Development and Evaluation of Pluronic Lecithin Organogel Topical Delivery of Tapentadol

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Abstract

Pluronic lecithin organogel (PLO) has become one of the most versatile and effective vehicles to transdermal delivery. PLO disrupts the lipid layers of the stratum corneum without damaging them. Tapentadol hydrochloride is a water soluble opioid analgesic indicated for the relief of moderate to severe acute pain. It is a centrally-acting synthetic analgesic. The factors low molecular weight (257.80 g/mol), low absolute bioavailability i.e. 32% and plasma half life (4 hrs) facilitates the formulation of controlled release topical drug delivery system for Tapentadol hydrochloride. Tapentadol hydrochloride was formulated into PLO gel. PLO of Tapentadol hydrochloride was formulated with HPMC, Carbopol, Xanthum gum and PolyoxWSR 205. PLO emulsion containing HPMC and Carbopol were found to be stable. The gelation temperature was found to be around 32-38°C. The formulation P7 containing 40% pluronic F-127, lecithin 3% was the optimised batch with drug release 87.03±5.13 (Dialysis membrane), 82.246 ±4.32 (Egg membrane), and 71.40±3.35 (Pig membrane). The formulation showed Maxwell and Voigt element for creep studies and had pseudoplastic flow.

Key words: Pluronic, Lecithin, Tapentadol, Organogel, Xanthum gum, HPMC

1. Introduction

Organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibers (Gupta et al. 2011). Most organogels are prepared by heating a mixture of the gelator and the liquid component to form an organic solution/ dispersion, followed by cooling of the latter, which sets into a gel. Common types of organogels include lecithin, pluronic lecithin (PLO), premium lecithin (PrLO), limonene GP1/PG, gelatin stabilized microemulsion based organogel (MBG), fatty acid derived sorbitan organogels, and poly (ethylene) organogels. Factor affecting organogels include organic solvent,
phase transition temperature, salt addition, temperature, molecular weight, polymers and surfactants (Marty, 2013). Organogels are used for delivery of drugs and many pharmaceutical ingredients through various routes like oral, parenteral, topical and transdermal (Vintiloiu and Jean, 2008; Murdan, 2005a; Garg et al., 2011).

A decade ago, pluronic lecithin organogel (PLO) has become one of the most versatile and effective vehicles against barrier stratum corneum to transdermal delivery. PLO disrupts the lipid layers of the stratum corneum without damaging them, as do harsher agents like dimethyl sulfoxide (DMSO), which dissolves the lipid layers. PLO allows the medication to slip through the stratum corneum into the systemic circulation via the dermal-epidermal blood flow so that it is more likely to be absorbed.

Topical drug delivery is becoming the choice because it is a non invasive drug delivery. Tapentadol hydrochloride is a water soluble opioid analgesic indicated for the relief of moderate to severe acute pain. It is a centrally-acting synthetic analgesic. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to µ-opioid agonist activity and the inhibition of nor-epinephrine reuptake. Mean absolute bioavailability after single dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. About 97% of the parent compound is metabolized. The major pathway of Tapentadol hydrochloride metabolism is conjugation with glucuronic acid to produce glucuronides. Tapentadol hydrochloride was chosen as the suitable candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal/topical drug delivery system as low molecular weight (257.80 g/mol), low absolute bioavailability 32%, plasma half life (4 hrs), effective in low plasma concentration as well as a high degree of first-pass metabolism (Sahoo et al., 2011; 2012 Aus PAR Palexia IR Tapentadol; Raritan, 2011).

The aim of present study was to develop and evaluate topical gel of Tapentadol hydrochloride so as to prevent its first-pass metabolism and reduction in the bioavailability, to achieve controlled release and to reduce its abuse tendency. The organogels are widely being appreciated for their controlled release effect, also PLO require no penetration enhancers as lecithin itself facilitates penetration of drug molecules thereby reducing the number of excipients required for formulation. The objectives for the present work was to formulate pluronic lecithin organogel delivery and to study the effect of polymers HPMC, carbopol, xanthum gum, polyox WSR 205 and NaCl on drug release from PLO of Tapentadol hydrochloride.

2. Material and Methods

2.1 Materials

Tapentadol hydrochloride was a gift sample from Optimus India Pvt. Ltd. Pluronic F-127 were purchase from Anafine Lab and Soy Lecithin were purchase from Vinayak Ingredients (India) Pvt. Ltd. All other chemical and reagent were of analytical grade.
2.2 Characterization of Tapentadol Hydrochloride

2.2.1 Physical properties

2.2.1.1 Appearance: Drug sample was evaluated visually for physical appearance.

2.2.1.2 Solubility: Solubility was checked in methanol.

2.2.1.3 Melting Range: Melting point of Tapentadol was determined by Thieles tube as per the procedure described in IP using liquid paraffin. The drug sample was dried at 60°C for 24 hours, reduced to fine and was placed in a capillary tube closed at one end. The tube was heated using an open flame and the melting temperature range was recorded.

2.2.2 UV Spectroscopic Studies: The UV spectrum was obtained using UV spectrophotometer (Varian Cary 100) in saline phosphate buffer (pH 7.4). Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of PBS and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 5 ml of aliquot was withdrawn and volume was made up to 10 ml using PBS to obtain the concentration of 50 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum wavelength. (Indian Pharmacopoeia, 1996)

2.2.3 FTIR Spectroscopy: The IR spectrum was recorded using Fourier Transform Infra-Red spectrophotometer (Varian, 640 IR) with diffuse reflectance principle. Sample preparation involved mixing the sample with potassium bromide (KBr). The spectrum was scanned over a frequency range 4000 - 400 cm$^{-1}$ (Indian Pharmacopoeia, 1996)

2.2.4 DSC: DSC thermogram was recorded using differential scanning calorimeter (DSC 823e, Mettler Toledo, Switzerland). Approximately 2-5 mg of sample was heated in a pierced aluminum pan up to 300°C at a heating rate of 10°C/min under a stream of nitrogen at flow rate of 50 ml/min.

2.2.5 Drug-Excipient Interactions

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. FTIR spectra were obtained by using an FTIR spectrometer (Varian, 640 IR). Only best formulation i.e. P7, H2 and C2 were taken into consideration for FTIR study. The drug Tapentadol hydrochloride, polymers Pluronic, Lecithin, HPMC, Carbopol and best formulations were studied for IR. Samples were mixed with (previously dried) potassium bromide and triturated to form fine homogenous mixture at 1:100 (Sample: KBr) ratio, respectively. Scans were obtained at a resolution of 4 cm$^{-1}$, from 4,000 to 600 cm$^{-1}$.

2.3 Formulation Studies

2.3.1 General method of preparation of PLO (Murdan, 2005a)

Pluronic lecithin organogel is mainly composed of Pluronic F-127, soy lecithin, and IPP/IPM. In general, it is made up of two phases, first pluronic phase (aqueous phase) and second lecithin phase (oil phase), i.e., pluronic gel combined with a lecithin based oil. Pluronic lecithin organogel gel looks and feels like a cream but is actually a gel. When the aqueous phase (pluronic gel) is combined with
the lecithin oil base creates an emulsion that forms together due to the pluronic gel and the viscosity of that gel at room temperature.

2.3.2 Preparation of Pluronic phase (aqueous phase)
Pluronic gels were formulated at different concentration levels of pluronic F-127 in ice cold water (Table 1), agitating continuously and placing the mixture overnight for complete dissolution of pluronic F-127. About 0.2% w/w potassium sorbate is added as preservative.

2.3.3 Preparation of Lecithin phase (oil phase)
Lecithin phase is prepared by dissolving lecithin in IPM (Table 1) and 0.2-0.3% w/w sorbic acid was added as preservative, then keeping the mixture overnight for complete dissolution of lecithin.

2.3.4 Preparation of PLO
The PLO gel was being prepared by mixing lecithin: IPM liquid phase and the pluronic phase together on a magnetic stirrer at 400 rpm. The addition of pluronic phase in the lecithin phase should be done drop by drop. Incorporation of air should be minimized and the temperature should be controlled from 18-22°C. (Table 1)

2.3.5 Preparation of Combination gels
For these gels, PLO emulsion 30% was used as base and the polymers where added on the % w/w basis (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Formulation table for pluronic lecithin organogel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>Contents %</td>
</tr>
<tr>
<td>Aqueous Phase</td>
<td></td>
</tr>
<tr>
<td>Pluronic F-127</td>
<td>20</td>
</tr>
<tr>
<td>Distilled water qs</td>
<td>100</td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td>0.2</td>
</tr>
<tr>
<td>Oil Phase</td>
<td></td>
</tr>
<tr>
<td>Lecithin</td>
<td>3</td>
</tr>
<tr>
<td>Isopropyl myristate (IPM) qs</td>
<td>100</td>
</tr>
<tr>
<td>Sorbic Acid</td>
<td>0.2</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
</tr>
<tr>
<td>Tapentadol Hydrochloride</td>
<td>-</td>
</tr>
</tbody>
</table>

Where, P1-P4 are Pluronic lecithin organogels without drug; P5-P8 are Pluronic lecithin organogels with drug
Table 2 Formulation table for combination organogel

<table>
<thead>
<tr>
<th>Contents</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>X</th>
<th>PX</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbopol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Xanthum gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Polyox WSR 205</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tapentadol Hydrochloride</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Where, H1-H3 Combination of PLO with HPMC; C1-C3 Combination of PLO with Carbopol-940; X: Combination of PLO with Xanthum gum; PX: Combination of PLO with Polyox WSR205

2.4 Evaluation of Organogels (Murdan, 2005a; Jadhav et al., 2009)

2.4.1 Organoleptic properties: Each formulation was tested for colour, odour, texture, and phase separation as well as feels upon application (stiffness, grittiness, greasiness, and tackiness).

2.4.2 Inversion Test: The container in which gel was formulated was inverted for confirming the gelation process.

2.4.3 Homogeneity Test (Agrawal et al., 2010)
Hundred milligram of gel was pressed between the thumb and the index finger in order to notice the consistency of gel that any coarse particles being attached or detached on finger.

2.4.4 Washability (Agrawal et al., 2010)
A small quantity (100 mg) of gel was rubbed on the skin of the back of the hand, than patch was washed with water and observed weather it is washable or not.

2.4.5 pH Determination (Agrawal et al., 2010)
A solution containing 1 g of gel in 30 ml of neutralized distilled water (pH 7) was prepared and subjected to pH measurement by using a digital pH meter (Equiptronics EQ 621). The pH meter was calibrated using pH- 4 and pH-7 by using standard buffer tablet.

2.4.6 Extrudability
A closed collapsible tube containing ointment was pressed firmly at the cramped end. When the cap was removed a weight of ‘x’ gm were allowed to fall onto the tube. Weight in grams required to extrude 0.5 cm ribbon of gel was noted. The extrudability apparatus was laboratory designed.
2.4.7 Determination of Drug Content (Kamble et al., 2011)
Accurately, 1 g of gel (equivalent to 50 mg of drug) was mixed with 50 ml of PBS. The flask was sonicated for 15 min, complete dispersion of content was ensured visually and make up the volume to 100 ml. Filter the solution using 0.45 μ membrane filter. From this solution, 1 ml of sample was withdrawn and diluted to 10 ml with PBS. % Content of Tapentadol hydrochloride was determined spectrophotometrically at 272 nm using double beam UV visible spectrophotometer, (Varian Cary 100). Each sample was analyzed in triplicate. The standard curve of Tapentadol hydrochloride was taken using different concentrations and the slope and intercept was calculated from the standard curve.
Further, the % drug content was calculated from the concentration using the equation

\[
\text{Drug Content} = \frac{\text{Concentration of sample solution}}{\text{Equivalent concentration of drug taken}} \times 100
\]

--------- (Eq.1)

2.4.8 Spreadabilty (Mandal and Sawant, 2010)
1 g of gel sample was placed between two glass slides and 250 g weight was placed on glass slide for 5 min to compress the sample to uniform thickness. Weight (50 g) was added to the pan. The time in sec required to travel a distance of 10 cm by the upper side slides was taken as a measure of spreadability. Spreadability was calculated by using the following formula.

\[
S = \frac{M \times L}{T}
\]

--------- (Eq.2)

Where S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides from each other.
In this experiment, M = 50 gm, L = 10 cm and time T was recorded in seconds.

2.4.9 Viscosity (Belgamwar et al., 2009)
Viscosities of the formulated organogels were determined using Brookfield Viscometer with Spindle no.7 (Model: RV DV-E 230) at 25° with the spindle speed of 10 rpm.

2.4.10 In-vitro drug release studies:

2.4.10.1 In-vitro diffusion study: Dialysis Membrane (Agrawal et al., 2010; Kumar and Katare, 2009)
Dialysis membrane-50 (Av. Flat width- 24.26mm, Av. Diameter- 14.3 mm) obtained from Hi-media laboratories Pvt. Ltd. was used for this study. In Keshary Chien diffusion cell, 1 gm of gel was kept in donor compartment. The entire surface of membrane was in contact with the receptor compartment containing 25 ml of phosphate buffer pH 7.4. The receptor compartment was continuously stirred (100 rpm) using a magnetic stirrer. The temperature maintained was 37±1°C. The study was carried out for 8 hours with the interval of 0, 1, 2, 3, 4, 5, 6, 7 and 8 hour. The surface area available for diffusion was calculated and was found to be 3.14 cm². The sample was withdrawn at predetermined time interval and same volume was replaced with fresh phosphate buffer. The absorbance of withdrawn sample was measured after suitable dilution at 272 nm to estimate drug concentration. The experiment was carried out in triplicate and average values were reported.
In-vitro diffusion study: Egg Membrane (Kumar and Katare, 2009)
Preparation of Egg membrane: Intact egg was placed in 0.1 N HCl for 24 hours, after 24 hours 1 N HCl was slowly dropped into the 0.1 N HCl for dissolving of calcium. The addition of 1 N HCl was stopped when complete calcium covering over the egg was dissolved. The soft balloon like egg was then punctured to remove the egg yolk and the white membrane. The membrane was washed with water and then placed over the cell for diffusion studies.

Ex-vivo diffusion study: Pig Membrane
Preparation of Pig membrane:
Excised skin of pig was obtained from slaughter house and was cleaned by washing with water. The skin was then cut into pieces larger than 3.14 cm² with a thickness of 1.2 mm and was mounted over the Keshary - Chien diffusion cell for diffusion studies.

2.5 Flux
PCP Disso V3 software was used to study the flux from the pluronic lecithin organogel.

Release Experiments

Model dependent method
In order to gain insight of the drug release mechanism from the pluronic lecithin organogel, release data of selected solid dispersions were examined according to the zero-order, first-order and Higuchi’s square root of time mathematical models, Hixson and Crowell powder dissolution method, Korsmeyer and Peppas model. The equations for all the models are shown below:

- Zero order: \( F = k \times t \)  
- First order: \( \ln F = k \times t \)  
- Higuchi Matrix: \( F = k \sqrt{t} \)  
- Hixson and Crowell: \( F=100 \times (1-(1-kt))^3 \)  
- Korsmeyer and Peppas model: \( F=k t^n \)

where \( F \) is the fraction of drug release, \( k \) is the release constant, \( t \) is the time and \( n \) is diffusion coefficient.

A \( n \) value 0.5 is considered consistent with a diffusion-controlled release, whereas a value of 1.0 indicates a zero-order release behavior, and intermediate values (0.5 > \( n \) > 1.0) are defined as anomalous non-Fickian transport mechanism.

Rheological Study
A complete rheological study is done for optimized formulation with good diffusion of drug on Viscotech Reologica Instruments AB, which is the cone and plate type viscometer. It included the different study of formulation as creep recovery, oscillation stress sweep and viscometry for the measurement of viscosity, creep recovery study, determination of flow properties of gelling solution, frequency sweep test, determination of thixotropic nature and viscoelastic nature of gelling solution. Viscosity measurement for optimized samples was done in triplicate, with each measurement taking approximately 300 seconds and at constant temperature.
2.8 Stability Study

The prepared optimized organogel preparation was subjected to stability studies in amber colored glass vials at three different temperatures (4°C, RT, and 60°C) and evaluated periodically (every 15th day) for percent drug content, pH, colour change, phase separation, and viscosity for a period of 60 days.

3. Results and Discussion

3.1 Characterization of Tapentadol hydrochloride and Polymers

3.1.1 Physical properties:
The drug was white crystalline powder, soluble in Methanol with melting point between 198 - 208°C.

3.1.2 UV Spectroscopic Studies
UV scan of standard Tapentadol hydrochloride was observed at wavelength 272 nm.
Concentration range 20µg/ml -100 µg/ml found to observe Beer-Lambert’s Law in this concentration range giving equation as $y = 0.007x + 0.021; R^2 = 0.998$

3.1.3 FTIR spectroscopy
The IR spectrum Tapentadol hydrochloride is shown in Fig. 1. The IR scan shows prominent peaks for the various groups N-H stretch at 3554 and C-O stretch1457.

![Fig. 1. IR spectrum of Tapentadol hydrochloride](image)
3.1.4 Differential Scanning Calorimetry

From Fig. 3DSC study, glass transition temperature of drug was observed to be 205.40 °C.
3.1.5 Compatibility Studies (Shaikh et al., 2006)
It is observed that no significant change was observed in the graph of Tapentadol hydrochloride and physical mixtures of the formulations indicating no interaction between the drug and polymers. (Fig. 1, 2 and 4)
Fig. 4. Scans for Compatibility studies for Tapentadol hydrochloride (TPT), Mixture A (Pluronic F-127, Lecithin and TPT), Mixture B (Pluronic F-127, Carbopol, HPMC and TPT), Mixture C (Pluronic F-127, Lecithin, HPMC, Carbopol and TPT)

3.2 Formulation Studies

The trial batches were formulated based on previous literature; the formation of gels was observed. As shown in Fig. 5 gel which is formed did not flow on inversion of the beaker, confirming the process of gelation. The selection of the batches for further studies was done after organoleptic evaluation like smell, texture, colour and odour.

Fig. 5. Process of Gelation
Table 3  Evaluation of batches for formation of gel

<table>
<thead>
<tr>
<th>Formulation Codes</th>
<th>Formation, Appearance and Stability of gel / emulsion</th>
<th>Result of the batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Stable Emulsion</td>
<td>Failed</td>
</tr>
<tr>
<td>P2</td>
<td>Stable Gel</td>
<td>Selected the batch for further studies</td>
</tr>
<tr>
<td>P3</td>
<td>Stable Gel, Viscous</td>
<td>Rejected due high Viscosity</td>
</tr>
<tr>
<td>P4</td>
<td>Stable Gel, Highly Viscous</td>
<td>Rejected due high Viscosity</td>
</tr>
<tr>
<td>P5</td>
<td>Unstable Emulsion, Broke</td>
<td>Failed</td>
</tr>
<tr>
<td>P6</td>
<td>Stable Emulsion</td>
<td>Failed</td>
</tr>
<tr>
<td>P7</td>
<td>Stable Gel</td>
<td>Selected the batch for further studies</td>
</tr>
<tr>
<td>P8</td>
<td>Stable Gel and Viscous</td>
<td>Rejected due high Viscosity</td>
</tr>
<tr>
<td>H1</td>
<td>Stable Emulsion</td>
<td>Failed</td>
</tr>
<tr>
<td>H2</td>
<td>Stable Gel</td>
<td>Selected the batch for further studies</td>
</tr>
<tr>
<td>H3</td>
<td>Stable Gel, Viscous</td>
<td>Rejected due high Viscosity</td>
</tr>
<tr>
<td>C1</td>
<td>Emulsion</td>
<td>Failed</td>
</tr>
<tr>
<td>C2</td>
<td>Gel</td>
<td>Stable</td>
</tr>
<tr>
<td>C3</td>
<td>Stable and Gel Viscous</td>
<td>Rejected due high Viscosity</td>
</tr>
<tr>
<td>X</td>
<td>Unstable, Broke</td>
<td>Failed</td>
</tr>
<tr>
<td>PX</td>
<td>Stable but formation of sticky and tacky mass</td>
<td>Failed</td>
</tr>
<tr>
<td>SC</td>
<td>Gel</td>
<td>Stable</td>
</tr>
</tbody>
</table>

Where, **P1-P4**: Pluronic lecithin organogels without drug; **P1-P4**: Pluronic lecithin organogels with drug; **H1-H3** Combination of PLO with HPMC; **C1-C3** Combination of PLO with Carbopol-940; **X**: Combination of PLO with Xanthum gum; **PX**: Combination of PLO with Polyox WSR205; **SC**: Combination of PLO with NaCl.

The formulations P1, P5, P6 failed because they were unable to gel due to insufficient concentration of pluronic F-127. Formulations P4, P8, H3, C3 were rejected as their viscosities were too high around 15000 centipoise which gave them consistency as thick as a paste (Table 3).

Formulations H1 and C1 failed because they had insufficient concentrations of HPMC and carbopol 940 respectively. These batches were stable as emulsions except P5.

Formulation X containing xanthum gum was unstable it broke the emulsion and therefore this combination with PLO was rejected. Formulation PX containing PolyoxWSR-205 formed a sticky mass which had no appreciable qualities like a gel and hence this combination with PLO was rejected.

The preliminary batch P1 which contains 20% pluronic as water phase (absence of drug). Emulsion was broken at concentration of 20% pluronic in water phase (in presence of drug).

Formation of gel was seen at 30% pluronic concentration as water phase (absence of drug).
The preliminary batches prepared were evaluated visually. The colour of gels varied from white to pale yellow depending on composition. All the gels were opaque in nature. The preliminary batches were scrutinized during the formulation process for studying the effect of variables like:

3.3 Effect of Temperature

The gel formation requires strict control over temperature during formulation process. Slight change in temperature can cause change in viscosity or can cause destabilization of gel. During preliminary batches many formulations failed due to temperature fluctuations. The safest temperature for formulation of gel was 20-25\degree C. The temperature is required to be maintained during complete addition of water phase in oil phase. Once the total amount of water phase is poured into the oil phase gradual increase in temperature by 5-8\degree C causes the emulsion to gel. The gelation temperature was found to be around 32-38\degree C. Chilling of PLO converts the gel into liquid, which later gets separated into oil and aqueous phases (usually took weeks for separation to occur) (Willimann and Luisi, 1991; Murdan, 2005b).

3.4 Effect of Stirring speed

400 rpm is the speed which generally causes homogenous mixing of the phases. Any increase or decrease in speed caused instability in the formulation. Increasing the speed reduced the viscosity whereas decreasing the speed broke the emulsion due to inadequate mixing. The speed of mixing needs to be lowered when the gelation point is near to avoid destabilization of gel.

3.5 Effect of drug in Formulation

The hydrophilic nature of drug permitted direct solubilization of drug into water phase without addition of any co-solvent. The trial batches without drug i.e. P1 and P2 showed formation of emulsion and gel at concentrations of 20\% pluronic and 30\% pluronic respectively. Presence of Tapentadol hydrochloride in water phase caused gelation to occur at higher concentrations of pluronic. The emulsification was seen at 30\% concentration of pluronic whereas gelation occurred at a concentration of 40\%. An increase in concentration of 10 \% pluronic for formation of emulsion and gel was seen in presence of drug. Pluronic along with gelation properties has surfactant properties. In presence of drug, pluronic aids the solubilization of drug in water phase, therefore necessitating an increase in 10\% increase in pluronic concentration. This change in concentration may be due to surfactant nature of pluronic. Also a notable change in the ratios of oil: water was observed in presence of drug. In absence of drug gelation occurred at ratio of 50:50 of oil and water but in presence of drug, the ratio changed to 30:70 of oil and water.

3.6 Amount of water phase added

Addition of water phase at once may cause the formulation to break. A gradual addition of small proportions of pluronic (water phase) at a certain time interval facilitates formation of gel.

3.7 Solubilization of pluronic in 0.9\% saline solution

Pluronic F-127 was dissolved in 0.9\% saline solution instead of water, a slight modification was
done to observe any difference in the formulation. It was observed that in 0.9% saline solution the gelation occurred at a faster rate and also the gel formed were colorless, different from the normal gels which were white in color.

3.8 Organooleptic evaluation of Organogels

Table 4 Organooleptic evaluation of Organogels

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Color</th>
<th>Homogeneity</th>
<th>Texture</th>
<th>Washability</th>
</tr>
</thead>
<tbody>
<tr>
<td>P7</td>
<td>Yellow</td>
<td>Homogenous</td>
<td>Smooth</td>
<td>Easily Washable</td>
</tr>
<tr>
<td>H2</td>
<td>White</td>
<td>Homogenous</td>
<td>Gritty</td>
<td>Not easily washable</td>
</tr>
<tr>
<td>C2</td>
<td>Colorless</td>
<td>Homogenous</td>
<td>Smooth</td>
<td>Not easily washable</td>
</tr>
</tbody>
</table>

Evaluation of pH, Drug content, spreadability, Extrudability and Viscosity

Table 5 Evaluation studies of Organogels

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>pH</th>
<th>Drug Content %</th>
<th>Spreadability g.cm/s</th>
<th>Extrudability gm</th>
<th>Viscosity centipoise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.0±0.3</td>
<td>92.94</td>
<td>12.8±0.1</td>
<td>100</td>
<td>8000</td>
</tr>
<tr>
<td>P7</td>
<td>6.1±0.3</td>
<td>88.42</td>
<td>6.1±0.1</td>
<td>170</td>
<td>9400</td>
</tr>
<tr>
<td>H2</td>
<td>6.3±0.3</td>
<td>90.48</td>
<td>5.5±0.1</td>
<td>150</td>
<td>9000</td>
</tr>
<tr>
<td>C2</td>
<td>6.3±0.3</td>
<td>90.48</td>
<td>5.5±0.1</td>
<td>150</td>
<td>9000</td>
</tr>
</tbody>
</table>

3.9 Flux

In transport phenomena (heat transfer, mass transfer and fluid dynamics), flux is defined as the rate of flow of a property per unit area, which has the dimensions [quantity]-[time]⁻¹-[area]⁻¹. Present work flux of the drug was determined through different membranes with an area measuring 3.14 cm². Maximum flux has seen in P7 formulation indicating more diffusion in all membrane as compare to other formulations. It was observed that with increase in viscosity flux of from organogels decreased.

Table 6 Flux of Organogels

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Average Flux Dialysis Membrane µg/cm²/min</th>
<th>Average Flux Egg Membrane µg/cm²/min</th>
<th>Average Flux Pig Membrane µg/cm²/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>P7</td>
<td>1431.24</td>
<td>1516.24</td>
<td>1482.38</td>
</tr>
<tr>
<td>H2</td>
<td>1098.12</td>
<td>1228.46</td>
<td>1161.35</td>
</tr>
<tr>
<td>C2</td>
<td>1146.61</td>
<td>1289.94</td>
<td>1174.17</td>
</tr>
</tbody>
</table>

3.10 Diffusion studies

The preliminary stable batches which were found visually stable and organoleptically appropriate
were subjected to *in-vitro* diffusion studies.

The formulations followed Korsmeyer-Peppas mathematical model for diffusion of drug in all membranes indicating the drug was released in a controlled pattern. This model is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. From table 7,8 and 9, $n$ value 0.5 is considered consistent with a diffusion-controlled release, whereas a value of 1.0 indicates a zero-order release behavior indicating drug release is independent of the initial concentration. In present study intermediate values (0.5 > $n$ > 1.0) indicated anomalous non-Fickian transport mechanism. The release mechanism is may be combination of erosion & diffusion or swelling and diffusion. In presence of soluble polymers HPMC and Carbopol water is absorbed into the systems, the polymer chains hydrate, swell and ultimately drug is dissolved away from the system. (Shchipunov, 2001; Penzes et al., 2005; Jagdale et al., 2013; Jagdale et al., 2014)

### 3.10.1 *In-vitro* study was performed using Dialysis Membrane: Fig. 6 gives release pattern. The best fit model found for all batches were Korsmeyer-Peppas.(Table 7)

![In-vitro release profile of P7, H2, and C2 using dialysis membrane](image.png)

**Table 7** Mathematical modelling and release kinetics

<table>
<thead>
<tr>
<th>Model</th>
<th>P7</th>
<th>H2</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td>0.9377</td>
<td>0.9702</td>
<td>0.9108</td>
</tr>
<tr>
<td>First Order</td>
<td>0.9735</td>
<td>0.9912</td>
<td>0.9812</td>
</tr>
<tr>
<td>Matrix</td>
<td>0.9930</td>
<td>0.9813</td>
<td>0.9797</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td>0.9960</td>
<td>0.9920</td>
<td>0.9922</td>
</tr>
<tr>
<td>Hixson Crowell</td>
<td>0.9848</td>
<td>0.9918</td>
<td>0.9695</td>
</tr>
<tr>
<td><strong>Best fit Model</strong></td>
<td>Korsmeyer-Peppas</td>
<td>Korsmeyer-Peppas</td>
<td>Korsmeyer-Peppas</td>
</tr>
<tr>
<td>Diffusion coefficient($n$)</td>
<td>0.5520</td>
<td>0.6252</td>
<td>0.6201</td>
</tr>
</tbody>
</table>
3.10.2 *In-vitro* study was performed using Egg Membrane; Fig. 7 gives release pattern. The best fit model found for all batches were Korsmeyer-Peppas. (Table 8)

![Fig. 7. In-vitro release profile of P7, H2, and C2 using Egg membrane](image)

**Table 8** Mathematical modelling and release kinetics

<table>
<thead>
<tr>
<th>Model</th>
<th>Formulation Code</th>
<th>P7</th>
<th>H2</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td></td>
<td>0.9591</td>
<td>0.9811</td>
<td>0.9188</td>
</tr>
<tr>
<td>First Order</td>
<td></td>
<td>0.9748</td>
<td>0.9868</td>
<td>0.9803</td>
</tr>
<tr>
<td>Matrix</td>
<td></td>
<td>0.9832</td>
<td>0.9674</td>
<td>0.9817</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td></td>
<td>0.9873</td>
<td>0.9911</td>
<td>0.9914</td>
</tr>
<tr>
<td>Hixson Crowell</td>
<td></td>
<td>0.9857</td>
<td>0.9909</td>
<td>0.9690</td>
</tr>
<tr>
<td><strong>Best fit Model</strong></td>
<td><strong>Korsmeyer-Peppas</strong></td>
<td><strong>0.9873</strong></td>
<td><strong>0.9911</strong></td>
<td><strong>0.9914</strong></td>
</tr>
<tr>
<td><strong>Diffusion coefficient(n)</strong></td>
<td></td>
<td><strong>0.5766</strong></td>
<td><strong>0.6500</strong></td>
<td><strong>0.5853</strong></td>
</tr>
</tbody>
</table>

3.10.3 *Ex-vivo* study performed using Excised Pig Membrane Fig. 8 gives release pattern. The best fit model found for all batches were Korsmeyer-Peppas. (Table 9)

**Table 9** Mathematical modelling and release kinetics

<table>
<thead>
<tr>
<th>Model</th>
<th>Formulation Code</th>
<th>P7</th>
<th>H2</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td></td>
<td>0.9605</td>
<td>0.9775</td>
<td>0.9157</td>
</tr>
<tr>
<td>First Order</td>
<td></td>
<td>0.9838</td>
<td>0.9915</td>
<td>0.9782</td>
</tr>
<tr>
<td>Matrix</td>
<td></td>
<td>0.9857</td>
<td>0.9752</td>
<td>0.9841</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td></td>
<td>0.9916</td>
<td>0.9919</td>
<td>0.9945</td>
</tr>
<tr>
<td>Hixson Crowell</td>
<td></td>
<td>0.9903</td>
<td>0.9910</td>
<td>0.9652</td>
</tr>
<tr>
<td><strong>Best fit Model</strong></td>
<td><strong>Korsmeyer-Peppas</strong></td>
<td><strong>0.9916</strong></td>
<td><strong>0.9919</strong></td>
<td><strong>0.9945</strong></td>
</tr>
<tr>
<td><strong>Diffusion coefficient(n)</strong></td>
<td></td>
<td><strong>0.5644</strong></td>
<td><strong>0.6568</strong></td>
<td><strong>0.5941</strong></td>
</tr>
</tbody>
</table>
3.11 Rheology Studies

The rheological properties of the gel are of importance in view of their convenient application on the skin. In the selection of the concentration of the gelling polymer, generally the lowest concentration which gels with a good viscosity is selected in case of topical preparations. Highly viscous solutions result in lesser spreadability and may cause inconvenience by pulling skin hair which reduces the acceptance of the product.

3.12 Creep Curve of Pluronic lecithin organogel P7

Creep curve is plotted to measure the viscoelastic nature of pharmaceutical formulation. Viscoelastic measurements are based on the mechanical properties of materials that exhibit both viscous properties of liquid and elastic properties of solids. (Fig. 10 a and b) Creep method is allows to examination of rheological materials under nearly quiescent equilibrium condition. To study creep curve a Maxwell element is used for non-Newtonian system as combined series of spring and dashpot. When dashpot combined in parallel as a mechanical model of a viscoelastic material, known as a Viogt element For the viscoelasticity studies by creep curve method compliance J (l/Pa) vs. Time (seconds) graph was plotted. Where the initial region AB showed the elastic region, region BC showed viscoelastic region, region CD is a linear portion corresponding to the piston in the dashpot at the bottom of the Maxwell-Voigt model representing viscous flow and region DEF is an instantaneous elastic recovery. The formulation P7 shows the combination of Maxwell and Voigt system. When stress is applied to the gel shows the elastic region followed by viscoelastic region. (Fig. 10 a and b)
Flow properties of formulation play important role from the aspect of ease of application to the patient hence it is important to understand the flow property of the formulation. Due to presence of polymer, the system should produce the Pseudoplastic flow also the drug which is soluble in vehicle facilitates the presence of pseudoplastic flow. (Fig. 11 a and b) Similar flow was observed with the marketed gel. It was observed that as stress increases rate of shear also increases which shows the graph with slight curvature. A pseudoplastic material displays a decrease in viscosity with an increase in shear rate, and is also known as “shear thinning”. In viscometer readings from a low to a high rpm and then back to the low rpm, and the readings fall upon themselves, the material is time independent pseudoplastic and shear thinning (Fig. 11 a and b)
3.14 Stability studies

Stability studies indicated that the formulations were stable at room temperature with no appreciable change in surface characteristics, viscosity ranging from 8054 to 8529, pH varying from 6.49±0.8 to 6.61±0.28 and drug content from ranging from 93.37±0.77 to 94.98±0.92. The formulations underwent considerable changes at 4°C and 60°C.

4. Conclusion

The purpose for formulation of Tapentadol hydrochloride PLO was to enhance bioavailability of the
drug by avoiding the first pass metabolism of drug. Tapentadol hydrochloride was formulated into PLO gel and gelation was confirmed by observing the flow on inversion of the beaker. Optimised PLO of tapentadol contained 3% of lecithin and 40% pluronic in the ratio of 30:70. Amongst the polymers HPMC, carbopol, xanthum gum and polyox WSR 205 which were added to PLO emulsion. Only HPMC and Carbopol were found to form stable gel. From the diffusion studies it was observed that HPMC and carbopol retarded the release of drug from the PLO. Slight change in temperature causes change in viscosity or can cause destabilisation of gel. The formulation P7 containing 40% pluronic F-127, lecithin 3% was the optimised batch. The formulation showed Maxwell and Viogt element for creep studies and had pseudoplastic flow.

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6. Declarations

Conflict of interest
The Author(s) declare(s) that they have no conflicts of interest to disclose.

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