IJPSR (2014), Vol. 5, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 January, 2014; received in revised form, 22 May, 2014; accepted, 29 May, 2014; published 01 June, 2014

MICROEMULSION BASED GELS FOR TARGETING NEUROPATHIC PAIN

Sneha Ranade*[1], Vaishali Londhe [1] and Amrita Bajaj [2]

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management SVKM's NMIMS [1], Vile Parle (West), Mumbai 400056, Maharashtra, India
Dr. Bhanuben Nanavati College of Pharmacy [2], Vile Parle (West), Mumbai 400056, Maharashtra, India

Keywords:

Microemulsion, Topical Gel, Pain, Local anaesthetic

Correspondence to Author:

Sneha Ranade

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management SVKM's NMIMS, Vile Parle (West), Mumbai 400056, Maharashtra, India

E-mail: sneharanade27@yahoo.com

ABSTRACT:

Background: Neuropathic pain is a type of chronic pain that occurs when nerves in the central nervous system become injured or damaged. Currently only a limited number of topical treatments are available to treat it. Hence an attempt was made to alleviate symptoms of neuropathic pain by topical application of a local anaesthetic drug.

Results: Microemulsions were formulated using Oleic acid as the oily phase and Tween 80 and ethanol in 1:1 ratio as the surfactant and cosurfactant respectively. The microemulsions thus formed were clear, transparent and aesthetic in appearance and showed low viscosity and near neutral pH. They exhibited electrical conductivity indicating they were o/w microemulsions. The particle size was in the submicron range while the polydispersity index was 0.4 indicating a uniform particle size distribution. A satisfactory and elegant gel was obtained using Xanthan gum as the gelling agent. *In-vitro* and *ex-vivo* drug diffusion indicated a sustained release of the drug over 8 hours. Anti-nociceptive activity was tested using hot plate and tail flick tests where the microemulsion based gels of Ropivacaine exhibited a marginally better efficacy as compared to the conventional Lidocaine gel.

Conclusion: Based on these findings, Ropivacaine can be used as a suitable local anaesthetic drug which acts topically in low doses and can provide significant pain inhibition when given as a microemulsion gel.

INTRODUCTION: During recent years there has been an increasing interest in enhancing the permeation of drugs into and through the skin. It is the most patient friendly and convenient technique in the treatment of topical diseases.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(6).2515-24

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(6).2515-24

It has the ability to restrict the therapeutic effect only on the affected area and to reduce systemic absorption. The main physical barrier of the skin is the stratum corneum which is the horny layer. So in order to facilitate permeation across the epidermis in to the dermis, for a substance permeating across the skin, diffusion through the stratum corneum appears to be the rate limiting step.

The dermis contains a variety of cell types, nerves, blood vessels and lymphatics embedded in a dense network of connective tissue [1].

The carriers accumulate in stratum corneum which is the dead skin or other upper skin layers are not expected to penetrate into viable skin. The common characteristic of all colloidal carriers is the submicron-sized particles which are intended to transport entrapped active molecules to the skin. Hence size appears to be an important factor in drug permeation through the skin. Microemulsions are colloidal drug carriers. Being lipidic vehicles they are one of the promising systems for topical delivery of drugs and have nowadays attracted the main interest due to their localized effect [2.]

A wide variety of molecules can be transported through microemulsion based delivery systems. Lipophilic as well as hydrophilic drug moieties for both transdermal and topical delivery are shown to greatly benefit from application in microemulsions when compared to conventional vehicles, like gels, ointments and creams. They are much more stable as compared to macro-emulsions in addition to their aesthetic properties like clarity and transparency. These favourable drug delivery attributes of microemulsions can mainly be attributed to the excellent lipid solubility properties in the skin layers [3].

Topical dosage forms to reduce pain and allodynia are increasingly gaining popularity due to the easy applicability and better patient compliance to such delivery systems. Many NSAIDS (Non-Steroidal anti-inflammatory drugs) and Local anaesthetics have been given through the topical route via microemulsions for pain relief, like meloxicam [4], Ibuprofen [5], Aceclofenac [6], Diclofenac [7], Celecoxib [8] and Lidocaine [9].

Ropivacaine is a long acting, amide type of local anaesthetic. It is available as an S isomer unlike other local anaesthetics which are racemic mixtures. It is a regional anaesthetic with an efficacy broadly similar to that of bupivacaine. The mechanism of nerve block is through depolarisation of the sodium channels [10].

Till date there are no marketed formulations available for topical administration of Ropivacaine. Ropivacaine exists only as an injectable formulation and hence topical formulations may present good commercial potential [11].

This work focuses on formulation of microemulsion based gels to alleviate and provide symptomatic relief to patients suffering from peripheral neuropathy caused by a variety of disease conditions like diabetes, HIV (human immunodeficiency Virus) and also cancers.

MATERIALS AND METHODS:

Materials: Ropivacaine was procured from VeryChem, China. Oleic acid, Tween 80 and Ethanol were procured from Qualigens and SD Fine chemicals. Transcutol, Labrasol, Maisine, Labrafac, Labrafil were gift samples from Gattefosse, Mumbai, India. All other solvents and reagents used were AR grade.

Saturation solubility studies of Ropivacaine in various oils and surfactants: In order to determine the most suitable oil and surfactant saturation solubility studies were carried out. Oleic acid, Isopropyl Myristate, Maisine, Peceol, Labrafac lipophile, Transcutol, Labrasol, Labrafac, Cremophore, PEG 400, Tween 80, Tween 20, Span 80, Span 20 were explored for incorporation in microemulsion 12. Excess amount of Ropivacaine was dissolved in 2ml of oils and surfactants, kept for 48 hours on the orbital shaker at 37^0C. After 48 hours the tubes were centrifuged and the supernatant was analysed after suitable dilutions as seen in **Figure 1**.

Preparation of microemulsions by Construction of pseudo-ternary phase diagrams: Various ratios of the surfactant to the Co-surfactant were evaluated (3:1, 2:1, 1:1 and 1:3). Increasing concentrations of the oil were taken and the S: CoS (surfactant: co-surfactant) mix was added in decreasing concentrations i.e the ratio of oil to the mixture of surfactant and co-surfactant was varied from 9:1 to 1:9. Mixtures of oil, surfactant and cosurfactant were prepared.

Water was added drop by drop under gentle stirring to the mixture. The compositions of microemulsion at which phase separation from homogeneous microemulsion to heterogeneous phases occurred were recorded i.e the point before turbidity. Pseudo ternary phase diagrams were plotted using Chemix software, version 3.6. The region of the microemulsion was depicted in black colour.

The largest region of microemulsion was checked using pseudo ternary phase diagrams as given in **figure 2** [13, 14].

Selection of placebo microemulsion formulations: From each phase diagram was constructed, different formulations were selected from the microemulsion region so that 1.25% of Ropivacaine could be incorporated into the oil phase while keeping surfactant concentrations at a minimum. Therefore, the following criteria were used for the selection of different formulations from the phase diagrams: solubility of drug in the oil phase, acceptable range of surfactants and cosurfactants, bench top stability as well as stability of the formulations to centrifugation.

Formulation of drug loaded Microemulsions formulation: To formulate drug loaded microemulsions, required quantity of Ropivacaine was dissolved in oil. The required amount of S: CoS (Surfactant: Cosurfactant) mixture was added under gentle stirring. Water was added drop wise till a clear and transparent solution was observed.

Formulation of Microemulsion Gels: In order to obtain a free flowing, transparent clear gel, formulation trials with various gelling agents like Poloxamer 407, carbopol 940 and xanthan gum were explored. Concentration of Carbopol 940 and Xanthan gum was varied from 0.3% w/w to 1% w/w while that of Poloxamer 407 was evaluated at 15%w/w, 20 % w/w and 25% w/w as shown in **table 1**. Briefly, after the microemulsion was prepared xanthan gum or Poloxamer 407 were sprinkled onto the microemulsion, gently stirred and allowed to swell overnight. Carbopol 940 was sprinkled, stirred and pH adjusted to 7 by use of few drops of diluted triethanolamine if required. The optimized formulation was selected on the basis of physical attributes of the gels, and it was manufactured as follows: Menthol, Methyl Paraben and Propyl Paraben were dissolved in few drops Ethyl alcohol and added to the S: CoS mixture. Purified water was used to titrate the oil, S: CoS mixture.

TABLE 1: FORMULATION TRIALS FOR MICROEMULSION BASED GEL PREPARATION

Sr. No.	Ingredient	MEC1	MEC2	MEC3	MEP1	MEP2	MEP3	MEX1	MEX2	MEX3
		%								
1	RB	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
2	Oleic acid	~5	~5	~5	~5	~5	~5	~5	~5	~5
3	S: CoS	~44	~44	~44	~44	~44	~44	~44	~44	~44
4	Carbopol 940	0.3	0.5	1	---	---	---	---	---	---
5	Poloxamer 407	---	---	---	15	20	25	---	---	---
6	Xanthan Gum	---	---	---	---	---	---	0.3	0.5	1
7	Water QS	100	100	100	100	100	100	100	100	100

Stability of Ropivacaine Microemulsions: The optimized formulation was centrifuged at 10000 rpm for 30 min to observe any phase changes or phase separation of the microemulsion. It was then subjected to heating and cooling cycles where turbidity, phase separations and degradation was evaluated.

Characterization of optimized microemulsion: The optimized microemulsion formulations were characterized as follows [5, 15],

1. **Droplet size and size distribution:** Droplet size was determined by photon correlation spectroscopy (PCS) that analyzes the fluctuations in light scattering due to Brownian motion of the droplets using a Zetasizer (1000 HS, Malvern Instruments).

2. **Viscosity and pH:** The viscosity of the formulations was measured using Brookfield DV pro II rheometer (Brookfield Engineering Laboratory) using spindle S64 at 25 +-0.5°C and rpm of 30. The pH of optimized Ropivacaine microemulsion was determined using a calibrated digital pH meter (Labindia, PICO).

3. **Conductivity:** Conductivity of optimized microemulsion formulation was measured to determine the continuous phase in the microemulsion and was performed using

conductivity meter where the flow of current was recorded (Lab India, PICO).

4. ***In vitro* drug diffusion studies:** Drug release from the promising microemulsions and the microemulsion based gels was studied through a dialysis membrane in triplicate. This membrane was soaked overnight in buffer and then mounted on Franz diffusion cells with a surface area of 3.14 cm^2 and receptor compartment with a capacity of ~20 ml. The receptor compartment was filled with Phosphate buffer solution (PBS) pH 6.8 as diffusion medium at 32±0.5^oC. The buffer in the reservoir compartment was stirred continuously at a constant speed. 100 mg of Microemulsion/ microemulsion based gel was accurately weighed and applied on the membrane. Aliquots were withdrawn and were suitably diluted, filtered if needed and then injected into HPLC (Perkin Elmer) for analysis of drug content.

5. ***Ex Vivo* drug Diffusion studies:** Fresh skin was excised from the porcine ear region and adhering fat and other cartilage tissues were removed, the skin was used immediately after excising. It was sandwiched between the recipient and donor compartments of the Franz diffusion cells. Aliquots were withdrawn at specific time points and were inject into the HPLC for analysis of drug content.

6. ***In Vivo* anti-nociceptive activity:** The experimental protocol was approved by Institutional Animal Ethics Committee (CPCSEA/IAEC/SPTM/P-49/2013).

   The Wistar rats were housed in animal house under standard conditions with free access to food and water.

   For both hot plate test and the tail flick test, the rats were allowed to acclimatize to the experimental room before the start of the experiment. The rats were divided into 3 groups, control, standard (Lidocaine gel) and test (Microemulsion based gel) containing 6 animals each in order to reduce chances of variability and obtain a good statistical co-relation. Students 't' test was applied to the results in order to determine level of significance in the results [16].

7. **Hot Plate Test:** The Formulation was applied to the paws of the animals. The temperature of the plate was monitored and kept constant throughout the experiment.The time points selected were 1 hour, 2hours, 4 hours, 5 hours and 7 hours. At every time point the animals were placed on the hot plate which was pre-heated to 55^oC. Licking of their fore and hind paws or jumping was recorded as the end point. A maximum latency period of 15 seconds was decided in order to reduce any damage to the animals.

8. **Tail flick test:** The Formulation was applied to the tip of the tail of animals to 5 cm above it. The time points selected were 2 hours, 4 hours, 6 hours. Tail flick test was performed by tail immersion method. The tail of the rats was immersed in a hot water which was kept at a constant temperature of 55^oC and monitored by the use of a thermometer suspended into it. The latency of tail withdrawal from the heat source, the hot water bath, was recorded.

9. **Histopathology studies [17]:** The histo-pathological skin evaluations were carried out using Wistar rats. The hair around the dorsal region of the rat skin were removed using a hair removing cream and it was observed for 24 hours in order to assess any irritation potentialof the hair removal process. The microemulsion gel formulation was topically applied for 24 h and the area was bandaged in order to avoid any scratching and removal of microemulsion gel by the rats. After 24 h, rats were sacrificed using cervical dislocation. The formulation was gently rubbed off and the rat skin was further dissected, stored in a 10% formalin solution for approximately 24 h, and was further processed for viewing under the microscope.

RESULTS AND DISCUSSION:

Solubility studies: From the saturation solubility studies it was noted that Oleic acid, span 80, Tween 80, Transcutol and Labrasol were found to solubilise the drug well as indicated in **figure 1**.

Although Span 80 could solubilise the drug well, it had a yellow tinge and was highly viscous which is not a desirable characteristic; hence it was not found to be a very suitable surfactant. Hence from these observations, oleic acid was selected as the oil phase while Tween 80, Transcutol and ethanol were screened as the surfactant and co surfactant. Ethanol appears to be a good surfactant as well as a good solvent justifying its use as a cosurfactant in many reported pseudo-ternary systems.

Microemulsions prepared with Tween 80 and Transcutol P was found to be clear in transparent but they were not highly stable to dilution with water, they formed opaque dispersions and hence they were not explored further. Phase diagrams were prepared using transutol and solutol as the surfactant and cosurfactant, but the microemulsion region obtained was small as compared to the microemulsion obtained using tween 80 and ethanol. It was also observed that this microemulsion too was not stable to dilution which could be due to the fact that they are not able to emulsify the system well. Pseudo ternary phase Diagrams (Chemix Software version 3.5) were plotted using oleic acid as the oil phase, Tween 80 as the surfactant and ethanol as the co-surfactant.

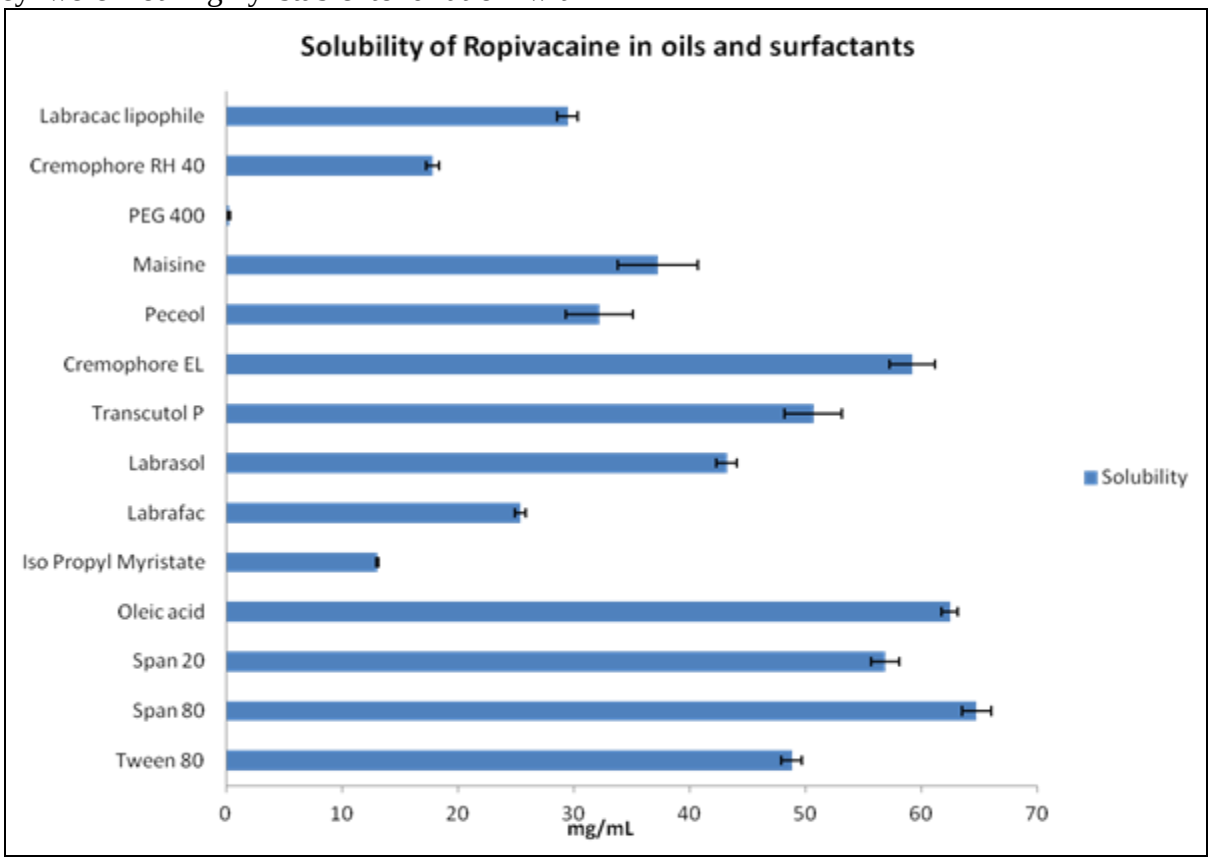

FIGURE 1: SATURATION SOLUBILITY STUDIES OF ROPIVACAINE IN OILS AND SURFACTANTS

Pseudo Ternary Phase diagrams: From the pseudo ternary phase diagrams (**Figure 2**), it was observed that as the ratio of Tween 80: Ethanol was increased from 1:1 to 3:1 there was a significant decrease in the microemulsion region, i.e. when the concentration of Tween 80 was increased and ethanol decreased the amount of surfactant and co-surfactant required for microemulsion formation became higher. This could be due to the fact that both oleic acid and water are miscible in ethanol which may lead to a reduction in the surface tension of the system [18].

A combination ration of 1:1 of Tween 80 and ethanol was selected as the surfactant and co-surfactant, the composition of the microemulsion was selected such that the concentration of surfactant and co-surfactant was within IIG (Inactive ingredients database) limits and the quantity of oil enough to solubilise the drug in the required dose. The appearance of the microemulsion was clear and transparent with a slight yellowish colour due to the presence of Tween 80 which imparts the colour.

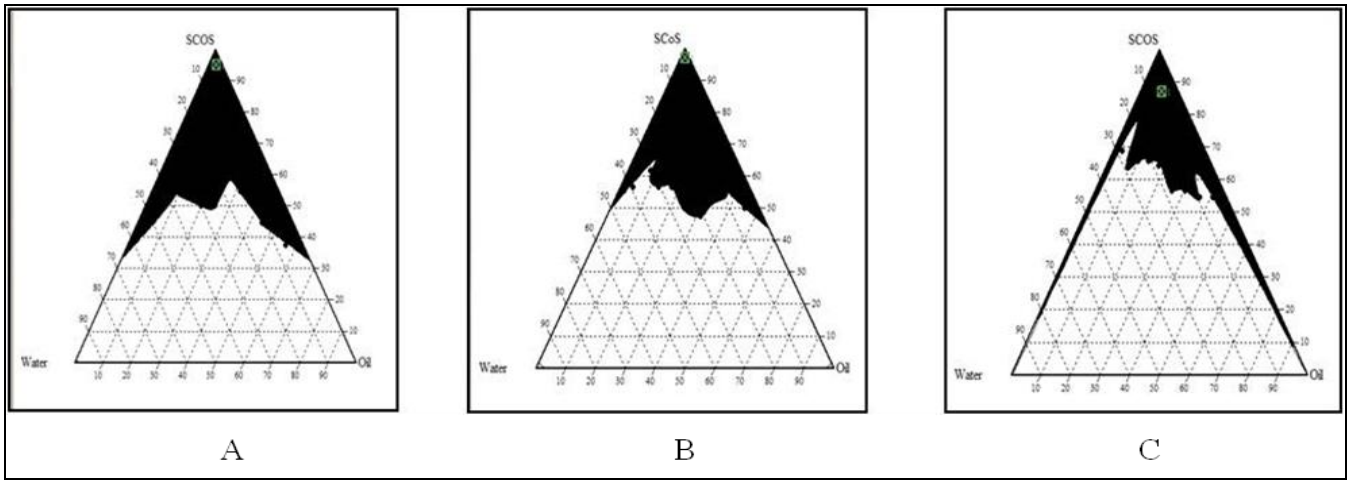

FIGURE 2: PSEUDO TERNARY PHASE DIAGRAMS OF OLEIC ACID AS OIL, TWEEN 80 AND ETHANOL AS SURFACTANT AND CO SURFACTANT IN DIFFERENT RATIOS a) 1: 1 ratio of surfactant and co surfactant, b) 2: 1 ratio of surfactant and co surfactant, c) 3: 1 ratio of surfactant and co surfactant

Formulation of drug loaded microemulsions: The final concentration of the oily phase was approximately 5 – 6% and S: CoS mixture concentration ranged from 40 – 45% whiles the rest was water. Addition of drug under gentle stirring in the oil and S: CoS mixture formed a clear one phase solution without any drug precipitation. Additional drug could also be added to the system which proves that the microemulsion has high drug loading capacity of up to 5% or more. Addition of water to the system under gentle stirring did not affect the transparency and stability of the microemulsions; it gave additional fluidity to the system. Since tween 80 is a surfactant, stirring of tween 80 generally causes formation of air bubbles, but no air entrapment was observed. This could be attributed to the addition of alcohol as the co-surfactant which acts as a defoaming agent, acting on the main surface of the foam. Ethanol, due to its rapid spreading and being in contact with the surface of the foam bubbles reduces the localized surface tension which leads to rapid bubble bursting. Hence when ethanol or other small chain alcohols are present in the system, foam.and air entrapment due to surfactants may be postulated to be negligible enhancing the aesthetic appeal of the formulations [18, 19].

Formulation of microemulsion Gels: Carbopol 940 produced slightly translucent gels and the viscosity was higher than optimum hence Carbopol was not evaluated further as a gelling agent. Transparent, clear gels were obtained using Poloxamer 407 and Xanthan gum in the concentrations of 20% w/w and 0.5% w/w respectively. Higher concentrations (1% w/w) of Xanthan gum produced highly viscous gels with entrapment of foam, which were not easily spreadable and were not of a pourable consistency. In the final formulation 0.5% w/w of Xanthan gum was selected as the gelling agent. Addition of menthol produced a cooling sensation on the skin and it also helped to mast the slightly unpleasant odour of oleic acid in the formulation. Since ethanol is present and it prevents the growth of microorganisms, the addition of methyl and propyl paraben as preservatives was debated upon, but to ensure long term stability they were added.

Characterization of microemulsion and microemulsion gels: The microemulsion was found to be stable to centrifugation as phase separation did not occur. It was also found stable to heating and cooling cycles which were applied and did not show any phase separation or turbidity. A slight browning of the microemulsion was observed on long term storage at 40^0C and 75% RH. But a similar trait was observed when oleic acid was charged in the stability chamber for the same period and under the same conditions of temperature and humidity.

Hence, we can infer that there is no interaction or incompatibility present in the microemulsion and that the darkening of the microemulsion at higher temperature and humidity can be attributed to oxidation oleic acid as in the case with most other oils. This needs to be further investigated.

The mean droplet size of the microemulsion was 195nm and inferred from this data to be in the sub micron size. Since the polydispersity index was less than 0.4 and a mono distribution was observed, it could be considered that the droplets were in uniform size range. A lower droplet size may lead to facilitation of the penetration of the drug from the microemulsion. Nano sized droplets can move easily into the stratum corneum, provide enormous increment in the interfacial area which in turn influences the transport properties of drug.

The apparent viscosity of the microemulsion was around 80cps which indicates that it is a low viscosity and flowable microemulsion. The viscosity of the microemulsion based gel was around 2400cps which could be considered as optimum for application to the skin as it does not require rubbing which may lead to unnecessary allodynia. The pH of the microemulsion was near neutral and hence it can be considered as safe for application onto the skin as given in Table 2.

The conduction values of microemulsion were higher than those observed with oil alone, but were lower than those obtained with water. This indicated that the microemulsion formed was o/w type. The amount of water incorporated was increased from 10% to 50% which is the concentration in the optimized microemulsion. At 10% water content, the microemulsion did not conduct and hence a negligible reading was obtained. At 50% concentration of water the conduction value of the microemulsion was 148µs/ cm. We can infer from these readings that phase inversion of the microemulsion occurs with an increase in the amount of water incorporation as given in table 2.

TABLE 2: PARAMETERS OF THE OPTIMIZED MICROEMLSION AND MICROEMULSION GEL FORMULATION

Sr. No.	Parameter	Observation
1	pH of microemulsion	6.3
2	pH of Microemulsion gel	6.8
3	Viscosity of Microemulsion	80cps ±5cps
4	Viscosity of Microemulsion based gel	2400cps ±10cps
5	Droplet size of microemulsion	195nm (mean value)
6	Polydispersity index of microemulsion	0.4
7	Electrical conductivity of the microemulsion	148µs/ cm

Carbopol 940 did not produce good transparent gels, Poloxamer based gels were not investigated further for diffusion studies due to the high amount of Poloxamer required for formation of gels hence only gels formulated incorporating Xanthan gum as the gelling agent were evaluated further for diffusion studies. Microemulsions with a higher 1% w/w Xanthan gum percentage did not show good *in-vitro* diffusion profile and less than 40% drug was found to have diffused at the end of 8 hours.

This could be attributed to the high viscosity of the gels. Lower concentrations of the gelling agents (0.5% w/w) in the microemulsion produced a good diffusion profile with a high flux value of 0.103ug/cm/hr. When observed *in-vitro* the standard deviation of % diffusion of the microemulsion gels at different time points was narrower as compared to that of the microemulsions, a factor being the uniformity in the viscosity which can lead to better control over the diffusion pattern.

It was also observed that even though there is a difference in the percentage of diffusion occurring between gels and microemulsions on the dialysis membrane but on porcine ear skin the gels as well as the microemulsions showed almost equal permeation suggesting that the oil, surfactant and co-surfactant along with the permeation enhancer have a major role in enhancing the permeation of the drug through a biological membrane. Presence of surfactant and co-surfactant lead to increased membrane fluidity consequently better permeation of drugs through the skin layers [20].

It is reported that certain fatty acids are effective skin penetration enhancers and are capable, in addition, of creating disorder in the lipid lamellae matrix. Topical application of oleic acid induces human stratum corneum lipid disorder *in vivo.* The intercalation of oleic acid into the lipid lamellae may lead to the reported enhancing effects of oleic acid on the drug permeation through the skin.

This could be the mechanism by which oleic acid enhances percutaneous absorption [21].

Ethanol alone may not lead to stratum Corneum lipid disorder; penetration enhancement by ethanol must occur through a different mechanism. Furthermore, the disorder of SC lipids induced by oleic acid depends upon the concentration in the applied solution and the time of treatment [22].

The optimized microemulsion showed a good sustained release for over 8 hours as is observed in **figure 3**.

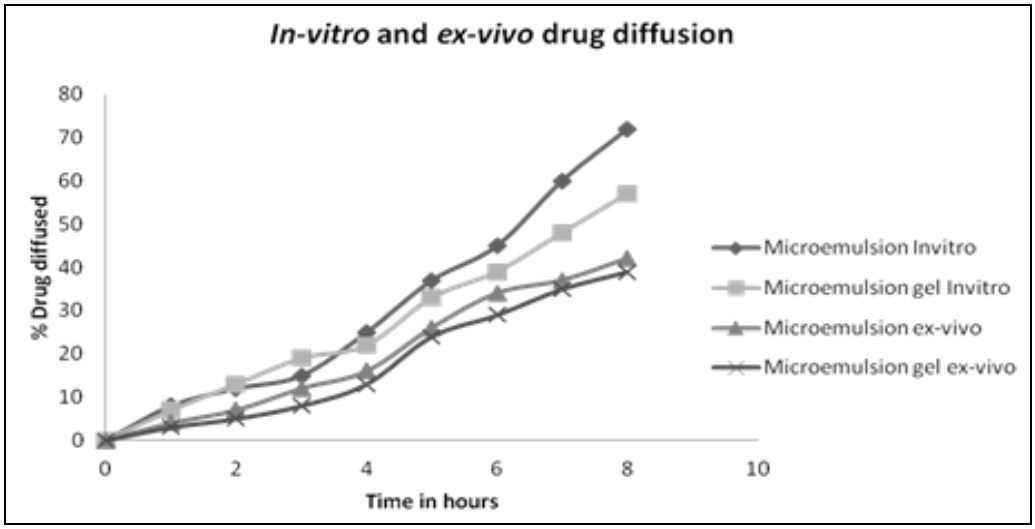

FIGURE 3: *IN-VITRO* AND *EX-VIVO* DRUG DIFFUSION OF MICROEMULSIONS AND MICRO-EMULSION GELS (n=3)

Anti-nociceptive activity: The optimized microemulsion gel was compared both with the control as well as the commercially available Lidocaine gel in order to gain an insight into the capacity of the microemulsion gels to inhibit pain transmission signals as compared to both standard and negative control. Lidocaine was selected as the standard, since its mechanism of action of blocking pain is similar to that of Ropivacaine *i.e.* blocking the nerve conduction by causing depolarisation of the sodium channels.

The anti-nociceptive activity studies, using both hot plate test and tail flick tests indicated that the optimized microemulsion gel showed a better inhibition of the pain perceived by the rat, as the latency time before the response given by the rat in case of both the tests is much higher than the standard Lidocaine gel. The P values of less than 0.05 were considered as statistically significant.

The P values of the control and test when compared were less than 0.05 at all-time points during the experiment and therefore it was statistically significant.

Application of Ttest between the test microemulsion gel and the standard Lidocaine gel yielded a P value higher than 0.05 and thus it was found to be insignificant at all-time points which implies that the capacity of the microemulsion gel to inhibit pain is equipotent or marginally better than the Lidocaine gel.

In addition to this data we also observed that the effect of pain inhibition were sustained over 7 hours, which also corroborates with the results observed in the *ex-vivo* drug diffusion studies wherein most of the drug is diffused over a period of 8 hours (**figure 4 and 5**).

Histopathological studies: The histopathological studies revealed that the microemulsions did not produce any irritation to the skin. There were no liaisons observed neither was there any significant change in the skin or any break in length of epithelium.

No ulceration was seen as observed in **figure 6**. Hence, Ropivacaine microemulsion gels may be considered as a safe option for application onto the skin.

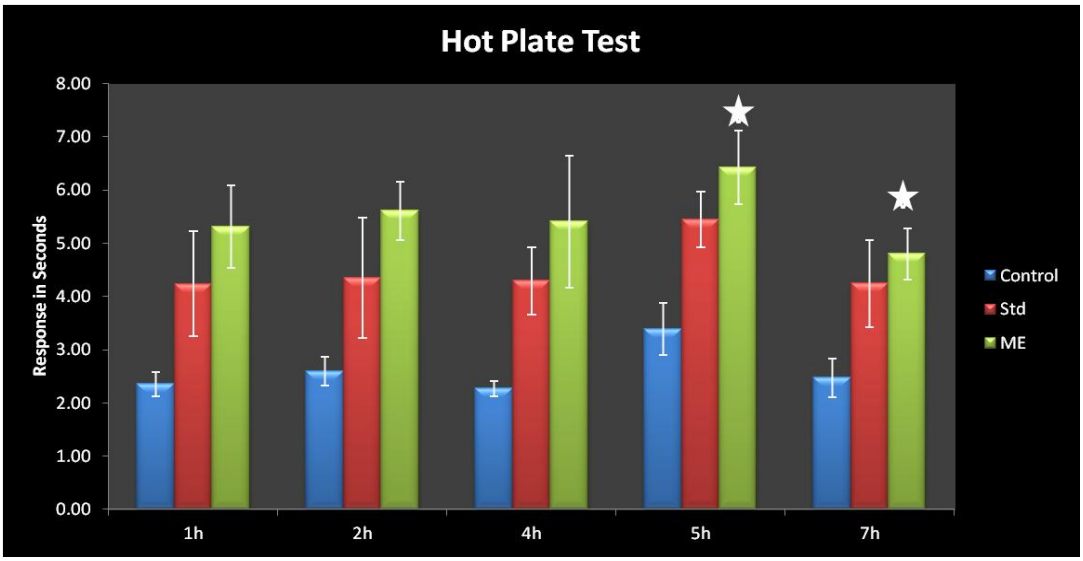

FIGURE 4: ANTI NOCICEPTIVE ACTIVITY TESTED ON RATS USING HOT PLATE TEST. Control, standard (commercially available Lidocaine gel) and the test (microemulsion based gel)

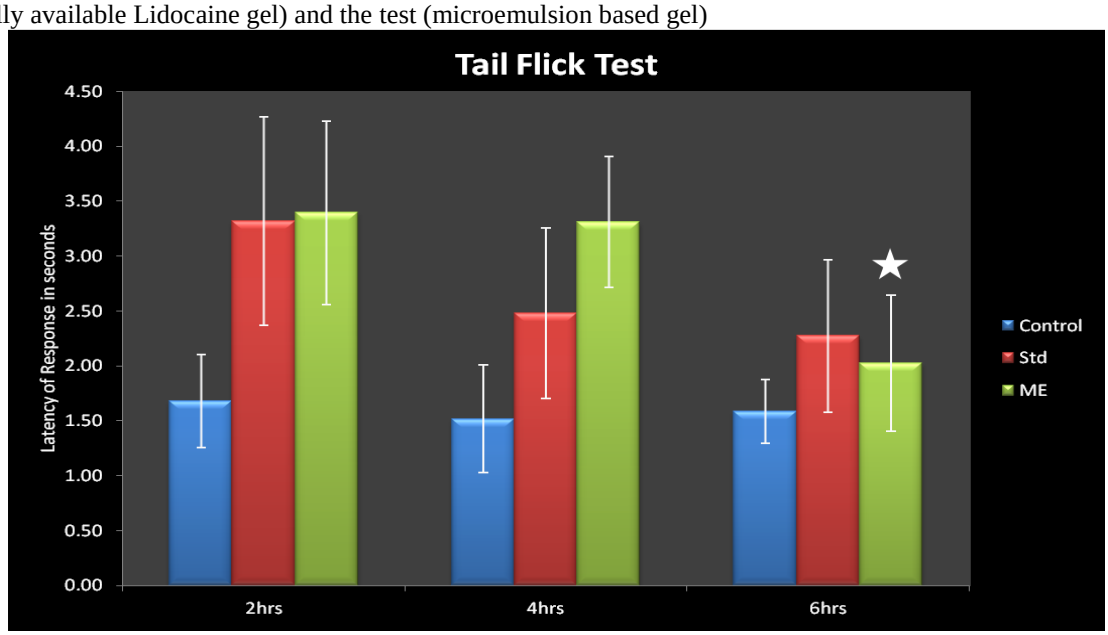

FIGURE 5: ANTI NOCICEPTIVE ACTIVITY TESTED ON RATS USING TAIL FLICK TEST. Control, standard (commercially available Lidocaine gel) and the test (microemulsion based gel)

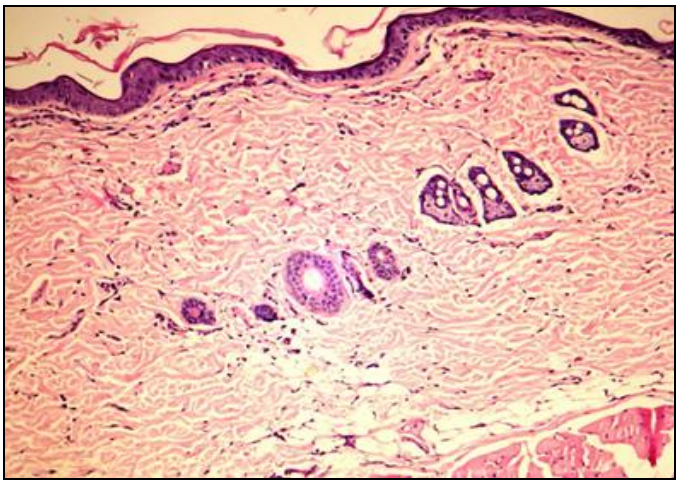

FIGURE 6: HISTOPATHOLOGICAL SECTIONING OF SKIN TO OBSERVE IRRITATION POTENTIAL OF MICROEMULSION BASED GELS

CONCLUSION: Aesthetic, clear and elegant microemulsion based gels were formulated which showed the desired sustained release profile over 7 - 8 hours. The gels were efficacious in alleviating pain for long periods of time as proven by anti-nociceptive activity studied on rats. Hence Ropivacaine microemulsion gels may prove to be a novel approach in management of peripheral neuropathic pain.

Abbreviations: NSAIDS: Non-Steroidal anti-inflammatory drugs, **HIV**: human immuno-deficiency virus **S: CoS**: Surfactant: Cosurfactant, **cps**: centipoise

Competing Interests: The author(s) declare that they have no competing interests

Acknowledgement: The authors thank Dr Danny Kao and Dr Najib Babul of Relmada Therapeutics Inc USA for sponsoring part of the project. Gattefosse, India for providing gift samples of oils, Mr Anup Ramdhave and Mr Mayuresh Garud for helping with the animal studies.

REFERENCES:

1. Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, Wurm EMT, Yoong C, Robertson TA, Soyer HP, Roberts MS: Nanoparticles and microparticles for skin drug delivery. Advanced Drug Delivery Reviews. 2011; 63: 470–491
2. Chauhan L, Muzaffar F, Lohia S: Design, Development and Evaluation of Topical Microemulsion. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(2): 604 -610
3. Kreilgaard M: Influence of microemulsions on cutaneous drug delivery. Advanced Drug Delivery Reviews. 2002, 54 (1): S77–S98
4. Yuan Y, Li SM, Moc FK, Zhong DF: Investigation of microemulsion system for transdermal delivery of meloxicam. International Journal of Pharmaceutics. 2006; 321: 117–123.
5. Chen H, Chang X, Du D, Li J, Xu H, Yang X: Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. International Journal of Pharmaceutics. 2006; 315: 52–58.
6. Modi J, Patel JK: Nanoemulsion-Based Gel Formulation of Aceclofenac for Topical Delivery. International Journal of Pharmacy and Pharmaceutical Science Research. 2011; 1 (1): 6-12
7. Sintov AC, Botner S. Transdermal drug delivery using microemulsion and aqueous systems: Influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems. International Journal of Pharmaceutics 2006; 311: 55–62.
8. Baboota S, Shakeel F, Ahuja A, Javed Ali, Sheikh S: Design, development and evaluation of novel nanoemulsion formulations for transdermal potential of celecoxib. Acta Pharm. 2007; *57*:315–332.
9. Junyapraserta VB, Boonmea P, Songkrob S, Krauelc K, Radesc T: Transdermal delivery of hydrophobic and hydrophilic local anesthetics from o/w and w/o Brij 97-based microemulsions. J Pharm Pharmaceut Sci. 2007; 10(3):288-298.
10. Lee PJ, Ahmad N, Langer R, Mitragotri S, Shastri VP. Evaluation of chemical enhancers in the transdermal delivery of Lidocaine. 2006, 308: 33–39.
11. http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm (last accessed on 15th Dec 2013)
12. Borhade V, Pathak S, Sharma S, Patravale V: Clotrimazole nanoemulsion for malaria chemotherapy. Part I: Preformulation studies, formulation design and physicochemical evaluation. International Journal of Pharmaceutics. 2012; 431: 138– 148.
13. Kanga BK, Lee JS, Chona SK, Jeong SY, Yuk SH, Khanga G, Lee HB, Cho SH: Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. International Journal of Pharmaceutics. 2004; 274: 65–73.
14. Barakat N, Fouad E, Elmedany A: Enhancement of skin permeation and anti-inflammatory effect of indomethacin using microemulsion. Asian J Pharm. 2011; 5:141-9.
15. Acharya DP, Hartley PG: Progress in microemulsion characterization. Current Opinion in Colloid & Interface Science. 2012; 17: 274–280.
16. Ustunda NO, Apaydınb SE, Yavas NU, Yavas A, Karasulua HS: Evaluation of skin permeation and anti-inflammatory and analgesic effects of new naproxen microemulsion formulations. International Journal of Pharmaceutics. 20114; 16: 136– 144.
17. Cui Y, Lingzhi L, Jun G, Zhang T, Zhang: Investigation of microemulsion system for transdermal delivery of ligustrazine phosphate. African Journal of Pharmacy and Pharmacology. 2011; 5(14):1674-1681.
18. Li G, Li Y, Meng Y, Tang H, Wan L, Zhao F. Alcohol Defoaming Agent Used In Method for Recycling Foam For Foam Drilling. WO2012010062. 2012.
19. Sha R, Meng Q, Jiang L. The addition of ethanol as defoamer in fermentation of rhamnolipids. Journal of Chemical Technology and Biotechnology. 2012; 87(3): 368–373.
20. Tiana Q, Renb F, Xua Z, Xiea Y, Zhang S: Preparation of high solubilizable microemulsion of naproxen and its solubilization mechanism. International Journal of Pharmaceutics. 2012; 426: 202– 210.
21. Engelbrecht TN, Schroeter A, Hau T, Neubert R: Lipophilic penetration enhancers and their impact to the bilayer structure of stratum corneum lipid model membranes: Neutron diffraction studies based on the example Oleic Acid. Biochimica et Biophysica Acta. 2011; 1808: 2798–2806.
22. Vivien HW, Potts MR, Guy RH: Oleic Acid Concentration and Effect In Human Stratum Corneum: Non-Invasive Determination by Attenuated Total Reflectance Infrared Spectroscopy *In Vivo.* Journal of Controlled Release. 1990; 12: 67-75.

How to cite this article:
Ranade S, Londhe V and Bajaj A: Microemulsion based gels for targeting Neuropathic pain. Int J Pharm Sci Res 2014; 5(6): 2515-24.doi: 10.13040/IJPSR.0975-8232.5(6).2525-34