative names for this system are often used such as swollen micelle, transparent emulsion, solubilized oil and micellar solution. Microemulsions are bicontinuous system that are essentially composed of bulk phases of water and oil separated by a surfactant/cosurfactant rich interfacial region. These systems have advantages over conventional emulsions in that they are thermodynamically stable liquid systems and are spontaneously formed.

Ketoprofen 2-(3-benzoylphenyl)-propionic acid, non-steroidal anti-inflammatory agent widely used for the treatment of rheumatoid arthritis and mild to moderate pain. Oral therapy of ketoprofen is very effective, but the clinical use is often limited because of adverse effects such as irritation and ulceration of the gastrointestinal tract. This drug has a relatively short half-life (1–3 hr) in plasma and has the potential to be delivered topically. In addition, it is an excellent drug for transdermal delivery amongst other NSAID. Furthermore, topical administration via the dermal route can bypass disadvantages of the oral route. Therefore, transdermal drug delivery has been considered to be an ideal route for ketoprofen administration. The use of penetration enhancer is valuable and important for achieving therapeutic plasma levels for many drugs, but penetration enhancer causes extensive damage to skin along with large increase in transdermal penetration rate. Hence, appropriate penetration rate and an acceptable level of irritation must both be jointly considered in the design of an optimum transdermal formulation.

Fig 1: Structure of Ketoprofen
Materials and Methods

Materials

Ketoprofen was purchased from the Solanki suppliers (Pune, India). All the Chemicals used as oleic acid, propylene glycol, Tween 20 were of analytical grade.

Methods

Identification of pure drug

Identification of pure drug was carried by Fourier Transform Infra-red spectrophotometry (Shimadzu 800s) scanned in the range of 200-400 nm.

Identification of drug by FTIR

FTIR (Shimadzu 8400s) spectrophotometer were used in the range of 400- 4000 cm\(^{-1}\) using potassium bromide discs (mixing ratio 1:1). The samples were hermetically properly sealed in aluminium pans and heated at a constant rate of 10\(^{\circ}\)C /min over a temperature range of 40-300\(^{\circ}\)C.

Determination of Melting point

Melting point of drug was determined by Thiele’s tube method. The small amount of drug in one closed end closed capillary attached to graduated thermometer and constant heat was supplied to the assembly suspended in paraffin bath. The temperature at which the drug melts is noted.

Formulation of Microemulsion

Weighed required quantity of drug (Ketoprofen). Ketoprofen drug was dissolved in oil (oleic acid) and this phase is sonicated for 5 min. The phase of surfactant and co- surfactant was prepared. Both the phases are mixed together by using magnetic stirrer. The addition of dropwise water was done to obtain 100 ml microemulsion. 100 ml microemulsion was prepared.

Table 1 Preparation of Optimized Microemulsion

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Batch 1</th>
<th>Batch 2</th>
<th>Batch 3</th>
<th>Batch 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen (gm)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oleic acid (ml)</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Tween 20 (ml)</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Propylene glycol (ml)</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Distilled water (ml)</td>
<td>32</td>
<td>39</td>
<td>46</td>
<td>53</td>
</tr>
</tbody>
</table>
Evaluation of Microemulsion

pH:

The pH of Microemulsion was determined using digital pH mete (Model EQ-610). Before measuring the pH of optimized microemulsion, the pH meter was calibrated with phosphate buffer 4 and 7. Then microemulsion was taken in glass beaker and electrode of pH meter was dipped into it for a minute and pH was noted.

Viscosity

The viscosity of microemulsion was determined by using Brookfield viscometer (Model LV) using spindle no 62. The apparent viscosity was measured at 10, 20, 30, 50 and 100 rpm. The Brookfield viscometer consist of cup which is stationery and spindle which is rotating. Different rotating size spindles are used and immersed in liquid. For liquids with low viscosity, large sized spindles are used (large diameter and surface area) are used and for high viscosity small spindles (small diameter and surface area) are used. Rotate the spindle in microemulsion till we get a constant dial reading in the display of viscometer. This procedure is repeated for three times to get a reproducible result.

Electrical conductivity

The conductivity measurement helps in determining whether the formulation is water continuous or oil continuous type. The solubilization of selected oily mixture was measured qualitatively by measuring the electrical conductivity. The conductivity of formulated samples was measured using conductivity meter (Model Systonics -Conductivity meter 304).

Drug content

Drug content of microemulsion was determined by dissolving accurately weighed 1 ml of microemulsion in 10 ml of methanol. After suitable dilution absorbance was recorded by using UV-visible spectrophotometer (UV-1800 Shimadzu, Japan) at 252 nm. The drug content is determined using an equation that includes a liner regression analysis of the calibration curve.

Zeta potential

Zeta potential is used to determine the stability of the prepared microemulsion. The charge on the surface of the particles is characterized by HORIBA SZ-100 by measuring the Zeta potential of the microemulsions. The sample is injected into a disposable cell and measurement of the particle electrophoretic moiety results in the calculation of Zeta potential.
Particle size determination

Samples were diluted using distilled water followed by measurement of particle size and Zeta potential in the triplicates and average values. Particle size of microemulsions was determined using HORIBA sz-100 (z type).

Scanning Electron Microscopy

SEM provides detailed image of the structure which is not possible by TEM. It is also used in the particle counting and size determination. The average magnification of scanning electron microscopy is 20X to 30,000X.

Results and Discussion

UV Spectroscopy

Calibration is defined as the process of assessment and refinement of the accuracy and precision method. It is the general method for determining the concentration of substance in an unknown sample by comparing to the unknown to set of standard samples of unknown concentration.

![Fig 2: Calibration curve of Ketoprofen](image)

IR Spectroscopy

![Fig 3: Interpretation of IR of Ketoprofen](image)
Identification and confirmation of pure drug (Ketoprofen) was carried out by observing obtained spectra. The IR spectrum of the ketoprofen showed the broad bands in the 3658, 3620, 3413 cm⁻¹ range, which are attributed to the stretching vibration of O-H group of ketoprofen.

**Melting Point**

The melting point of Ketoprofen was found to be 95°C.

**pH, Drug Content**

The pH of microemulsion of topical delivery should be always considered within this range. pH of different microemulsions was checked and it was shown in table. Drug content of all microemulsions was done and result was shown in table:

<table>
<thead>
<tr>
<th>Batches</th>
<th>pH</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>98.85</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>90.12</td>
</tr>
<tr>
<td>3</td>
<td>5.8</td>
<td>94.21</td>
</tr>
<tr>
<td>4</td>
<td>6.1</td>
<td>95.23</td>
</tr>
</tbody>
</table>

The higher the amount of drug more it will show concentrated formulation. These formulations range from concentrated aqueous.

**Viscosity**

Viscosity was determined and results was shown in table

<table>
<thead>
<tr>
<th>Viscosity (RPM)</th>
<th>Batch 1 (cP)</th>
<th>Batch 2 (cP)</th>
<th>Batch 3 (cP)</th>
<th>Batch 4 (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>129</td>
<td>156</td>
<td>240</td>
<td>840</td>
</tr>
<tr>
<td>20</td>
<td>144</td>
<td>160</td>
<td>183</td>
<td>601</td>
</tr>
<tr>
<td>50</td>
<td>153</td>
<td>186</td>
<td>136</td>
<td>387</td>
</tr>
<tr>
<td>100</td>
<td>154</td>
<td>189</td>
<td>113</td>
<td>277</td>
</tr>
</tbody>
</table>

**Determination of Particle size and Zeta potential:**

<table>
<thead>
<tr>
<th>Batches</th>
<th>Particle size</th>
<th>Zeta Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103.2</td>
<td>-12.7</td>
</tr>
<tr>
<td>2</td>
<td>185</td>
<td>-12.3</td>
</tr>
<tr>
<td>3</td>
<td>417.3</td>
<td>-17.5</td>
</tr>
<tr>
<td>4</td>
<td>502.7</td>
<td>-22.8</td>
</tr>
</tbody>
</table>
The particle size of microemulsion is determined by the rate and extent of drug release absorption. The small size of the particle is required for rapid absorption as well as enhanced bioavailability of the formulation. Particle size of optimized microemulsion was found to be 377.3 nm; such globules were considered to be suitable for topical administration.

The zeta potential governs the stability of microemulsion, it measures the value for stability sample. The negative zeta potential indicates the droplets of microemulsion having no charge i.e. the system is stable. Zeta potential was found to be -12.7 mV.

**Electrical Conductivity**

**Table 6: Determination of electrical conductivity**

<table>
<thead>
<tr>
<th>Batches</th>
<th>200 ms</th>
<th>20 ms</th>
<th>2 ms</th>
<th>200 μs</th>
<th>20 μs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>000</td>
<td>00.0</td>
<td>0.05</td>
<td>051</td>
<td>1.</td>
</tr>
<tr>
<td>2</td>
<td>000</td>
<td>00.0</td>
<td>0.04</td>
<td>036</td>
<td>1.</td>
</tr>
<tr>
<td>3</td>
<td>000</td>
<td>00.0</td>
<td>0.03</td>
<td>026</td>
<td>1.</td>
</tr>
<tr>
<td>4</td>
<td>000</td>
<td>00.0</td>
<td>0.01</td>
<td>014</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Electrical conductivity is utilized to identify nature of o/w or w/o microemulsion. It is measured using an electroconductometer, used to identify whether there is an oil or water as a continuous phase. It also identifies the phase inversion phenomenon.
**Scanning Electron microscopy**

![SEM Image](image)

Fig 6 : SEM of optimized formulation

The optimized batch of microemulsion was subjected to SEM analysis for morphology and surface topography. The SEM analysis of the microemulsion shows hexagonal and bicontinuous structure.

**Conclusion**

The current research work is focused on the preparation of safe, efficient and more compatible microemulsion which will enhance utility of these novel vehicles. The microemulsion protects labile drug, control drug release and reduce patient variability. The microemulsion can be used to optimize drug targeting without a concomitant increase in systemic absorption. The role of microemulsion is used to overcome problems of poor aqueous solubility of highly lipophilic drug compound. It provides high, consistent and reproducible bioavailability. The microemulsion preparation shows transparent yellow colour. The zeta potential determines the stability of formulation. To avoid the adverse side effect, a ketoprofen microemulsion for topical use was formulated.

**Acknowledgement**

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**References**