Formulation and Characterization of Tapentadol Loaded Emulgel for Topical Application

Nitin Prabhakar Ambhore*, Panchxari Mallapa Dandagi, Anand Panchxari Gadad, Paresh Mandora
Department of Pharmaceutics, KLE University College of Pharmacy, Belagavi-590010, Karnataka, INDIA.

ABSTRACT

Background: Tapentadol is a centrally acting analgesic drug which falls under class III drug as per biopharmaceutical classification systems having poor bioavailability. Aim: Therefore, present study was aimed at solubility and permeability enhancement of Tapentadol using emulosomes loaded emulgel drug delivery system. Methods: Emulgel was prepared using data light liquid paraffin, Tween 20 and PEG 400 as Surfactant and Co-surfactant respectively. For preparation of stable Emulgel, micro emulsion region was identified by constructing pseudo ternary phase diagram containing different proportion of surfactant: co-surfactant (1:1, 2:1 and 3:1), oil and water. Ex vivo drug release study was done and compared to in vitro drug release of optimized formulation X2Q1. Physico-Chemical Evaluation: Total nine Emulgel formulations were prepared and evaluated for self-emulsification time, dispersibility, droplet size analysis, stability studies, turbidimetry, zeta potential, drug content and in vitro and ex vivo drug release. Results: Among all the formulations, optimized formulation X2Q1 with 1.5% carbopol 981 and optimized Q1 emulsion formulation showed in vitro drug release of 90.03 % at the end of 8 hrs. Based on results of self-emulsification time & dispersibility, droplet size analysis, drug content and in vitro drug release the X2Q1 formulation was selected as an optimized formulation which showed a maximum drug release in vitro and extended drug release up to eight hrs. The optimized formulation found to be stable, non-irritant and safe for topical drug delivery. Conclusion: Hence emulgel formulations can be a potential alternative to traditional oral drug delivery systems of Tapentadol to improve its bioavailability.

Key words: Tapentadol, Microemulsion, Emulgel, Skin Permeation, Optimization, Topical Delivery.

INTRODUCTION

Tapentadol is a centrally acting analgesic believed to act through a dual mechanism as opioid receptor agonist and an inhibitor of norepinephrine reuptake, approved for treatment of moderate to severe pain in adults 18 years and older. It is also specifically indicated for controlling the pain of diabetic neuropathy when opioid medication is required. The short biological half-life (about 4 hr) and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 600 mg/day. It is 18 times less potent than morphine in terms of binding to human mu-opioid receptors. Tapentadol is available in the dose of 50 mg, 75 mg, and 100 mg in the form of oral tablets. Tapentadol has an oral bioavailability of 31.9 ± 6.8%, protein binding of 20% and t1/2 of 4 hrs. It is metabolized hepaticaly. Oral drug delivery is most desirable route of administration because of its high patient satisfactoriness, flexibility in formulation and stability. Factors that often impact the absorption of orally administered drugs include frequent dosing which results in fluctuation of plasma drug concentration and finally toxicity. The low bioavailability and very less half life the frequency of administration is more causes poor patient compliance. The low oral bioavailability and
short half life intend to go for topical route of admin-
istration. Topical delivery can be defined as the application of drug containing formulation to skin to directly treat the general disease with the intent of confining the pharmacological or other effect of the drug to the surface of skin or within the skin. Most widely used semisolid preparations includes gels, creams, ointments etc. The USP defines gel as a semisolid system consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpen-
etrated by liquid. The gel contains larger amount of aqueous or hydro alcoholic liquid in a network of colloidal solid particles which may consist of inorganic or organic substances. Inspite of many advantages of gels a major limitation is in the delivery extended release of hydrophobic drugs. So to over this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. When emulsions and gels are used in combined form the dosage form is referred to as “Emulgel”. The presence of gelling agent in the water phase converts the classical emulsion into an emulgel. The Emulgel are hydrogel containing randomly distributed oil micro droplets. Emulsions are biphasic systems in which one immisc-
ible liquid is dispersed into other due to which the system becomes unstable and so stabilized by adding emulsifying agent. Emulsion itself is a controlled release system where entrapped drug particles in internal phase pass through the external phase and then slowly gets absorbed into the skin. The gel forms a cross linked network where it captures small drug particles and provides its release in a control manner. Emulgel are emulsions either oil-in-water or water-
in-oil type which are gelled by mixing with a gelling agent. They have high patient acceptability because of its favourable properties such as being thixotropic, greaseless, easily spreadable, easily removables, emollient, nonstaining, long shelf life, bio friendly, transparent and pleasing appearance.

Microemulsions are homogeneous, transparent, thermodynamically stable dispersions of water and oil stabi-
ized by addition of surfactant, usually in combination with co-surfactant and whose droplet size is in the range of 20-200 nm. Since microemulsions have large surface area, they can incorporate in their core larger quantities of molecules which are insoluble in continuous phase. The main difference between emulsion and micro-
emulsion is the size and the shape of the droplets and since the size of the droplets in microemulsion is much smaller than the wavelength of visible light the micro-
emulsions are transparent. The microemulsions are prepared with high concentration of surfactant which is in greater solubilisation of drugs and also requires lesser amount of energy. To overcome the disadvantages of Tapentadol in the oral delivery an attempt has been made in the present study to formulate emulgel of Tapentadol by incorpo-
rating microemulsion of tapentadol in the gel base.

MATERIALS AND METHODS
Tapentadol HC3 was procured from Precises Chemi-
pharma Pvt. Ltd, Mumbai. Light liquid paraffin was procured from S.D Fine Chem Limited Mumbai. Tween 20, PEG4080, Carbopol 940 NF, Carbopol 934 NF was procured from Hi-media Pvt Ltd Mumbai. Carbopol 981 NF was procured from Lubrizole Mumbai.

Saturation Solubility of Oils, Surfactant and Co-Surfactant
Saturation Solubility in Oils Excess amount of drug was added to 10 ml vials containing 10 ml of oils (Castor oil, sunflower oil, coconut oil and oleic acid) and then it was kept on a mechanical shaker for 72 hrs. After 72 hrs solution was centrifuged for 30 minutes and then the su-
pernatant was filtered and then UV absorbance was taken at 273 nm by suitable dilution with buffer.5,6

Saturation Solubility in Surfactants Excess amount of drug was added to 10ml of vials containing 10 ml of surfactants (Tween 20, Tween 60, Tween 80) and it was kept on a mechanical shaker for 72 hrs. After 72 hrs solution was centrifuged for 10 min at 3000 rpm and then the supernatant was filtered and then UV absorbance was taken at 273 nm by suitable dilution with buffer.

Saturation Solubility of Tapentadol with Co-Surfactant Excess amount of drug was added to 10ml of co-surfac-
tant (PEG 400, PEG 600 and Propylene Glycol) and it was kept on a mechanical shaker for 72 hrs. After 72 hrs solution was centrifuged for 10 min at 3000 rpm and then the supernatant was filtered and then UV absorbance was taken at 273 nm by suitable dilution with chloro-
form.6,7

Construction of pseudosternary phase Diagrams Pseudosternary phase diagrams were constructed using Chemix school 3.60 software. The method used for study was water titration method. The surfactant and co-surfactant was mixed in the ratio of 1:1, 2:1 & 3:1 keeping the co-surfactant concentration constant and varying the surfactant concentration. The surfactant and co-surfactant were mixed in a ratio and vortexed for 5 mins. Then the oil was added to surfactant and co-surfactant in the ratio ranging from 1.9 to 9.1 respect-
ively. The water was added to the mixture drop by drop by burette and then the mixture was observed for any turbidity or gel formation. The point at which turbidity or gel formation is observed is considered as the end point of titration. The data obtained was feed in the Chemix School 3.60 software to obtain the area of emulsion.8,9

Preparation of Emulsion Water titration method was employed for the preparation of emulsion. The concentrations of oil, water, surfactant and cosurfactant were varied in each case keeping the concentration of drug constant and displayed in Table 1. Predetermined amount of drug was accu-
ately weighed and dissolved in oil. Surfactant and co-surfactant were added to oily solution of the drug and mechanically stirred (Magnetic stirrer) form an emulsion. Water was added drop wise to the emulsion till the formation of a transparent mixture. Formation of transparent solution indicates formation of microemulsion.

Evaluation of Prepared Microemulsion Drug Content of Emulsion 1 ml of emulsion was taken and it was added to 10 ml volumetric flask and then the volume was made with chloroform and then further dilutions were made and UV absorbance was taken at 273 nm. The blank was prepared by preparing microemulsion without drug and then further dilutions were made and UV absorbance was taken at 273 nm. The volumetric flask and serial dilutions were made with chloroform and then the UV readings were taken, the values obtained was used to calculate the concentration of drug in emulsion.

Globule Size Determination The globule size distribution of the formulations was measured by Dynamic Light Scattering Particle Size Analyzer (Nanotrac Particle Size Analyzer). The range of the analyzer is 0.02 mm to 2.8 μm. 0.1 ml of the emul-
sion was taken and it was diluted to 250 ml with distilled water and then the readings were taken.

Zeta Potential The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. Zeta potential was measured by using Zeta meter instrument.

Formulation of Emulgel The gel base was prepared by soaking the gelling agent overnight in a sufficient quantity of water and then the emulsion equivalent to 0.5% was incorporated in the gel base to give emulgel. The different batches of emulgel were prepared according to the formulation chart given in Table 2 and 3.

Characterisation of Emulgel Physical Examination The prepared Emulgel formulations were inspected visually for their color, homogeneity and consistency.

Drug Content 1 gm of emulgel was accurately weighed and it was dissolved in 100 ml of chloroform and it was kept for sonication for 2 hrs. The solution was passed through filter paper and filtered. The absorbance was measured spectrophotometrically at 273 nm against corresponding Emulgel without drug as blank. Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve. Experiments were carried out in triplicates.

pH The pH of various emulgel formulations were deter-
mined by using digital pH meter. 1 g. of emulgel was dissolved in 100 ml distilled water and stored for 2 hrs. The measurement of pH of each formulation was done in triplicate.

Viscosity The measurement of viscosity of the prepared emulgel was done with a Brookfield Rheometer. The emulgel was rotated at 1 rpm and the corresponding dial reading was noted. The viscosity of the gel was obtained by that reading. The viscosity was measured in cPs.

Spreadability It indicates the extent of area to which emulgel readily spreads on application to skin or affected part the upper slide was noted down. A weighed quantity (350 mg) of emulgel was taken on a glass plate (10×5 cm). Another glass plate (10×5 cm and 5.8 ± 1 g) was dropped from a distance of 5 cm. The diameter of the circle of spread was measured after 1 min.10

Extrudability Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of emulgel in

526 Indian Journal of Pharmaceutical Education and Research | Vol 51 | Issue 4 | Oct-Dec, 2017

Mandora et al.: Tapentadol loaded emulgel for topical application


Mandora et al.: Tapentadol loaded emulgel for topical application
In vitro Release Study

The in vitro drug release studies of the Emulgel were carried out in modified Franz diffusion cell using dialysis membrane. The membrane was soaked in Phosphate buffer of pH 6.8 which was used as dissolution media which was added to the receptor compartment. The donor compartment was kept in contact with receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37 ± 0.5°C. Sample (1ml) was withdrawn at suitable time intervals and replaced with the equal amount of fresh dissolution media. Samples were analysed spectro photometrically at 273 nm and the cumulative % drug release was calculated. The graph is plotted of % cumulative drug release versus time.

Ex Vivo Drug Diffusion

The abdominal skin of full thickness was excised from the rats weighing 105-120 g, free from any visible sign of disease. This was mounted in the donor compartment. The Emulgel was placed over it and the permeation study was carried out. The drug release was compared with that of optimized tapentadol emulgel formulation.

Skin Irritation Test

The skin irritation test was performed on the male wistar rats. The animals were divided in three groups i.e. control, standard and test. The back skin of the rat from the standard group was applied with 0.9% of saline which is the standard irritant and the test group was applied with 0.03% tapentadol emulgel. The animals were observed for any skin irritation like erythema or edema and score was given accordingly.

Stability Studies

Short term stability study was performed on the optimized formulation. The formulation was subjected to different conditions of temperature and relative humidity i.e. 25°C / 60 % RH and 40°C / 80 % RH for a period of 2 months. Samples were withdrawn at the interval of 1 month and were evaluated for rheological properties, drug content.

RESULTS AND DISCUSSION

Saturation Solubility in Oils, Surfactant and Co-Surfactant

The various oils used for study were oleic acid, coconut oil, castor oil and sunflower oil and liquid paraffin. The solubility in light liquid paraffin was found to be 3mg/ml that was the maximum solubility compared to other oils. The graphical representation is shown in Figure 1. The different type of surfactants used for solubility studies were Tween 20, Tween 60, Tween 80, Span 20, Span 80 and co-surfactants were used PEG 400, PEG 600 and Propylene glycol. The maximum solubility among surfactants were found in case of Tween 20 i.e. 10 mg/ml and in case of co-surfactants is of PEG400 i.e. 15mg/ml. The results of the solubility of surfactant and its graphical representation was shown in Figure 2 and 3. So based on the solubility light liquid paraffin (oil), Tween 20 (surfactant) and PEG (co-surfactant) were selected for the preparation of emulsion.

Construction of Pseudoternary Phase Diagram

The construction of phase diagrams makes it easy to find out the concentration range of components for existence range of microemulsions. The selected oil, surfactant and co-surfactant based on solubility studies were used to construct the phase diagrams. The method used is water titration method. All possible regions for emulsion formation at all possible ratios of surfactant: co-surfactant: oil was represented. Based on solubility study the oil, surfactant and co-surfactant having highest solubility were selected and then for the construction of pseudoternary phase diagram construction the ratio of co-surfactant was kept constant but the ratio of surfactant was varied from 1:1, 2:1 and 3:1. The water was added drop wise through burette till turbidity was observed. The microemulsion region in the phase diagram is the region where clear and transparent formulation was produced shown in Figure 4.

The region shaded purple in the phase diagrams were selected from each ratio of oil: Smix was of 2 months. Samples were withdrawn at the interval of 24hrs the animals were observed for any skin irritation like erythema or edema and score were given accordingly.

Table 1: Formulation Table of Tapentadol Emulgel

<table>
<thead>
<tr>
<th>Sr no.</th>
<th>Formulation code</th>
<th>S:Cos ratio (S/60)</th>
<th>Oil: Smix ratio</th>
<th>Amount of drug added (mg)</th>
<th>Approx Theoretical drug content (mg)</th>
<th>Total volume of mixture (ml)</th>
<th>Amount of water (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P1</td>
<td>1.1</td>
<td>1.9</td>
<td>2.3</td>
<td>230.209</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>P2</td>
<td>1.1</td>
<td>2.8</td>
<td>2.5</td>
<td>200.350</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>P3</td>
<td>1.1</td>
<td>3.7</td>
<td>2.5</td>
<td>190.000</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>Q1</td>
<td>2.1</td>
<td>1.9</td>
<td>2.5</td>
<td>226.430</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>Q2</td>
<td>2.1</td>
<td>2.8</td>
<td>2.5</td>
<td>217.703</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>Q3</td>
<td>2.1</td>
<td>3.7</td>
<td>2.5</td>
<td>205.37</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>R1</td>
<td>3.1</td>
<td>1.9</td>
<td>2.5</td>
<td>213.90</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>R2</td>
<td>3.1</td>
<td>2.8</td>
<td>2.5</td>
<td>211.035</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>R3</td>
<td>3.1</td>
<td>1.9</td>
<td>2.5</td>
<td>207.50</td>
<td>10</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)

Table 2: Formulation Table of Tapentadol Emulgel for Polymer Concentration 1.5%

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>X1P1</th>
<th>Y1P1</th>
<th>Z1P1</th>
<th>Z2Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol emulsion equivalent to 0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
</tr>
<tr>
<td>Carbopol 981</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Glyceryl</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Triethanol amine</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Methyl Paraben</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Propl Paraben</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Distilled water q.s</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)

Table 3: Formulation Table of Tapentadol Emulgel for Polymer Concentration 2%

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>X1P1</th>
<th>Y1P1</th>
<th>Z1P1</th>
<th>Z2Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol emulsion equivalent to 0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
<td>0.25%</td>
</tr>
<tr>
<td>Carbopol 981</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Glyceryl</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Triethanol amine</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Methyl Paraben</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Propl Paraben</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Distilled water q.s</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)
The area of microemulsion increased as the concentration of surfactant increases.

Formulation of Emulsion

The percentage of surfactant: co-surfactant (Smix) and oil was prepared by adding the quantities obtained from pseudoternary phase diagrams. The 250 mg of drug was added to the formulation based on its solubility in surfactant, co-surfactant and oil. The mixture was kept for stirring on magnetic stirrer till the drug completely solubilizes and then it was kept for 24 hrs to attain the equilibrium. The formed emulsion was transparent in appearance.

The formulation P1, P2, P3 contains the surfactant: cosurfactant ratio 1:1 and the oil: Smix ratio was varied from 1:5 to 3:7 same way in Q1, Q2, Q3 contains the surfactant: Co-surfactant ratio 2:1 and oil: Smix ratio 1:9 to 3:7 and in the formulation R1, R2, R3 contains the surfactant: co-surfactant ratio of 3:1 and oil: Smix ratio same as in above formulations. The prepared emulsions were then evaluated for drug content and droplet size.

Evaluation of Prepared Microemulsion

Drug Content

The percentage drug content of all the nine formulations of Tapentadol emulsion was determined and the percentage of drug present was showed in Table 4. The drug content varied from 78% to 95%. The formulation Q1 has drug content of 95.13% and that of P1 was 94.01% and of R1 was 92.97%. The highest drug content was found in case of Q1 formulation due to greater solubilisation of drug as compared to others and even as the quantity of water required to formed the microemulsion was less in case of 1:1 ratio of surfactant: co-surfactant, 1:9 ratio of oil: Smix.

Globule Size Determination

The globule size of all the prepared microemulsion was evaluated using neotrac. The particle size obtained was reported in Table 4. On the basis of result obtained it was found that the globule size decrease as the concentration of surfactant increased. The globule size of the formulations P1 and Q1 was found to be 176 and 116nm respectively. The formulation P1 and Q1 was selected as optimized microemulsion formulation based on globule size as it was ranging in microemulsion region and there was not much difference in the drug content of the two formulations. The formulation R1 had highest globular size compared to formulation P1 so it was not selected as increase in globular size delays diffusion rate.

Zeta Potential Determination

The Zeta potential of all formulations was found to be in the range of -28.08 to -9.513 and it’s displayed in given Table 4. The zeta potential showed that the formulations showed moderate to good stability.

Preparation of Emulgel

Emulgel was prepared using different gelling agent such as carbopol 934, carbopol 940 and carbopol 981 in the concentration of 1.5%w/v and 2%w/v. The mentioned gelling agents were swelled in distilled water for 24 hrs and high viscosity solution was obtained. The Tapentadol loaded microemulsion was slowly added to the viscous solution of gelling agent by continuous stirring and then clear emulgel was obtained. The carbopol as an aqueous gel matrix is a continuous phase and the dispersion of oily droplets within the meshes of 3-D network of gel increases the viscosity of microemulsion significantly. The optimized formulations of microemulsions i.e. P1 and Q1 was incorporated into the gel base. The quantity of microemulsion added was equivalent to 0.25% of Tapentadol, 0.02% of triethanolamine was added to adjust the pH of formed emulgel, glicerin 1% and the preservatives like methyl Paraben and Propyl Paraben was added to the formulation, the quantity of preservative added was 0.03% showed in Table 2 & 3.

Characterisation of Emulgel

Physical Appearance

All the prepared formulations were buff white in appearance and they showed good homogeneity and consistency.

Drug Content

The percentage drug content of prepared emulgel was found in the range of 74.6 to 96.23%. The results were displayed in the Table 5. The highest drug content i.e. 96.23% was obtained for the formulation X2Q1 containing optimized Q1 formulation of emulsion and gelling agent present in the concentration of 1.5% of Carbopol 981.

pH

The pH of all the formulation was found to be ranging from 5.5 to 6.3 which was found to be acceptable to avoid any skin irritation. The results in the form of Table are shown in the Table 5.

Viscosity

Viscosities of different Tapentadol emulgel formulations are shown in Table 6. The viscosity ranged between 11970 to 48229 cPs. The results showed that the emulgel formulations prepared by using carbopol 940 showed higher viscosity as compared to that of the others. The viscosity is represented graphically in the Figure 6. The low viscosity was found for the X2Q1 formulation containing the low concentration i.e. 1.5% of carbopol 981 polymer which is a low viscosity polymer and the addition of microemulsion Q1. It was found that as polymer concentration increases viscosity also increases. The Q1 microemulsion formulation it contains the larger amount of surfactant concentration as compared to the P1 so its viscosity decreases as mentioned by Ghodekar et al. in his work antifungal activity of microemulsion based fluconazole gel for so the viscosity of emulgel containing the optimized formulation Q1 and carbopol 981 concentration 1.5% was found to be the lowest i.e. X2Q1 formulation as compared to the formulation containing optimized formulation P1 and carbopol 981 concentration of 1.5%. The higher the concentration of surfactant and

Preparation of Emulgel

Emulgel was prepared using different gelling agent such as carbopol 934, carbopol 940 and carbopol 981 in the concentration of 1.5%w/v and 2%w/v. The mentioned gelling agents were swelled in distilled water for 24 hrs and high viscosity solution was obtained. The Tapentadol loaded microemulsion was slowly added to the viscous solution of gelling agent by continuous stirring and then clear emulgel was obtained. The carbopol as an aqueous gel matrix is a continuous phase and the dispersion of oily droplets within the meshes of 3-D network of gel increases the viscosity of microemulsion significantly. The optimized formulations of microemulsions i.e. P1 and Q1 was incorporated into the gel base. The quantity of microemulsion added was equivalent to 0.25% of Tapentadol, 0.02% of triethanolamine was added to adjust the pH of formed emulgel, glicerin 1% and the preservatives like methyl Paraben and Propyl Paraben was added to the formulation, the quantity of preservative added was 0.03% showed in Table 2 & 3.

Characterisation of Emulgel

Physical Appearance

All the prepared formulations were buff white in appearance and they showed good homogeneity and consistency.

Drug Content

The percentage drug content of prepared emulgel was found in the range of 74.6 to 96.23%. The results were displayed in the Table 5. The highest drug content i.e. 96.23% was obtained for the formulation X2Q1 containing optimized Q1 formulation of emulsion and gelling agent present in the concentration of 1.5% of Carbopol 981.

pH

The pH of all the formulation was found to be ranging from 5.5 to 6.3 which was found to be acceptable to avoid any skin irritation. The results in the form of Table are shown in the Table 5.

Viscosity

Viscosities of different Tapentadol emulgel formulations are shown in Table 6. The viscosity ranged between 11970 to 48229 cPs. The results showed that the emulgel formulations prepared by using carbopol 940 showed higher viscosity as compared to that of the others. The viscosity is represented graphically in the Figure 6. The low viscosity was found for the X2Q1 formulation containing the low concentration i.e. 1.5% of carbopol 981 polymer which is a low viscosity polymer and the addition of microemulsion Q1. It was found that as polymer concentration increases viscosity also increases. The Q1 microemulsion formulation it contains the larger amount of surfactant concentration as compared to the P1 so its viscosity decreases as mentioned by Ghodekar et al. in his work antifungal activity of microemulsion based fluconazole gel for so the viscosity of emulgel containing the optimized formulation Q1 and carbopol 981 concentration 1.5% was found to be the lowest i.e. X2Q1 formulation as compared to the formulation containing optimized formulation P1 and carbopol 981 concentration of 1.5%. The higher the concentration of surfactant and
lower the concentration of gelling agent lower the viscosity.

Spreadability
Spreadability is the term expressed to denote the extent of area to which the emulsion spreads on application to skin or affected part. The therapeutic efficacy of formulation depends upon its spreading value. The spreadability value ranged from 2.0 to 3.9 as shown in Table 6. The spreadability is dependent on the viscosity of formulation. The formulation X1P1 having viscosity 11970 has high spreading coefficient of 3.9gm/cm/sec. The spreadability depends on the concentration of polymer and its viscosity. The emulgel with low concentration of gelling agent i.e. 1.5% carbopol 981 showed increase in spreadability value.

Ex Vivo Skin Permeation Study
Ex vivo skin permeation study of optimized formulation (X2Q1) was carried out using the skin of male wistar rat in Franz diffusion cell showed in Figure 6. The diffusion was carried out in 50 ml of pH 6.8 phosphate buffer maintained at 37°C ± 0.5°C. The maximum percentage cumulative drug release at the end of 8 h was found to be 73.14% and was compared with optimized formulation X2Q1 showed in Figure 6.17

Skin Irritation Test
The Wistar Rats were used for the skin irritation test. The control group was not applied with any formulation, the standard group was applied with the saline (0.9%/w/v) a standard irritant and the test group was applied with the optimized formulation X2Q1 and it was observed for irritation at the end of 24 hrs. In case of standard group there was moderate erythema with barely precipitable edema and score given to it was 2 and the test group showed no irritation. Since no irritations persist the optimal formulation passes the skin irritation test.16

Stability Studies
The Optimized Formulation X2Q1 showed no change in appearance after 60 days of storage. Slight increased in pH after 30 and 60 days was noticed. The pH of the formulation increased slightly after 30 and 60 days. This can be attributed to concentration of drug and polymer over a long period. The values of viscosity showed little alteration. Minor decrease was observed in the drug release over a period of 60 days when stored at room temperature and 40°C/75% RH. Hence, it can be concluded that the formulation X2Q1 exhibited acceptable stability profile at room temperature (25 ± 2°C) for a period of two months and at 40°C/75% RH for a period of one month.19

In this study an attempt was made to formulate emulgel of Tapentadol for topical delivery. DSC thermograms revealed that there was no interaction between polymer and the drug, hence, they were compatible. Based on saturation solubility study Light liquid paraffin, Tween 20 and PEG 400 were selected for the preparation of emulsion. The pseudoternary phase diagram constructed with surfactant:co-surfactant ratio of 1:1 showed the least microemulsion area and that with 3:1 ratio showed the maximum microemulsion area. Based on the globule size and drug content two optimized formulation were selected for incorporation into gel base i.e. P1 and Q1. The emulgel formulations were prepared with carbopol as gelling agent with concentrations of 1.5% and 2% and the optimized emulsion formulations i.e. P1 and Q1 were incorporated into the gel base. The formulation

Table 4: Drug Content, Globular Size and Zeta Potential of Emulgel Formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Globular size* (nm)</th>
<th>Drug Content</th>
<th>Zeta Potential* (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>176.8 ± 0.22</td>
<td>94.01 ± 0.23</td>
<td>-47.9 ± 3.74</td>
</tr>
<tr>
<td>P2</td>
<td>399 ± 0.07</td>
<td>90.12 ± 0.37</td>
<td>-44.3 ± 2.34</td>
</tr>
<tr>
<td>P3</td>
<td>504 ± 0.06</td>
<td>81.00 ± 0.05</td>
<td>-38.4 ± 3.69</td>
</tr>
<tr>
<td>Q1</td>
<td>116 ± 0.07</td>
<td>95.13 ± 0.07</td>
<td>-59.9 ± 1.80</td>
</tr>
<tr>
<td>Q2</td>
<td>338 ± 0.00</td>
<td>91.00 ± 0.00</td>
<td>-50.0 ± 1.32</td>
</tr>
<tr>
<td>Q3</td>
<td>454 ± 0.12</td>
<td>80.06 ± 0.12</td>
<td>-47.3 ± 1.43</td>
</tr>
<tr>
<td>R1</td>
<td>199.5 ± 0.08</td>
<td>92.97 ± 0.08</td>
<td>-35.0 ± 4.13</td>
</tr>
<tr>
<td>R2</td>
<td>202.4 ± 0.00</td>
<td>89.00 ± 0.01</td>
<td>-28.0 ± 2.13</td>
</tr>
<tr>
<td>R3</td>
<td>347 ± 1.19</td>
<td>78.00 ± 1.19</td>
<td>-35.6 ± 2.09</td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)

Table 5: Appearance, Drug Content, PH of Emulgel Containing Carbopol 981, Carbopol 934 and Carbopol 940

Table 6: Viscosity, Spreadability and Extrudability of Emulgel containing Carbopol 981, Carbopol 940 and Carbopol 952

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Viscosity (cP)</th>
<th>Spreadability (gm/cm² sec)</th>
<th>Extrudability (gm/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1P1 (carbopol 981 1.5%)</td>
<td>94.51 ± 0.82</td>
<td>6.14 ± 0.065</td>
<td></td>
</tr>
<tr>
<td>X2Q1 (carbopol 981 1.5%)</td>
<td>96.25 ± 1.09</td>
<td>5.58 ± 0.012</td>
<td></td>
</tr>
<tr>
<td>Y1P1 (carbopol 934 1.5%)</td>
<td>90.09 ± 0.81</td>
<td>6 ± 0.0081</td>
<td></td>
</tr>
<tr>
<td>Y2Q1 (carbopol 934 1.5%)</td>
<td>91.76 ± 0.68</td>
<td>5.5 ± 0.014</td>
<td></td>
</tr>
<tr>
<td>Z1P1 (carbopol 940 1.5%)</td>
<td>82.86 ± 1.09</td>
<td>6.35 ± 0.041</td>
<td></td>
</tr>
<tr>
<td>Z2Q1 (carbopol 940 1.5%)</td>
<td>85.81 ± 6.97</td>
<td>6.3 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>X1P1 (carbopol 981 2%)</td>
<td>89.16 ± 7.45</td>
<td>6.12 ± 0.052</td>
<td></td>
</tr>
<tr>
<td>X2Q1 (carbopol 981 2%)</td>
<td>93.86 ± 7.50</td>
<td>5.51 ± 0.37</td>
<td></td>
</tr>
<tr>
<td>Y1P1 (carbopol 934 2%)</td>
<td>77.53 ± 4.17</td>
<td>6.03 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>Y2Q1 (carbopol 934 2%)</td>
<td>84.05 ± 4.47</td>
<td>5.79 ± 0.1925</td>
<td></td>
</tr>
<tr>
<td>Z1P1 (carbopol 940 2%)</td>
<td>75.61 ± 0.77</td>
<td>6.35 ± 0.31</td>
<td></td>
</tr>
<tr>
<td>Z2Q1 (carbopol 940 2%)</td>
<td>74.6 ± 0.60</td>
<td>6.12 ± 0.017</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)

Table 6: Viscosity, Spreadability and Extrudability of Emulgel containing Carbopol 981, Carbopol 940 and Carbopol 952

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Viscosity (cP)</th>
<th>Spreadability (gm/cm² sec)</th>
<th>Extrudability (gm/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1P1 (carbopol 981 1.5 %)</td>
<td>11930 ± 122.8943</td>
<td>3.83 ± 0.047</td>
<td>117.4333 ± 0.744</td>
</tr>
<tr>
<td>X2Q1 (carbopol 981 1.5 %)</td>
<td>10970 ± 80.82</td>
<td>3.9 ± 0.00</td>
<td>14.92667 ± 0.600</td>
</tr>
<tr>
<td>Y1P1 (carbopol 934 1.5 %)</td>
<td>37531 ± 612.58</td>
<td>3.4 ± 0.0462</td>
<td>6.63 ± 0.497</td>
</tr>
<tr>
<td>Y2Q1 (carbopol 934 1.5 %)</td>
<td>36469 ± 4414</td>
<td>3.66 ± 0.047</td>
<td>6.11667 ± 1.017</td>
</tr>
<tr>
<td>Z1P1 (carbopol 940 1.5 %)</td>
<td>4183 ± 1489</td>
<td>3.43 ± 0.047</td>
<td>2.67333 ± 0.253</td>
</tr>
<tr>
<td>Z2Q1 (carbopol 940 1.5 %)</td>
<td>4250 ± 192</td>
<td>3.5 ± 0.081</td>
<td>4.57333 ± 0.489</td>
</tr>
<tr>
<td>X1P1 (carbopol 981 2 %)</td>
<td>17993 ± 840</td>
<td>2.13 ± 0.04</td>
<td>9.098667 ± 0.925</td>
</tr>
<tr>
<td>X2Q1 (carbopol 981 2 %)</td>
<td>20660 ± 715.742</td>
<td>2.3 ± 0.08</td>
<td>10.31 ± 1.070</td>
</tr>
<tr>
<td>Y1P1 (carbopol 934 2 %)</td>
<td>38527 ± 888.568</td>
<td>2.2 ± 0.00</td>
<td>5.09999 ± 0.601</td>
</tr>
<tr>
<td>Y2Q1 (carbopol 934 2 %)</td>
<td>38620 ± 180.003</td>
<td>2.3 ± 0.124</td>
<td>5.476667 ± 0.513</td>
</tr>
<tr>
<td>Z1P1 (carbopol 940 2 %)</td>
<td>49229 ± 910.220</td>
<td>2.03 ± 0.047</td>
<td>1.85 ± 0.563</td>
</tr>
<tr>
<td>Z2Q1 (carbopol 940 2 %)</td>
<td>45913 ± 640.172</td>
<td>2.3 ± 0.816</td>
<td>2.366667 ± 0.296</td>
</tr>
</tbody>
</table>

*Data are expressed as Mean ± S.D. (n=3)

Mandora et al.: Tapentadol loaded emulgel for topical application

Mandora et al.: Tapentadol loaded emulgel for topical application

Mandora et al.: Tapentadol loaded emulgel for topical application
Tapentadol was proven to be a suitable candidate for formulating emulgel for topical delivery to achieve better patient compliance.

CONCLUSION

Self-emulsifying drug delivery system of Tapentadol was successfully prepared and evaluated for its solubility enhancement purpose. Based on solubility study data light liquid paraffin, Tween 20 and PEG 400 were selected for construction of pseudo ternary phase diagram. From the results of pseudo ternary phase diagram, nine formulations were prepared and evaluated for self-emulsification time and dispersibility, droplet size analysis, stability studies, turbidity, zeta potential, drug content and in vitro drug release. Optimized formulation of emulgel showed a significant increase in drug release rate in vitro and ex vivo. Hence, it can be concluded that the emulgel formulations can be potentially used as an alternative to the traditional oral formulations for the poorly bioavailable and having short half-life drugs like Tapentadol to improve its drug delivery and bioavailability.

ACKNOWLEDGEMENT

The authors express deep gratitude to Preciems Chem Pharma Ltd., Mumbai, for providing the gift sample of the drug Tapentadol. The authors are also immensely grateful to KLES College of Pharmacy, Belagavi for providing all the facilities required to carry out the research work.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICT OF INTEREST

There are no conflicts of interest.

ABBREVIATION USED

PEG: Polyethylene glycol; PG: Propylene glycol; RH: Relative humidity; DSC: Differential Scanning Calorimeter.

REFERENCES


SUMMARY

Tapentadol is an opioid analgesic. Tapentadol is indicated for the treatment of Moderate to severe pain for both acute (following injury, surgery, etc.) and chronic musculoskeletal pain. Tapentadol has poor oral bioavailability of 31.9 ± 6.8% and it causes gastric side effects such as nausea, vomiting, stomach discomfort.

The emulgel formulation contains combinations of emulsion and gel. The emulsion is a very good vehicle for the delivery of hydrophobic drug but it is thermodynamically unstable. The emulsion when incorporated into the gel increases the stability of the emulsion. The emulgel is a dual control release system. The emulgel being thixotropic, greaseless, spreads easily non-staining so it offers a better patient compliance.

Preformulation studies were performed on the drug and excipients. The FTIR analysis revealed that the drug and excipients used were compatible with each other. Light liquid paraffin, Tween 20 and PEG 400 were selected for the construction of pseudoternary phase diagrams and emulsion was prepared based on the saturation solubility results.

The pseudoternary phase diagram showed that the surfactant: co-surfactant ratio 1:1 showed minimum microemulsion area but 3:1 ratio showed the maximum microemulsion area. The prepared emulsions were evaluated for drug content and globule size and the results showed that P1 and Q1 formulation were selected as optimized formulation showing globule size of 176 nm and 116 nm respectively and drug content of 94.01 and 95.13%.

The optimized emulsion formulations were then incorporated into the gel base to give the emulgel by varying the gelling agent concentration i.e. 1.5% and 2%. The prepared emulgel formulations were evaluated for percent drug content, pH, viscosity, spreadability, extrudability and percentage cumulative drug release.

The optimized formulation was subjected to skin irritation test and no irritation was observed on the wistar rat’s skin so the formulation can be considered as safe for use. The ex vivo study was conducted using abdominal skin of wistar rat and was compared with in vitro cumulative drug releases. Short term stability studies were carried out on the optimized formulation XQ2 at 25°C ± 2°C and 40 ± 2°C and the results showed physicochemical stability.

Based on the drug content, viscosity, spreadability, percentage cumulative drug release Tapentadol can be considered as an ideal candidate for the formulation of emulgel.

About Authors

Papesh Mandora: Obtained His post-graduate in 2016 from Dept. of Pharmaceutics, Faculty of Pharmacy, KLE University, Belagavi. He worked in the area of Topical formulations carrier to improve the drug permeation across skin.

Panchaxari Mallappa Dandagi: Is a Professor, Department of Pharmaceutics, Faculty of Pharmacy, KLE University, Belagavi. He is working on areas of targeted drug delivery system viz., Colon drug delivery system using pH dependent polymers and also Ocular drug delivery system through Nano and microspheres.

Anand Panchakshari Gadad: Is a Professor and Head, Department of Pharmaceutics, Faculty of Pharmacy, KLE University, Belagavi. He is working on areas of targeted drug delivery system viz., Gastroretentive drug delivery system, PolymERIC nanoparticles, enhancing solubility of poorly soluble drugs, etc

Nitin Prabhukar Ambhore: Is a Research Scholar, Department of Pharmaceutics, Faculty of Pharmacy, KLE University, Belagavi. He is working in the area of ocular Nanosuspensions to improve the bioavailability.