SUMMARY & CONCLUSION
5.1. Introduction
In clinical drug therapy, topical application allows localized drug delivery to the site of interest. This enhances the therapeutic effect of the drug while minimizing systemic side effects. Improved efficacy and aesthetic properties are achieved through several approaches in efficient and novel, topical targeted delivery systems. However, stratum corneum (SC) of the skin is the rate controlling membrane for the transport of drugs and other xenobiotics. It is lipophilic in nature. Skin can offer several advantages as a topical route for drug delivery if the drug effectively traverses this lipophilic barrier. Methods for improving cutaneous delivery rely either on various chemical enhancement techniques or the more complex physical enhancement strategies e.g., iontophoresis, sonophoresis and electroporation.

International Association for the Study of Pain (IASP) definition of neuropathic pain is the “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. Neuropathic pain can be unrelenting and is characterized by burning, aching or itching with superimposed lancinating pains. Current treatment for painful peripheral neuropathy includes the use of antiepileptic gabapentinoids (e.g., gabapentin, pregabalin), antidepressants (e.g., amitriptyline, desipramine), topical local anesthetics and opioids. Many patients have suboptimal relief with monotherapy and treatment is frequently multimodal, involving the use of two or more drugs from different pharmacologic classes. Painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia and HIV-neuropathy are among the most widely investigated peripheral neuropathies.

Topically applied local anesthetics hold promise for the treatment of neuropathic pain by virtue of their action as sodium channel blockers at the peripheral sites of nerve dysfunction. Neuropathic pain is related in part to neural signals arising at the level of the skin [Sato; 1991, Campbell; 2006 & 2001]. Thus a clinical and scientific rationale exists for directing therapy directly to the skin. [James N.C; US Patent] Topical lidocaine, in the form of a lidocaine patch (Lidoderm® 5% [USA], Versatis® 5% [EU]) is one of three approved treatments in the United States for management of postherpetic neuralgia (along with gabapentin and pregabalin). Lidoderm patch provides only modest pain relief in patients with postherpetic neuralgia [Javeria AH; 2012].
addition to the various limitations on the use of Lidoderm Patch, the bioavailability of the Lidoderm patch is quite poor; less than 5% of the lidocaine in the patch is absorbed over the dosing interval and has to be considered as “third line” treatment for neuropathic pain.

Mepivacaine has a number of potential pharmacologic advantages over lidocaine, including (i) an intrinsic vasoconstrictor effect which would be expected to reduce the rate at which drug is cleared away from peripheral (skin) sites of pain generation, and (ii) the lowest potential for neurotoxic effect on developing or regenerating primary cultured neurons (among the local anesthetics lidocaine, bupivacaine, mepivacaine, and ropivacaine), with lidocaine having the highest neurotoxic potential. Compared with Lidoderm patch, a mepivacaine gel or cream dosage form may have several advantages, including improved bioavailability and greater suitability for distal neuropathies, such as painful diabetic neuropathy and HIV neuropathy which primarily involve the feet.

In view of the pharmaceutical and efficacy related limitations of Lidoderm patch, there is a need for an alternative, topically applied local anesthetic for the treatment of peripheral neuropathy. Therefore, the aim of the research work was to develop pharmaceutically elegant, non-greasy, hydrogels, nanoemulsion based gels and topical spray formulations of mepivacaine. A number of strategies were planned for formulation development and evaluation of the novel topical delivery systems such that they demonstrate robust stability and in vitro/ex vivo diffusion and permeability. The results are presented and discussed in various chapters in this thesis. The rationale and the plan of the research work are described in Chapter 1.

5.2. Preformulation Studies

5.2.1. Standardization of drugs and excipients: Mepivacaine base and its pharmaceutically acceptable hydrochloride salt were used for the purpose of research work and were standardized as per monographic specifications and Certificate of Analysis. Table 2.1 and 2.2 illustrates various tests and observations and specifications for the both forms of mepivacaine. The drugs passed the tests for identity, purity and the results were found to comply with the pharmacopoeial limits and were used for further incorporation in the formulation of topical drug delivery systems.
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All the excipients such as Carbopol 980NF, HPMC K4M, propylene glycol, oleic acid, Transcutol P, Labrasol, carvone, eugenol, Eudragit RL100, Kollidon K30 and Lutrol F68 were standardized and complied as per the tests given in the respective monographs and Certificate of Analyses provided by the manufacturers and were used in formulation development of topical dosage forms of mepivacaine.

5.2.2. Analytical Method Development and Validation: For estimation of drug in formulations, tape strips, various layers of skin and plasma; simple, accurate, precise and less time consuming assay methods were developed and validated as described in Chapter 2.5.

The UV spectra for both salt and the base form are depicted in Fig 2.14. For HPLC analysis of drug, the mobile phase consisted of phosphate buffer solution pH 6.8: acetonitrile (60: 40 v/v). The retention times for mepivacaine base and mepivacaine HCl were 5.6 and 5.4 mins respectively (Fig 2.19 & Fig 2.20).

For estimation of total drug in different layers of porcine and rat skin used during ex vivo and in vivo dermatopharmacokinetics studies, HPLC methods were developed in presence of skin matrices. An HPLC method was also developed for estimation of drugs in rat plasma. The chromatograms are depicted in Figs 2.23 and 2.31.

All the developed analytical methods were validated for linearity and range, precision, accuracy and percent recovery as per the ICH guidelines. The assay methods developed and validated for mepivacaine were observed to be sensitive, specific, and accurate with high precision and % recovery.

5.3. Formulation Development of Topical Delivery Systems of Mepivacaine salt and base

5.3.1. Novel Topical Mepivacaine hydrogels formulated using permeation enhancers

Topical gels are transparent to opaque semisolids semi-solid formulations containing a high ratio of solvent to gelling agent. Initially, preliminary trials were conducted to select and optimize the concentration of gelling agent, solvent, and penetration enhancer for formulation development of mepivacaine HCl hydrogels. Mepivacaine HCl at two different concentration levels, 5% and 10% w/w was used to investigate the drug release
profiles. Three prototype hydrogel formulations were optimized for mepivacaine HCl 10% strength. Mepivacaine HCl 5% hydrogels were formulated based on the optimized formulae of 10% hydrogel formulation. Once the preliminary studies were completed, further formulation optimization was carried out using statistical Design of Experiments method by considering the concentration of gellant, Carbopol 980 NF, co-solvents propylene glycol and ethanol as independent variables and % drug permeated at the end of 10 hrs, viscosity (Pa.s) and flux (µg/cm²/hr) as the dependent variables. Box Behnken Design of Experiment (using Design Expert® software, version 8.1.) was used. Various batches (17 in number) were formulated using low, medium and high values of the independent variables and their responses obtained on carrying out the in vitro diffusion studies are shown in Table 3.1.6.

The relative impermeability of stratum corneum offers major resistance to percutaneous absorption of most of the drugs. Therefore, attempts were made to reduce this barrier resistance reversibly by using penetration enhancers along with co-solvents like ethanol and propylene glycol. Various penetration enhancers incorporated in the hydrogel formulations included isopropyl myristate, transcutol P, menthol, eugenol, carvone, oleic acid, eucalyptol, geraniol, limonene, labrasol, Brij-35. Amongst these, eugenol and carvone showed maximum enhancement of the rate of drug diffusion across the barrier membrane, thus, it was incorporated in the optimized formulations. The in vitro % drug diffused were 85.85% and 87.56% from eugenol and carvone based hydrogels respectively formulated using HPMC K4M as gallant.

In vitro and ex vivo permeation studies were carried out to select the optimum formulation. Physico-chemical characteristics such as gel viscosity, spreadability, pH and drug content were assessed. The ex vivo permeation profiles of optimized mepivacaine HCl 5% hydrogels were compared with the in house formulated Lidocaine HCl 5% gel and the marketed Lidoderm patch (containing Lidocaine base 5%) and the comparative results of topical flux and permeability co-efficient are in Table 3.1.17 and drug diffusion profiles is seen in Figs 3.1.23 and 3.1.24.

For mepivacaine HCl 10% formulations, MH10-HC, MH10-HE and MH10-CE were considered as the optimized batches with 65.46%, 60.97% and 58.99% drug permeation through porcine skin in 12 hrs respectively, viscosity of 12.63, 13.52 and 32.53 Pa.s
respectively, pH of 6.25, 6.32 and 6.79 respectively and flux of 278.34, 302.54 and 269.10 µg/cm²/hr respectively (Table 3.1.16).

For mepivacaine HCl 5%, optimized formulations MH5-CE, MH5-HE and MH5-HC exhibited 57.25%, 54.29% and 58.56% drug permeated through porcine skin in 12 hrs, viscosity of 30.25, 12.37 and 13.56 Pa.s respectively, pH of 6.59, 6.31 and 6.24 respectively, flux of 260.5, 273.24, and 281.21 µg/cm²/hr respectively.

To ascertain the release kinetics, the *ex vivo* diffusion data for the optimized formulations were applied to zero order, first order, and Higuchi kinetics and Korsmeyer Peppas models. The results of $R^2$ for all the batches are tabulated in Table… and release profiles are shown in Fig 3.1.21. Since the value of release exponent for the proposed model was greater than 1 ($n > 1$) in case of all the formulations, the release mechanism was found to be non-Fickian super case II (typical zero order) release mechanism.

The formulations were subjected to long term and accelerated stability studies as per ICH guidelines. The samples were kept at 8°C ± 2°C, 25°C ± 2°C/60 ± 5% RH, 30°C ± 2°C/65 ± 5% RH and 40°C ± 2°C/75 ± 5% RH as per ICH guidelines. The physicochemical attributes were assessed at various time points to confirm the stability of the formulations. Mepivacaine HCl 10% and 5% w/w hydrogels were found to be stable at refrigeration, room temperature and accelerated temperature and no appreciable changes were observed in the physicochemical parameters such as clarity, viscosity, spreadability, pH and drug content at all the stability storage conditions.

Since formulation MH10-HC exhibited maximum % drug permeated at the end of 12h of 65.46%, and flux of 273.24 µg/cm²/hr amongst the three optimized prototypes of mepivacaine HCl 10% hydrogel formulations, this formulation was taken ahead to further re-confirm the *in vitro-*ex vivo results by investigating dermal penetration and targeting, pharmacokinetic and pharmacodynamic studies in animal models.

5.3.2. **Nanoemulsion based gels of mepivacaine for topical delivery**

Nanoemulsions are optically transparent nanometric sized emulsions with particle sizes between 100 and 500 nm, composed of the oil, surfactant, co-surfactant and water [Gutierrez J.M., 2008; Kong M., 2011]. However, the application of the nanoemulsion to the skin is inconvenient due to low viscosity [Lawrence M., 2000]. To increase their
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viscosity and to make them more suitable for the topical application, gelling agents have been incorporated to form nanoemulsion gels.

Stable nanoemulsion based hydrogel formulations for topical delivery of mepivacaine were formulated as described in Chapter 3.2. Solubility of mepivacaine base was evaluated in various oils, surfactants and co-surfactants to identify the components of the nanoemulsion. Nanoemulsions were formed by spontaneous emulsification technique. The pseudo-ternary phase diagrams for nanoemulsion regions were constructed using oleic acid as oil, a blend of a high HLB surfactant, caprylo caproyl macrogol-8-glyceride (Labrasol) and low HLB cosurfactant, purified diethylene glycol monethyl ether, Transcutol P (1:1 ratio) and water as hydrophilic phase. Phase diagrams were constructed to obtain the optimum concentration ranges of oil, surfactant and co-surfactant as in Fig 3.2.3. Once the preliminary studies were completed, further formulation optimization was carried out considering the concentration of oil, $S_{\text{mix}}$ (surfactant-cosurfactant mix) and water as independent variables and % drug permeated at the end of 12 hrs and flux ($\mu\text{g/cm}^2$/hr) as the dependent variables. Box Behnken Design of Experiment (using Design Expert software, version 8.1.) was used. Responses of the 17 different batches formulated using factorial design are shown in Table 3.2.8. The optimized mepivacaine 5% nanoemulsion formulations were evaluated for globule size, polydispersity index, zeta potential, thermal stability, centrifugation stress, specific gravity, viscosity and drug content. The microstructures of nanoemulsion were investigated by means of conductivity, pulsed-gradient spin-echo NMR spectroscopy (PGSE-NMR), small-angle neutron scattering (SANS), and differential scanning colorimetry (DSC). Conductivity data revealed direct proportionality to the increase in water concentrations as shown in Fig 3.2.18. In PGSE-NMR, the diffusion co-efficients of the internal pseudo phase was determined by the diffusion of the droplet and was slower than that of the pure components. The diffusion of surfactant mixture was also slower because of the formation of monolayer around the droplet. From the values reported in Table 3.2.15, it can be concluded that the nanoemulsion formed was of o/w type of nanoemulsion and not w/o or bicontinuous in structure. From the SANS data (Fig 3.2.32 & 3.3.33), it can be seen that size of the globules in the nanoemulsion samples increased as the concentration of oil was increased confirming o/w type of nanoemulsion.
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DSC studies (Fig 3.2.21-3.2.24) further confirmed that the developed and optimized nanoemulsion had water as an external phase and hence was an o/w type of nanoemulsion system.

The effect of increasing drug concentration on globule size in the nanoemulsion system was also investigated. The optimized mepivacaine 5% HCl and base nanoemulsion consisted of (%, w/w) oleic acid 5%, Labrasol 21%, Transcutol P 21% and distilled water 48%. Carbopol 980 was used as a gel matrix and to formulate nanoemulsion-based hydrogels for improving the viscosity. Mepivacaine HCl 5% nanoemulsion gels were formulated using the optimized mepivacaine base 5% nanoemulsion gel formula and were compared for their physico-chemical characteristics and ex vivo permeation profiles (Fig 3.2.17). The ability to diffuse mepivacaine in vitro via porcine skin from developed and optimized nanoemulsion was assessed by using Franz diffusion cells. The cumulative amount of drug permeated at 12 h (μg/cm²), steady-state flux Jss (μg/cm²/h) and permeability coefficient kp (cm/s) were determined in order to optimize the nanoemulsion based gel formulations.

The nanoemulsions were able to solubilize up to 5% mepivacaine without phase separation. The permeation data showed that nanoemulsion based hydrogel formulations have increased mepivacaine flux to five folds over the control mepivacaine 5%. Significant ex vivo permeation of mepivacaine was attained from the nanoemulsion vehicle. Oleic acid exhibited both excellent solubility of 680±0.6 mg/2ml and hence exhibited significant skin permeation enhancing effect for mepivacaine. This may be due to nano sized droplets, presence of drug in the solubilized form and presence of surfactant and cosurfactant in the form of permeation enhancer. 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. It may be hypothesized that the presence of surfactant and co-surfactant led to increased membrane fluidity consequently better permeation of drugs through the skin.

5.3.3. Metered dose topical spray formulations

Drug was incorporated into metered dose topical spray formulations by using a simple technology. This technology eliminates use of propellants that are difficult to handle as well as their cost is a limiting factor. The objective of the study was to develop non-
occlusive, quick drying metered dose topical spray formulations using different polymers and to evaluate their performance in-vitro and ex-vivo. Polymeric sprays were developed in which the drug was dissolved in a polymeric solvent system containing plasticizers. Metered dose topical spray formulations of mepivacaine base 5% were developed by making use of film forming polymers to prolong the drug diffusion characteristics. Solubility of different polymers in various combinations of ethanol and acetone were assessed. Polymers like Eudragits, Kollidon, Aqualon etc. soluble in ethanol and acetone system were used to investigate film forming characteristics. Ethanol: Acetone combination in the ratio 8:2 was found to deliver non tacky, quick drying films of polymers. Polymers such as Eudragit and PVP showed desirable uniform spray pattern when examined on Whatmann paper and non tacky, quick drying films were obtained. Series of formulations were prepared using permutations of polymers, enhancers and solvent system. The rate of drug diffusion was determined by diffusion studies using Franz-diffusion cells. Ex vivo permeation studies were carried out on full thickness porcine skin using static Franz-diffusion cells. A two-factor, three-level full factorial design was used for formulation optimization by varying the independent variables, concentration of plasticizer (Lutrol F68 and Propylene glycol). Percent cumulative drug permeated, in vitro and flux (µg/cm²/hr) were used as dependent variables. Combination of Eudragit RL100 with Kollidon K-30 as film forming polymers along with novel plasticizers, Lutrol F-68 5% and propylene glycol 1% were used for the preparation of spray formulations. The spray formulations which showed desirable spray films were selected for further characterization. Significant amount of the drug permeated in the receptor medium during both in vitro (89.31%) and ex vivo studies (68.65%) from Formulation S33 indicating efficient topical delivery of the drug through the membrane. Ex vivo diffusion studies showed that the drug followed Higuchi kinetics and diffusion controlled release mechanism with R² value of 0.906 (Table 3.3.12). The developed metered dose topical sprays were evaluated for physicochemical properties. The developed spray formulation exhibited acceptable physicochemical properties in terms of viscosity, volume of solution delivered upon each actuation, spray angle, spray pattern, pH, ex- in vivo film formation time, appearance of the film,
flexibility of the film and water washability. DSC thermograms of the drug and dry polymer mixture showed absence of drug polymer interaction [Fig 3.3.25-3.3.31]. Polymers such as Eudragit RL100 and Kollidon K-30, plasticizers Lutrol F68 and propylene glycol showed desirable spray films which were non-tacky and quick drying. Concentrations of polymers had a great impact on the spray characteristics and the sprays formed were distance specific. Novel optimized metered dose topical sprays were formulated with desired spray angle of 79.8± 0.4°, spherical and uniform spray pattern, short ex- in vivo film formation time of 50 s ±30 s, viscosity of 21.2 ± 2.7cps and uniform appearance of the film, flexibility of the film and water washability and stability. The stability studies revealed that the formulations were stable at both long term and accelerated temperature/humidity conditions as depicted in Table 3.3.14 and Fig 3.3.32 and 3.3.33 and hence were suitable for topical applications.

5.4. Preclinical Studies
In order to expose a large number of patients to topical mepivacaine in clinical trials, it is important to evaluate the dermal and ocular irritancy potential, pharmacokinetics and pharmacodynamics and the toxicity potential of the developed and optimized topical mepivacaine in established animal models. The studies and results are as described in Chapter 4.
All the preclinical studies carried out during the research work were conducted as per the protocols approved by the Institutional Animal Ethical Committee of C.U. Shah College of Pharmacy, SNDT Women’s University, Mumbai (IAEC/CUS/2010-2011/15) and Government Ayurvedic College, Patiala, Punjab. The studies were conducted in accordance with the Standard Operating Procedures requirements of CPCSEA (Committee for the Purpose of Control and Supervision on Experiments on Animals).
The preclinical studies, Chapter 4 were conducted in six parts: In vivo skin penetration and targeting studies, pharmacodynamic studies, pharmacokinetics, toxicity and safety studies, ocular irritation and skin irritation studies.

5.4.1. In vivo skin penetration and targeting Studies
Developed mepivacaine topical formulations were evaluated comparatively for their skin penetration as well as their drug localizing ability in vivo by quantifying the drug levels
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present in three different layers of the skin, the SC, epidermis and dermis. To analyze the drug targeting potential of all the three optimized formulations, Confocal laser scanning microscopy was used to find out the depth of fluorescence observed in different skin strata. For effective treatment of peripheral neuropthic pain, mepivacaine applied topically must penetrate into the deeper layers of skin i.e., dermis where the cutaneous receptors reside. At the end of 8 h post-application, tape stripping method of assessing drug penetration and deposition revealed that the nanoemulsion based gels of mepivacaine promoted the penetration of drug to the deeper skin tissues i.e., dermis which was significantly higher as compared to polymeric mepivacaine HCl 10% gel and comparable to 5% mepivacaine base metered dose topical spray. The nanoemulsion based gel formulation of mepivacaine base 5% appears to have performed best for one of three reasons, or some combination thereof, namely (i) lipophilic nature of the drug, (ii) the nanoemulsion nature of the dosage form; and/or (iii) the fact that it was a 5% dosage form and the absorption is rate limited by the concentration. These results were reconfirmed by confocal laser scanning microscopy depicted in Fig 4.10 and Fig 4.11. The prominently efficient delivery of nile red by mepivacaine nanoemulsion suggests their enhanced penetration and consequent fusion with the membrane lipids in the depths of the skin i.e., to the dermis where the cutaneous receptors reside to provide cutaneous analgesia.

5.4.2. Pharmacodynamic studies

Efficacy studies were carried out to assess the potential of the test articles to provide long lasting cutaneous analgesia by cutaneous truncii muscle reflex studies (CTMR) in rats. The anti nociceptive activity was assessed using two behavioural tests viz, Hot Plate Analgesiometer and Tail Flick Test. Following local anesthetic block in mice, the tail flick test and hot plate test were useful for quantifying the duration of sensory anesthesia, and helped to differentiate between the effects of various formulations of mepivacaine. The results of the Hot plate test are as shown in Table 4.12 whereas those of Tail flick study are summarized in Table 4.13. Cutaneous analgesia was evaluated using the cutaneous trunci muscle reflex (CTMR), which was characterized by the reflex movement of the skin over the back produced by twitches of the lateral thoracospinal muscle in response to local dorsal cutaneous
stimulation. The topical application of the three mepivacaine formulations (polymeric gel, nanoemulsion based gel and metered dose spray) for a period of 3 hrs with occlusion was found to exert a marked cutaneous analgesic effect in rats without producing any acute toxic effects in rats. The duration of activity of the cutaneous analgesic effect of the test articles was found to range between at 5 to 7 hours post treatment (Fig 4.14).

5.4.3. Pharmacokinetic Studies
Pharmacokinetics of the developed topical formulations of mepivacaine was studies in Chinchilla rabbits. Various pharmacokinetic parameters like $C_{\text{max}}$, $T_{\text{max}}$ and $AUC_{0-t}$ were determined and reported in Table 4.17 and Figs 4.15a-c. The low systemic absorption rate indicated that mepivacaine might have accumulated significantly in the layers of the skin which was desired to achieve anti-neuropathic response. Plasma mepivacaine concentrations remained well below systemically toxic concentrations, and no obvious clinical side effects were observed in any rabbits used in the study.

5.4.4. Toxicity Studies
Acute and repeated dose toxicity studies were conducted for 14 and 21 days respectively as per OECD guidelines using Wistar rat as animal model. During the acute toxicity studies, the animals were dosed at higher dose level, 20mg/kg and repeat dose toxicity studies were conducted at three dose levels viz 10, 20 and 30 mg/kg. Animals were observed for presence of tremors, convulsions, salivation, diarrhea, lethargy, body weight and food intake. Various heamatological and biochemical parameters were also assessed and all the parameters were found to be within the normal limits at all the three dose levels during repeat dose toxicity studies. All the rats undergoing high dose treatment in repeat dose toxicity were subjected to full gross necropsy. Histopathology of all major organs such as liver, kidney, heart and lung did not reveal any distinct pathological alterations [Fig 4.16-4.19]. Examination of application site i.e., skin area demonstrated no dermal changes on repeated application of mepivacaine topical formulations.

5.4.5. Irritation Studies
The potential of the developed mepivacaine topical formulations to produce ocular irritation (reversible changes in the eye) or corrosion (irreversible tissue damage) when
applied to the eye of rabbits was assessed (Section 4.5). Also its potential to produce dermal irritation and corrosion when applied to the skin of rabbits/rats was investigated (Section 4.6). Primary Irritation Index (PII) of the formulations was calculated (Tables 4.31-4.33). Ocular application of the mepivacaine topical formulations and their vehicle controls did not produce any significant change in the ocular lesion score in terms of the corneal opacity, iritis, conjunctival hyperemia and chemosis over 72 hours and may be considered "not irritating" to the rabbit eye (Figs 4.20-4.21). Topical application of all the three optimized mepivacaine formulations for 24h did not exert any significant irritant effect on rabbit skin over a 72-hour observation period post-application and did not produce any significant histopathologic changes in rabbit skin (Fig 4.23-4.25). Therefore, the developed and optimized topical formulations of mepivacaine were considered safe for single dose topical administration without producing any acute irritant effect on skin.

5.5. Conclusion
Topical delivery of mepivacaine via various formulation approaches has been investigated in the present research work. Novel clear, stable, hydrogels, nanoemulsion based gels and metered dose film forming sprays of mepivacaine base and its pharmaceutically acceptable HCl salt at 5% and 10% concentrations respectively for topical delivery has been developed and optimized. The formulations were developed to modulate the drug diffusion and accumulation at the intended site to exhibit the desired response.

Topical hydrogels of mepivacaine HCl were developed using co-solvents and penetration enhancers. The optimized hydrogels exhibited desired consistency, homogeneity, spreadability and stability. Since, the polymers were water soluble; consequently, water washable gels were formed and offered benefits like ease of application and ease of removal.

Nanoemulsion system composed of oleic acid as oil, Smix of labrasol: Transcutol P and distilled water have been proposed for topical delivery of mepivacaine. A topically applied nanoemulsion is expected to penetrate the stratum corneum and exist intact in the horny layer. Once it enters into the stratum corneum, nanoemulsions may simultaneously alter both the lipid and the polar pathways. Greater drug penetration
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Enhancing activity of nanoemulsions may be attributed to the combined effects of both the lipophilic and hydrophilic domains of nanoemulsions.

Novel metered dose topical spray formulations of mepivacaine base were developed using different polymers. Solution spray formulations were developed and filled in containers with metered dose spray pumps to provide propellant free delivery. The metered dose topical spray of mepivacaine base will prove as an alternative to conventional topical delivery for relief of neuropathic pain.

The limitations offered by the Lidoderm topical patches were eliminated in our developed mepivacaine topical formulations. The developed formulations showed physico-chemical stability, enhanced permeation, improved cutaneous bioavailability and anti-nociceptive activity. In addition, the developed drug delivery systems were non toxic and non-irritant.

5.6. Future Scope of the Research Work:

Pilot plant scales up studies are proposed. Other novel nanocarriers such as nanoparticles, liposomes, nanostructured lipid carriers could be explored in an attempt to reduce the concentration of mepivacaine that can be incorporated in the nanocarriers to achieve drug targeting to the cutaneous receptors and anti-neuropathic response. Efficacy studies using other established pain models such as Chronic Constriction Injury and Spinal Cord Ligation in animals can be explored. Further Clinical studies are recommended to prove the therapeutic efficacy in humans for translating the research outcome from bench to bed.

Patent Application entitled “Dermal pharmaceutical compositions of 1-methyl-2’,6’-pipecoloxylidide and method of use” has been published in EP, EP 2557924, A1 dated 20-02-2013 and WIPO Application WO/2011/130455 published 20-10-2011. Our research project collaborators hold “Mepivacaine Orphan drug status” for two indications-Treatment of Painful HIV associated neuropathy and post-herpetic neuralgia. To our knowledge, in the prior art, with possible exception of application by skin infiltration, there are no recommendations or approved mepivacaine products for topical application for the management of neuropathic pain. The novelty of the research findings is derived based on the confirmation of topical delivery potential of mepivacaine hydrogels, nanoemulsions and metered dose spray formulations.