DESIGN OF TRAMADOL HYDROCHLORIDE LOADED SOLID LIPID NANOPARTICLES BASED GELS FOR PAIN MANAGEMENT

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ABSTRACT

Objective: To formulate and characterize Tramadol hydrochloride loaded Solid Lipid Nanoparticles based gels, to understand in vitro drug diffusion profile and evaluate the developed formulations for topical application for pain management. Materials and Methods: Precirol ATO 5, Compritol 888 ATO and Tween 80 were used to prepare the Tramadol hydrochloride loaded Solid Lipid Nanoparticles based on solvent evaporation method and characterized using Zetasizer, Scanning electron microscopy and Differential scanning calorimetry. Tramadol hydrochloride loaded solid lipid nanoparticles were prepared and then incorporated in gel base for topical delivery. Results: The nanoparticles were in the size range of 300-400nm with zeta potential between -20 to -30mV. The SLN exhibited circular structure with better encapsulation efficiency. Sustained release topical gel of Tramadol hydrochloride lipid nanoparticles was prepared using the lipids Precirol ATO 5, Compritol 888 ATO with Tween 80 as surfactant by solvent evaporation method. Drug release followed diffusion controlled kinetics and released the drug for prolonged periods with enhanced dermal penetration. Conclusion: Gel formulation of Tramadol hydrochloride SLN is promising approach for prolonging the topical residence time and thereby better therapeutic effects.

KEYWORDS: Entrapment efficiency, Solid Lipid nanoparticles, Surfactant, Sustained release.
INTRODUCTION
Topical preparations are used for the localized pain management at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The major advantage of topical delivery systems is that they bypass first pass metabolism. Avoidance of the risks of intravenous therapy and of the varied conditions of gastrointestinal absorption including pH changes, gastric emptying time, presence of enzymes are some of the other advantages of topical preparations. Topical delivery enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose.\(^1\)

Topical delivery is preferably beneficial in pain management & antibacterial and anti fungal therapies. Topical drug delivery includes two basic types of products viz. External topicals that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area (e.g. gels, lotions, sprays, etc) and Internal topicals that are applied to the mucous membranes orally, vaginally or on anorectal tissues for local activity (e.g. solutions, sprays, drops, etc).

Pain is a complex constellation of unpleasant, emotional, sensory and cognitive experiences stimulated by real or perceived tissue damage and manifested by certain autonomic psychological and behavioral reactions.\(^2\) Nociception is the encoding and processing in the nervous system of noxious stimuli. It is the afferent activity in the central and peripheral nervous systems produced by stimulation of specialized nerve endings called "nociceptors" or "pain receptors" which sense and respond to parts of the body which suffer from damage. Nociceptive pain results from activity in neural pathways secondary to actual tissue damage or potentially tissue-damaging stimuli. When nociceptors get irritated, they get activated and transfer pain signals (via the peripheral nerves as well as the spinal cord) to the brain. The pain is well localized, constant and often associated with ache. Nociceptive pain is typically responsive to anti-inflammatory agents and opiates. Topically applied opioids predominantly have central effects which play a primary role on the peripheral nervous system and in decrease of nociceptive afferent responses.\(^3\)

During the last few decade lipids have gained much interest as carriers for the delivery of both, poorly water soluble as well as water soluble drugs. The availability of novel lipid additives with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid based formulations as a means for drug delivery. The absorption of drug from lipid based nanoformulations depends on various
factors, including particle size, degree of emulsification, rate of dispersion and potential precipitation of drug upon dispersion.

Lipid based drug delivery systems (LDDS) consist of diverse group of formulations, each consisting of different functional and structural properties that are amenable to modifications achieved by varying the composition of lipid excipients and other additives. Generally, most lipid drug delivery systems used as solid lipid nanocarriers have high stability, feasibility of incorporating both hydrophilic and hydrophobic substances, high carrier capacity and feasibility of variable routes of administration, including oral, parenteral, topical and pulmonary routes.

Solid Lipid Nanoparticles (SLN) are sub-micron colloidal carriers composed of physiological lipids, dispersed in water or in an aqueous surfactant solution. The most important advantage of these carriers is their low risk of toxicity. Small size (50-1000nm) of lipid particles ensures close contact with stratum corneum, and may enhance dermal penetration of drug. SLN have distinct occlusive properties due to the formation of an intact film on the skin surface upon drying, which decreases transepidermal water loss and favors the drug penetrating through the stratum corneum. Besides the nonspecific occlusion effect, the enhanced drug penetration might be related with SLN themselves, the highly specific surface area of nanometer sized SLN facilitates the contact of encapsulated drug with stratum corneum. The nanometer sized particles can make close contact with superficial junctions of corneocyte clusters and furrows between corneocyte islands, which may favor accumulation for several hours allowing for sustained drug diffusion through the skin.

Semi-solid formulations in all their diversity dominate the systems for topical delivery. Widely used topical agents like ointments, lotions, creams have many limitations. They are usually very sticky causing minute discomfort to the patient. Moreover they do not have sufficiently high spreading coefficient and need to be applied with rubbing. They even exhibit the problems of stability. Due to such factors, within the major group of semisolid preparations; the use of gels has increased both in cosmetics and in pharmaceutical preparations.

Gels are transparent to opaque semisolid formulations containing a high ratio of solvent to gelling agent. A gel is a colloid which is typically 99% by weight liquid, which is immobilized by surface tension between liquid phase and a macromolecular network of fibers.
built from a small amount of a gelatin like substance present. Gels containing large amounts of oleaginous substances provide an emollient effect to dry, irritated skin. More importantly, bases made up of non-volatile oleaginous substances like hydrocarbon bases can form an occlusive barrier on the skin that prevents escape of moisture from the skin into the environment. As a result, moisture accumulates between the skin and the gel layer that causes hydration of the stratum corneum. Hydration of stratum corneum allows opening up of intra- and inter-cellular channels and pathways for easier passage of drug molecules.\(^7\) Moreover, the moisture layer provides a medium for dissolution of the drug. Since only the dissolved drug is presented to the skin as an individual molecular entity, it is able to enter the stratum corneum; skin occlusion generally results in enhanced percutaneous drug absorption. Some well-formulated gels have been successful in facilitating greater drug permeation into the skin, when compared with ointments, wherein the drug may be dispersed as fine particles. Gel formulations generally provide faster drug release compared with ointments and creams, and are superior in terms of use and patient acceptability.

Till date there are no marketed formulations available for topical administration of Tramadol hydrochloride. Tramadol hydrochloride exists only as an injectable and oral formulation and hence topical formulations may present good commercial potential.

Patients perceive that oral treatments can potentially lead to more adverse effects as compared to topical treatment. The rationale of this project is the application of opioid analgesics directly on the site of pain, even if the sensation is a referred pain from another source. Also, topical delivery gives good aesthetic appeal, simpler and easier application and thus, is highly patient compliant.

Tramadol hydrochloride, a centrally acting oral analgesic, has high solubility and bioavailability in the biological fluids and thus possesses a major drawback of adverse effects (since it reaches a high concentration in the central nervous system in a shorter period of time). So, to reduce the limitations of the drug on oral and parenteral administration (which are the only drug delivery systems available currently), development of topical formulation of Tramadol hydrochloride was considered.

The natural barrier for topical delivery is skin, which makes the drug delivery difficult. To have optimum diffusion, the affinity of the drug for the skin is critical. For this purpose, topical dosage forms like gels are preferred. In order to obtain good diffusion and permeation
of the drug in skin, Solid Lipid Nanoparticles were formulated, as the occlusive property of SLN on skin provides increased drug penetration particularly via skin moisturization.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride (drug) was obtained as gift sample from Indeus Life Sciences Pvt. Ltd., Mumbai. Tween 80 was purchased from S.D. Fine Chem Ltd., India. Compritol 888 ATO and Precirol ATO 5 were obtained as gift samples from Gattefosse Pvt. Ltd., Mumbai, Glyceryl monostearate(GMS) and stearic acid were obtained as gift samples from Mohini Organics Pvt. Ltd., Carbopol 980 and 971 & Poloxamer 407 were obtained as gift samples from Lubrizol Pvt. Ltd., Triethanol amine was purchased from Lobachem Pvt. Ltd. The objective of this study was to formulate and evaluate Tramadol hydrochloride loaded solid lipid Nanoparticles based gels for effective topical delivery.

Formulation development

A. Formulation of Tramadol hydrochloride loaded Solid Lipid Nanoparticles (SLN)

The SLNs were prepared by Solvent Evaporation Technique.

In brief, the organic phase (i.e. solid lipids viz. Precirol ATO 5/Compritol 888 ATO/Stearic acid/GMS in different proportions) was dissolved in suitable solvent (chloroform/ethanol/isopropyl alcohol). The aqueous phase consisted of the accurately weighed quantity of drug dissolved in double distilled water and varied concentrations of hydrophilic surfactants (Tween80/Poloxamer 188) were added to it. Then, the organic phase was injected dropwise in the aqueous phase under an over head stirrer agitated at a uniform speed for one and a half hour followed by addition of cold water (causing lipid recrystallization) to the dispersion and continued stirring for another half an hour.

The dispersion was then subjected to High Pressure Homogenization (HPH) at 10,000 psi (10 cycles) for size reduction of the formed SLN.

SLN dispersion containing 0.5% and 1% w/v drug were prepared and evaluated.

B. Preparation of drug solution

Drug was dissolved in a suitable solvent (water) to get the required concentration of drug solution to be used for comparison with SLN dispersion during invitro diffusion studies.
C. Preparation of Tramadol hydrochloride loaded Nanogels (SLN based gels)

Different gelling polymers (Carbopol 980/Carbopol 971/Hydroxy Propyl Methyl Cellulose K4M) in varied concentrations were tried for preparing Nanogels. The gelling polymer was accurately weighed and dispersed in the weighed quantity of SLN dispersion and was kept aside for 1 hour (for optimum swelling of the polymer).

Then, glycerol and preservatives dissolved in weighed quantity of purified water (containing the drug) were added to the above dispersion and triethanol amine was added dropwise with slow and continued stirring with a glass rod to adjust pH (upto neutral). Gels containing 0.5% and 1% w/w drug concentrations were prepared and evaluated.

D. Preparation of conventional gel of Tramadol hydrochloride

Conventional gel was made using the same gelling polymer which was optimized for Nanogels. Here, the gelling polymer was weighed and soaked in measured amount of purified water for 1 hour (for optimum swelling of the polymer). Then, glycerol and preservatives dissolved in weighed quantity of purified water were added to the above dispersion and triethanol amine was added dropwise with slow and continued stirring with a glass rod to adjust pH (upto neutral).

Fourier Transform Infra Red (FTIR) Spectroscopy

IR spectra were recorded on Fourier Transform Infrared spectrophotometer (IR Affinityl, Shimadzu) using potassium bromide pellet method. The baseline correction was made using dried potassium bromide. Then the spectrum of mixture of drug and potassium bromide was run followed by drug with excipients in the wavelength region from 4000 to 400 cm\(^{-1}\).

Differential Scanning Calorimetry (DSC) studies

Thermal stability of drug and its interaction with the excipients, if any, was evaluated by DSC studies. The study was carried out using Differential Scanning Calorimeter (DSC, Mettler Toledo e822, Japan). Accurately weighed samples were carefully placed in DSC boats and heating curves were recorded in temperature range of 35–305\(^\circ\)C at a heating rate of 10\(^\circ\)C/min under inert atmosphere (\(N\)\(^2\) 8ml/min).

Development and Validation of Analytical Method

UV-Visible spectrophotometric method was developed and was found to be linear in concentration range of 30 - 180 μg/ml at 271 nm for Tramadol hydrochloride in phosphate
buffer solution (PBS) pH 7.4. The developed method was validated for linearity, precision, accuracy, reproducibility, robustness, limit of detection and limit of quantification.

**Evaluation of developed formulations**

**SLN Dispersion**

1. **Particle size measurements**
   
   Particle size analysis of SLN dispersion was carried out by dynamic light scattering with Malvern Zetasizer. The polydispersity index of the formulation was also determined.

2. **Zeta potential measurements**
   
   Zeta potential of SLN was measured using Malvern Zetasizer.

3. **pH**
   
   pH of developed formulations was determined by pH meter.

4. **Morphology Studies**
   
   Morphology of SLN was observed using Scanning Electron Microscopy (SEM) analysis.

5. **Drug content**
   
   Tramadol hydrochloride content in SLN dispersion was measured by dissolving known quantity of SLN dispersion in solvent (methanol) and recording the absorbance at 272 nm using UV/VIS Spectrophotometer.

6. **In-vitro diffusion studies**
   
   In-vitro drug diffusion profile of SLN dispersion and drug solution was determined on a Franz Diffusion cell over a period of 24 hours on Dialysis membrane (150 Da) using phosphate buffer pH 7.4. Percentage of drug diffused was determined spectrophotometrically at λmax of 271nm.

**Nanogel**

i) **Physical appearance**
   
   The prepared Nanogel formulations were inspected for their color, homogeneity, consistency and pH.

ii) **Spreadability measurement**
   
   Spreadability of Nanogel was determined by a spreadability testing apparatus.
The apparatus was made of wooden block with scale and two glass slides having a pan mounted on a pulley. Excess formulation was placed between two glass slides and 100g weight was placed on the upper glass slide for 5mins to compress the formulation to uniform thickness. Weight (100g) was added to the pan. The time in seconds required to separate the two slides was taken as a measure of spreadability.

The spreadability was calculated by using the following formula

\[ S = \frac{m \times l}{t} \]

where \( S \) is spreadability; \( m \) is weight tied to the upper slide; \( l \) is length of glass slide and; \( t \) is time taken in seconds.

iii) Extrudability measurement

It is a usual empirical test to measure the force required to extrude the material from the tube. The method adopted for evaluating the extrudability is based on the quantity in percentage of gel extruded from the aluminium collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of SLN gel in 10 seconds.

iv) Rheological study

The viscosity of Nanogel formulation was determined at 25±1°C using a Brook Field viscometer (DV III ultra-model no. D 220).

v) Drug content determination

Tramadol hydrochloride content in Nanogel was measured by dissolving known quantity of Nanogel in solvent (methanol) and recording the absorbance at 272 nm using UV/VIS Spectrophotometer.

vi) In vitro drug diffusion and ex vivo skin permeation studies

In vitro diffusion of Tramadol hydrochloride Nanogel and conventional gel was determined using Franz diffusion apparatus. Phosphate buffer pH 7.4 was used as diffusion medium. Dialysis membrane (150 Da) was mounted on Franz diffusion cell in between the donor and the receptor compartment. The gel was placed over the dialysis membrane. The temperature of the diffusion medium was maintained at 37±1°C by a thermostatic arrangement. Sink conditions were obtained by magnetic stirring at 500-600rpm. Aliquots of 2ml were withdrawn at predetermined time intervals and replenished by equal volumes of fresh diffusion medium. Withdrawal of sample aliquots was carried out for a period of 24 hrs at the time intervals of 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours. The drug concentration in the withdrawn
aliquots was determined spectrophotometrically and was calculated using standard calibration curve.

*Ex-vivo* skin permeation and retention studies of Tramadol hydrochloride Nanogel and conventional gel were performed using porcine ear skin.

The excised skin membrane was mounted on Franz diffusion cell after thorough washing with hot distilled water and removal of subcutaneous fats. Phosphate buffer pH 7.4 was used as diffusion medium. The gel was applied over the skin membrane. The temperature of the diffusion medium was maintained at 37±1°C by a thermostatic arrangement. Sink conditions were maintained by magnetic stirring at 500-600rpm. Aliquots of 2ml were withdrawn at predetermined time intervals and replenished by equal volumes of fresh diffusion medium. Withdrawal of sample aliquots was carried out for a period of 24 hrs at the time intervals of 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours. The drug concentration in the withdrawn aliquots was determined spectrophotometrically and was calculated using standard calibration curve. Tramadol hydrochloride flux through the skin was calculated by plotting the cumulative amounts of drug penetrating the skin against time and determining the slope of the linear portion of the curve and the χ-intercept values (lag time) by linear regression analysis. Drug fluxes (µg/cm² h⁻¹), at steady state, were calculated by dividing the slope of the linear portion of the curve by the area of the skin surface through which diffusion took place. At the end of 24th hr, the skin was minced into small pieces, homogenized and extracted with methanol and suitably diluted and analyzed spectrophotometrically to evaluate retention of drug in skin.

vii) Stability studies
Optimized formulations were subjected to stability studies as per ICH guidelines (Q1A) R2 for a period of three months. The samples were analyzed at mentioned intervals.

viii) Skin Irritation Studies
Skin irritation potential of the developed formulations was studied using Albino Wistar Rats (Institutional Animal Ethics Committee (IAEC) approval no – CPCSEA/IAEC/BNCP/P-48/2015).

The animals were housed in propylene cages, with free access to standard laboratory diet and water and were acclimatized for 7 days before experimentation. Hair was removed from dorsal side of rats, 24h prior to the application of the formulation. Formulation containing 5-
10 mg of drug was applied on the shaven skin of rats by uniform spreading within area of 4 cm² and the site of application was occluded with cotton bandage. The applied formulation was removed and the skin was observed visually for changes such as erythema (redness) and edema (inflammation).

**ix) Anti-Nociceptive Activity**

Hot plate test was performed on Albino Wistar rats for determination of anti-nociceptive (analgesic) activity of the developed nanogels. Nanogels and placebo formulations were applied to hind paw of the Wistar rats.

Cut off period: 15 seconds
Temperature: 55±1°C (constant)
Observations: Licking of the paws and jumping.

Observations were made after 1, 2, 3, 4, 5, 6, 7 and 8 hrs of application of formulation. Licking of the paw or jumping/lifting of the leg were observed and time was noted digitally. Latency period of response of formulation and blank formulation were compared with control group of rats.

**RESULTS AND DISCUSSIONS**

The optimized formulations were developed and investigated as follows:

**Formulation development**

- **Selection of solvent**

  Solubility studies showed the drug was freely soluble in water and methanol, while the lipids were soluble in ethanol and chloroform; except for Compritol 888 ATO being soluble only in chloroform. Hence, chloroform was selected as the solvent.

- **Selection of lipids and surfactants**

  Based on the entrapment efficiency, visual appearance and particle size (as observed in Motic microscopy) combination of two solid lipids, Compritol 888 ATO and Precirol ATO 5 in the ratio of 1:1 was selected, Tween 80 was selected as the aqueous surfactant (1%) and 0.5% of drug was loaded.
**Selection of gelling polymer**

Based on the swelling of the gelling polymer in the dispersion, Carbopol 980 (1%) was selected. The optimized formulation of Tramadol hydrochloride SLN gel containing glycerol as humectant, methyl and propyl paraben as preservatives and triethanolamine as pH adjustor, yielded good feel on human skin with a pH between 5.5-6.5.

- **FTIR** and **DSC** study results showed that there was no apparent interaction between API and excipients.

![Fig. 1: IR spectra of Tramadol hydrochloride.](image1)

![Fig. 2: DSC graph of pure API.](image2)
Distinct peaks were observed in FTIR indicating no interactions of drug with excipients and endotherm of the drug was not observed in DSC indicating complete entrapment of the drug in the formulation.

Analytical method development
UV-visible spectrophotometric method for Tramadol hydrochloride was developed in phosphate buffer pH 7.4 and methanol and was found to be linear in the concentration range of 30-150µg/ml with $R^2 = 0.999$ at 271 and 272 nm respectively.

Characterization and evaluation of formulation
SLN Dispersion

Visual Examination
The optimized SLN formulation was an opaque dispersion and appeared like a homogenous single-phase liquid, when observed for visual clarity against black background. No traces of undissolved drug or other solid ingredients were found in the SLN dispersion.

Morphology
SEM image is indicative of morphology of the nanoparticles. The particles of optimized dispersions were spherical in shape.
Fig. 4: SEM image of Tramadol hydrochloride loaded Solid Lipid Nanoparticles.

- **Particle size**
  All the particles were in the nanometer range of 300-400 nm which indicated the suitability of formulation for topical drug delivery. Polydispersity index signifies the uniformity of particle size within the formulation. PDI is a measure of particle homogeneity. If PDI value is closer to 0, it indicates narrow size distribution of the particles. PDI of optimized dispersion was below 0.5 which indicated prepared dispersion is monodisperse and will remain stable.

- **Zeta potential**
  Zeta potential is an important parameter for prediction of stability. Because of the presence of fatty acids in the structure of the excipients used, generally the surface charge of the particles is negative. Zeta potential of the formulations was found to within -30 to -20 mV, indicating negative charge of the particles which prevents aggregation of the particles.

- **Entrapment efficiency**
  Entrapment efficiency of prepared SLN dispersion was found to be within 59-68% which indicates good drug loading capacity of the formulation.

- **In vitro studies**
  Results obtained for *in vitro* drug diffusion study using dialysis membrane 150 Da, showed sustained release of drug from SLN dispersion as 98% of drug was diffused in 24 hours from SLN dispersion, whereas in case of drug solution, almost 99% of drug was diffused within 4hrs.
Nanogels

- **Visual Examination**
The prepared Tramadol hydrochloride SLN based gel formulations were white, odourless and viscous with a smooth and homogeneous appearance.

- **pH**
  pH was between 5.5 to 6.5 of the developed nanogel.

- **Spreadability**
  For topical preparations, spreadability is one of the important parameters. The spreadability is important for ease of application of topical preparation and better patient compliance. Spreadability of optimized formulation was in the range of 19 to 28 gm.cm/sec.

- **Extrudability**
  It is important test for semisolid preparations. Pressure required to extrude semisolid preparation is depended on the viscosity and consistency of the formulation. More quantity of SLN based gel extruded at little applied pressure on tube which may result in better patient compliance. The extrudability of the gel was in the range of 16 to 19 g/cm².

- **Viscosity**
  Rheological behavior of the SLN based gel systems indicated that the systems were non-Newtonian in nature showing decrease in viscosity at the increasing shear rates. The viscosity of optimized SLN-based gel was in the range of 12300 to 12500cPs.
- **Drug Content**
  Drug content of prepared SLN based gels was 98-102% which indicates good drug loading capacity of the formulation and required dose of drug was available for the pharmacological action.

- **In vitro drug diffusion profiles**
  Results obtained after *in vitro* drug diffusion study using dialysis membrane 150 Da, showed sustained release of drug from Nanogel, as 85% drug was diffused in 24 hours from Nanogel, whereas in case of conventional gel, almost 95% of drug was diffused within 6hrs.

  ![Graphical representation of in vitro diffusion studies.](image)

- **Ex vivo drug diffusion profiles**
  Results obtained after *ex vivo* drug diffusion study using dialysis membrane 150 Da, showed sustained release of drug from Nanogel, as 91% of drug was diffused in 24 hours from Nanogel whereas in case of conventional gel, almost 99% of drug was diffused within 6hrs.

  ![Graphical representation of ex vivo diffusion studies.](image)
• **Skin irritation studies**

The potential of developed Tramadol hydrochloride formulations to produce dermal irritation when applied to the skin of rats was investigated. Primary Irritation Index (PII) of the formulations was determined. Topical application of the optimized Tramadol hydrochloride formulations (for 24h) did not exert any significant irritant effect on rat skin over a 72-hour observation period post-application. Therefore, the developed and optimized topical formulations of Tramadol hydrochloride were considered safe for topical administration without producing any acute irritant effect on skin.

• **In vivo studies**

The anti nociceptive activity was assessed using the behavioural test viz, Hot Plate test. The duration of activity of the cutaneous analgesic effect of the test animals was upto 8 hours post treatment.

• **Stability studies**

The nanogels were kept on stability in the final container and closure at room temperature, at 40°C and 75% RH for accelerated stability and at 4°C in the fridge. Stability Studies after 1, 2, 3 months indicated that no change in colour, odour, appearance or assay was observed. *In-vitro* diffusion studies were performed and there was no change observed in the diffusion profile after 3 months of accelerated stability.

**CONCLUSION**

In the present study, an attempt was made to check the topical availability of Tramadol hydrochloride in treatment of pain by acting at the sensory afferents in the skin, by preparing drug loaded SLN based gel formulations. The SLN dispersion was prepared by solvent evaporation technique using Precirol ATO 5 and Compritol 888 ATO as lipid matrix. The prepared SLN dispersions were characterized for various parameters such as particle size and zeta potential and its result indicated narrow particle size distribution and steric stability. Entrapment efficiency results assured good loading capacity. In-vitro drug diffusion study showed optimum release upto 24 hours. Formulation was also characterized for Scanning Electron Microscopy to determine morphology of particles. SLN based Carbopol 980 gel was also evaluated for physicochemical properties, spreadability, viscosity, diffusion study, skin irritation study, anti nociceptive study which showed desirable properties, release, activity
and non-irritant behaviour. Thus, it was seen that SLN have the potential to localize the drug at the site and could be useful for site-specific delivery of drugs to the skin.

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