CHAPTER 2
LITERATURE REVIEW
DRUG PROFILES
2.1 LITERATURE REVIEW

Literature survey on novel topical delivery systems like film forming delivery, microemulsions, film-forming metered dose sprays and solid lipid nanoparticles was carried out support the research methodologies to be undertaken in this research project.

Baheti described neuropathic pain arising due to injury to central or peripheral nervous system. The author demonstrated that sensory nerves and the motor nerves were affected and the symptoms being spontaneous pain, abnormal evoked pains and at times paroxysmal evoked pain. The author described the types of Neuropathic pain as Diabetic neuropathy, postherpetic neuralgia and painful polyneuropathy. The author detailed the treatment modality into pharmacological pain management and pain management in terms of interventions. Pharmacological treatments included analgesics, anticonvulsants, antidepressents and local anaesthetics (Baheti, 2001).

Baron, et al., defined neuropathic pain and gave examples of neuropathic pain which included painful polyneuropathy, post herpetic neuralgia and trigeminal neuralgia, and post-stroke pain. The authors further explained an interdisciplinary approach, that centred around pharmacological treatment in neuropathic pain management (Baron, et al., 2010).

Stanos & Galluzzi, showcased topical therapies as they offer advantages over medications that are systemically administered, topical delivery advantages include the requirement of a lower total systemic daily dose for patients to achieve pain relief, site-specific drug delivery, and avoidance of first-pass metabolism, major drug interactions, infections, and systemic side effects. The authors discussed about capsaicin and topical Diclofenac and mention the treatment of patients with chronic soft-tissue pain. Further the efficacy of capsaicin and Lidocaine were highlighted in the management of postherpetic neuralgia and diabetic peripheral neuropathic pain. Exhaustive data assessment conclude that topical therapies may be safer, well-tolerated, and very effective alternative to oral analgesics in the management of patients with neuropathic pain (Stanos & Galluzzi, 2010).

Lopes, described microemulsions as fluid and isotropic nanocarriers, offering several advantages as a topical delivery system in comparison to other dermatological formulations, such as ease of preparation, thermodynamic stability and penetration-enhancing properties. The important determinant factors which modulate drug release and cutaneous and transdermal transport are composition, charge and internal structure. They have definitive impact on delivery and go a long way in making microemulsions appealing for topical and
transdermal administration, and by modulating the formulation design, improve the potential and efficacy of the final system (Lopes, 2014).

Zhang et al studied the microemulsion microstructures, key formulation variables, and their relationship to drug transdermal permeation enhancement. Isopropyl myristate, Labrasol, and Cremophor EL as oil, surfactant, and co-surfactant were used to produce a microemulsion system with high water soluble capacity. Electrical conductivity measurement (EC), differential scanning calorimetry (DSC), electro-analytical cyclic voltammetry (CV), dynamic light scattering (DLS) were used to characterise microstructures of the microemulsions. The skin permeation of hydrophobic and hydrophilic model drugs, was studied using Franz-cells and dermatomized porcine skin in the microemulsion formulations. The authors concluded that permeation of all drugs from microemulsions was enhanced significantly compared with the control propylene glycol formulation (Zhang & Michniak-KohnB, 2011).

Yuan et al explored linker-based lecithin microemulsions for transdermal delivery of lidocaine with a permeability enhancement effect, and a greater amount of lidocaine absorbed in the skin. They treated the lidocaine-loaded skin as an in situ patch and studied the release of lidocaine from the skin modelled by using a differential mass balance which yields a first order release profile. The authors evaluated the release profile of lidocaine as a function of the concentration of lidocaine in the microemulsion, the application time, and the microemulsion dosage; and compared the two systems, it was found that the mass transfer coefficient of linker microemulsions systems was larger than that of polymer-based patches thus suggesting that release kinetics are directly related to the morphology of the microemulsion. released 90% of their content over a 24-h period which performed much better compared to other polymer-based patches (Yuan & Acosta, 2009).

Shukla et al have developed stable oil-in-water (o/w) microemulsions used as vehicles for dermal drug delivery using lidocaine (lignocaine) and prilocaine in oil form (eutectic mixture), a blend of a high (Tween 80, hydrophilic-lipophilic balance (HLB) = 15.0) and a low (Poloxamer 331, HLB = 1.0) HLB surfactant and propylene glycol-water as hydrophilic phase. These microemulsions were able to solubilize up to 20% eutectic mixture of lidocaine and prilocaine without phase separation. The dispersity of the oil phase was investigated by dynamic light scattering. Small colloidal droplets for stable microemulsions of 5~10 nm were observed. At constant surfactant and hydrophilic phase concentration, increasing the total drug concentration in the microemulsion resulted in an increase in the droplet size of the
dispersed, colloidal phase. It was observed that a monolayer of surfactant surrounds the oil (eutectic mixture) core. Colloidal droplets of the microemulsion interact via hard sphere with supplementary attractive interaction. This observed interparticle attractive interaction could explain the phase behaviour with respect to change in the basicity of the hydrophilic phase as well as the increase in volume fraction of the dispersed, colloidal phase. It was also observed that the stability and size of this dispersed phase depends on the pH of the composition (Shukla, et al., 2003).

Mostafa et al., formulated low dose biologically active fraction from the oleogum resin of Boswellia carterii in transdermal microemulsions to enhance anti-inflammatory activity of Boswellia species. The authors tested bioactive fraction of the oleogum resin of Boswellia carterii for solubility in different Components and assayed the bioactive fraction by high performance liquid chromatography at 210 nm. They also evaluated ME systems for drug content and tested optimized systems for characterization, permeation, skin irritancy and in vivo evaluation of anti-inflammatory activity. The two systems selected; were composed of Tween 80: PEG 400 at 1:1 and 2:1 ratio, with oil content 7.78 and 17.5%, respectively. These systems showed showed high encapsulation efficiency >83%, small droplet size <100 nm, and suitable pH for topical application. The microemulsions were non-irritant and provided higher and prolonged efficacy and better patient compliance (Mostafa, et al., 2014).

Ustundag et al evaluated an NSAID naproxen in microemulsion as a delivery vehicle. Several formulations were first prepared using isopropyl myristate (IPM) as oil phase, Span 80, Labrafil M, Labrasol, Cremophor EL as surfactants, ethanol as co-surfactant and distilled water or 0.5 N NaOH solution as aqueous phase and they were characterised for the physicochemical properties such as electrical conductivity, droplet size, viscosity, pH and phase inversion temperature. The permeability of Naproxen through the microemulsions evaluated in-vitro using diffusion cells fitted with rat skins showed in vitro, showed an increased permeation rate between 4.335-9.040 times over the control formulation. The study also proved that naproxen from the microemulsion successfully permeated across the skin from the microemulsion with the highest flux rate from a formulation of naproxen, with hardly any skin irritation thus indicating that the microemulsion formulation may be considered an appropriate vehicle for the topical delivery of Naproxen (Ustundag, et al., 2014).
Huang, et al., evaluated Sodium Nonivamide Acetate (SNA) as a microemulsion formulation for topical application. The microemulsions formulated were of a mixed surfactant of Tween 80 and Span 20 as surfactant, ethanol was used as co-surfactant, isopropyl myristate (IPM) was used as an oil phase and water as an external phase. Evaluation parameters of the microemulsion were the ratio of oil phase/surfactant/aqueous phase, various cosurfactant and polymer on the character and permeability of microemulsion. Droplet size of this SNA microemulsion was at a mean of 64 to 208 nm. Moreover SNA microemulsions showed potent enhancement effect for parent drug transdermal delivery by a 3.7-7.1-fold increase, in comparison with the control group. Ethanol as co-surfactant in the microemulsion showed the highest enhancement effect. Viscosity of microemulsion with the incorporated polymer also increased resulting in the decrease in penetration rate of SNA and the permeability of SNA delivered from microemulsion was higher than SNA from volatile vehicles (pH 4.2 buffer containing 25% ethanol) thus suggesting that microemulsions could also be an effective vehicle for topical delivery of SNA (Huang, et al., 2008).

Sabale et al., developed microemulsion-based hydrogel formulations for topical delivery of bifonazole. They studied the relative increase in the solubility and skin permeability of the drug. They used Oleic acid as the oil phase of microemulsions, as it demonstrates a good solubilizing capacity of the microemulsion systems. Further pseudo-ternary phase diagrams for microemulsion regions were constructed by using oleic acid as the oil, surfactant used was Tween 80 and they incorporated isopropyl alcohol (IPA) as the cosurfactant. Skin permeability of various microemulsions of bifonazole using Franz diffusion cells fitted with rat skins was studied. Gel matrix of Hydroxy Propyl Methyl Cellulose K100 M was used to construct the microemulsion-based hydrogel for improving the viscosity of microemulsion for topical administration. The microemulsion-based hydrogel thus optimised was tested for viscosity, spreadability, skin irritancy, skin permeability, stability, and antifungal activity in comparison with a marketed bifonazole cream. This study indicated that the studied microemulsion-based hydrogel had a potential for sustained action of drug release and it may act as promising vehicle for topical delivery (Sabale & Vora, 2012).

Patel et al., evaluated the effect of formulation components on the in vitro skin permeation of microemulsion drug delivery system with Fluconazole. The pseudo-ternary phase diagrams for microemulsion regions were constructed using Lauryl Alcohol as the oil, Labrasol as the surfactant and ethanol was used as cosurfactant. The formulations, highest permeation rate and appropriate physicochemical properties were observed from that containing 2%
Fluconazole, 10% Lauryl Alcohol, 20% Labrasol/EtOH (1:1), and 68% double-distilled water. The efficacy of microemulsion formulation was dependent upon the contents of water and Lauryl Alcohol as well as Lab/EtOH mixing ratio establishing that the percutaneous absorption of Fluconazole from microemulsions enhances with increasing the Lauryl Alcohol and water contents, and with decreasing the Lab/EtOH ratio in the formulation. The widest zone of inhibition of *Candida albicans* (used as a model fungus) was with this formulation as compared to reference formulation, with a good stability at the end of 3 months, thus establishing microemulsion as a topical delivery vehicle for fluconazole (Patel, et al., 2009).

*Kitagawa, et al.*, formulated a microemulsion consisting of isopropyl myristate, 150 mM NaCl solution, Tween 80 and ethanol and examined the skin delivery of quercetin in a microemulsion formulation using excised guinea-pig and Yucatan pig skin in Franz diffusion cells and tested lipid peroxidation in skin by using iron(II) and citrate. Quercetin is poorly soluble in aqueous and organic vehicles and thus requires an improved delivery system of microemulsion. Intradermal delivery of quercetin significantly increased, so also its solubility, using a w/o microemulsion as a vehicle. Quercetin permeability increased into the skin, but no transfer was observed into the receptor compartment thus confirming that quercetin retained in the skin dose-dependently inhibited lipid peroxidation indicating the potential use of microemulsions for the topical delivery of quercetin, where it exerts antioxidative effects (Kitagawa, et al., 2009).

*Shishu et al.*, developed various microemulsions using isopropyl myristate/Captex 355/Labrafac as an oil phase, Tween 20 as surfactant, Span 20 as cosurfactant, and water/dimethylsulfoxide (1:3) as an aqueous phase for the topical delivery of acyclovir. They used transcutol, eucalyptus oil, and peppermint oil as permeation enhancers. *In vitro* permeation studies using Franz diffusion cells through mice skin were performed. The optimum formulation that contained 2.5% Transcutol as the penetration enhancer showed 1.7-fold enhancement in flux and permeation coefficient as compared to control formulation. During in vivo antiviral studies performed in female mice against induced herpes simplex virus I infection, a single application of microemulsion formulation containing 2.5% Transcutol given 24 h post-injection demonstrated complete suppression of development of herpetic skin lesions (Shishu, et al., 2009).

*Paolicelli et al.*, reported a system for topical application based on solid lipid nanoparticles of ketoconazole (SLN) entrapped into polysaccharidic hydrogels. Three different lipid phases
(compritol, precirol and a mixture of precirol/almond oil) were employed to prepare SLN and all the nanoparticles were characterized for their mean particle diameter, poly-dispersion index and zeta potential. The formulations showed high encapsulation efficiency and offered UV protection to the drug. The incorporation of KTZ-loaded SLN into dextran hydrogels produced systems having rheological characteristics suitable for topical application (Paolicelli, 2011).

Kheradmandnia et al, proposed Solid lipid nanoparticles (SLNs) as suitable colloidal carriers for delivery of drugs with limited solubility. Ketoprofen as a model drug was incorporated into SLNs fabricated from beeswax and carnauba wax using Tween 80 and egg lecithin as surfactants. The characterization of SLNs with variable lipid and surfactant composition was performed. The SLN’s showed a high drug entrapment efficiency of 97%, which indicates their ability to incorporate a poorly water-soluble drug such as ketoprofen (Kheradmandnia, et al., 2010).

Li et al, prepared SLNs of Tetrandrine (TET) which is a poorly water-soluble bisbenzylisoquinoline alkaloid. Precirol® ATO 5, glyceryl monostearate, and stearic acid were used as the lipid matrix for the SLNs, while Lipoid E80, Pluronic F68, and sodium deoxycholate were used as emulsifying and stabilizing agents. Tetrandrine SLNs were prepared by a melt–emulsification and ultrasonication technique. The physicochemical characteristics of the TET–SLNs were investigated along with the entrapment efficiency. Small particle size and high entrapment efficiency was observed (Li, et al., 2011).

Bikkad, et al., formulated HP-loaded solid lipid nanoparticles (HP-SLN) with skin targeting to minimizing the adverse side effects and providing a controlled release in order to minimise adverse effects like irritation, pruritus and stinging caused by halobetasol. HP-SLNs were formulated by solvent injection method and formula was further optimized by the application of 3(2) factorial design. The authors further evaluated nanoparticulate gels and compared with the commercial product with respect to ex-vivo skin permeation and deposition study on human cadaver skins and finally skin irritation study. Average size between 200 nm and 84-94% Entrapment Efficiency HP-SLN was seen and DSC studies revealed no drug-excipient incompatibility and amorphous dispersion of HP in SLN. Prolonged drug release up to 12 h was seen in ex vivo study and in vitro drug deposition and skin irritation studies showed that HP-SLN formulation could avoid the systemic uptake, better accumulative uptake of the drug.
was seen and was nonirritant to the skin compared to marketed formulation thus indicating that the studied HP-SLN formulation represents a promising carrier for topical delivery of HP, having controlled drug release, and potential of skin targeting with no skin irritation (Bikkad, et al., 2013).

*Jeon, et al.*, studied surface-modified solid lipid nanoparticles (SLNs) containing retinyl palmitate (Rpal) were prepared by the hot-melt method using Gelucire 50/13(®) and Precirol ATO5(®) with addition of Dicetyl phosphate (DCP) to negatively charge the surfaces of the SLNs and thereby enhance the skin distribution properties of Rpal. A size of 100 nm with an even polydispersity index (PDI), and the high absolute zeta-potential value sufficient to maintain the colloidal stability of the SLNs was observed. It was also observed that DCP-modified negative SLNs enhanced the skin distribution of Rpal 4.8-fold and Rpal reached to a greater depth in comparison to neutral SLNs. Anti-wrinkle effects of the DCPmod-SLN formulations were significantly superior in comparison, concluding that the DCPmod-SLN system presented is a good candidate for topical Rpal delivery (Jeon, et al., 2013).

*Wavikar et al.*, evaluated a topical nanolipidgel of terbinafine hydrochloride (TRB), an antimycotic agent, for enhanced skin deposition and improved antifungal activity. A topical solid lipid nanoparticle loaded with terbinafine was formulated by high-pressure homogenization technique and the stable TRB SLN dispersion was incorporated into a gel using 1% Carbopol 980 NF. Further rheological evaluation and texture analysis of the TRB NLH along with skin permeation, skin deposition, antifungal activity, and occlusivity studies of the nanolipidgel formulation were carried out. The SLN dispersion containing 10% of glyceryl monostearate, 3% of Tween 80, and 1% Plurol Oleique was found to be the most stable and had a particle size and zeta potential value of 148.6±0.305 nm and -20.4±1.2 mV. Rheological and texture properties were excellent with TRB NLH and an increased skin deposition of the drug over plain (3-fold) and marketed TRB formulation (2-fold) was observed with excellent antifungal activity and moreover had significantly enhanced antifungal activity against Candida albicans. TRB NLH demonstrated efficient occlusivity and was non-irritant to the rabbit skin with no signs of erythema or edema. The authors concluded that solid lipid nanoparticles-based topical nanolipidgel of terbinafine can be an efficient, industrially scalable, and cost-effective alternative to the existing conventional formulations (Wavikar & Vavia, 2013).
Dasgupta, et al., evaluated different parameters based on variation of concentration of lipid and co-surfactant by comparing the SLN gel formulation of the same dispersion with the SLN dispersion and with the marketed gel formulation of aceclofenac. Solid lipid nanoparticles were prepared by high speed homogenization and ultra-sonication method with fixed amount of aceclofenac (10%) and pluronic F68 (1.5%) and the particle size, zeta potential and span were found to be in the range of 123 nm to 323 nm, -12.4 to -18.5 and 0.42 to 0.86 respectively with the lipid concentration increasing from 7.5% to 40%. The highest entrapment efficiency was found to be 75% with the formulation that had lipid concentration of 30% and 0.85% of phospholipon 90G (Phospholipid as co-surfactant). Particle surface morphology was measured by scanning electron microscope (SEM). Permeation rate and controlled release property of xanthan gum loaded SLN gel formulations and SLN dispersion was studied through the excised pig skin for 24hr and it was found that release rate of SLN gel formulation was more controlled as compare to SLN dispersions. In vivo pharmacodynamic study was carried out for 24 hr by injecting 0.1ml (w/v) CFA (Complete Fraud's Adjuvant). From the in vitro and in vivo study it was found that action of aceclofenac was enhanced by prepared SLN dispersion and gel formulations. The results indicated the utility of both SLN dispersion and SLN gel system for transdermal delivery of aceclofenac as excellent and logical (Dasgupta, et al., 2012).

Jensen, et al., studied the effect of skin barrier damage on the penetration profile of a corticosteroid applied in solid lipid nanoparticles (SLN) composed of different lipids, varying in polarity as application of a drug to skin with an impaired epidermal barrier, is likely to affect the penetration profile of the drug substance as well as the carrier into the skin. The authors carried out studies in vitro using impaired and intact porcine ear skin, and compared SLN with a conventional ointment. A significantly higher amount of corticosteroid remained in the skin, intact as well as barrier impaired, when SLN was used as a vehicle, the being affected by the type of lipid used in the formulation and related to lipid polarity and drug substance solubility. The permeation of the drug substance across the skin was significantly reduced when formulated in SLN and applied to intact skin, as compared to the ointment. Thus in both barrier-impaired and intact skin, a higher amount of drug substance remained in the skin during application of SLN for 6, 16, and 24h, as compared to the ointment, implying the applicability of SLN to create a drug reservoir in skin, with the drug localized distinctively in the stratum corneum (Jensen, et al., 2011).
Pathak et al., formulated solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for improving the dermal delivery of a local anaesthetic agent lidocaine (LID). They characterised SLN and NLC for particle size distribution, polydispersity index, entrapment efficiency, X-ray powder diffraction pattern (XRD), thermal behaviour by differential scanning colorimeter (DSC) and surface morphology by transmission electron microscopy (TEM) and the LID-loaded SLN and NLC were formulated into hydrogels for topical application. In vitro permeation profiles of LID SLN gel, LID NLC gel, and a marketed LID formulation (Xylocaine gel) were evaluated by using guinea pig skin and in vivo efficacy evaluated on guinea pig using pinprick test. TEM studies showed the LID SLN and NLC formulations almost spherical nature. XRD and DSC studies of LID SLN suggested amorphization of drug in the carrier system and the SLN formulation was stable with respect to particle size, polydispersity, and entrapment efficiency for 6 months at accelerated stability conditions. The in vivo and in vitro permeation studies of LID-SLN gel and LID NLC gel resulted in fivefold and sixfold increase in duration of anesthesia, respectively, as compared to control (Pathak & Nagarsenker, 2009).

Morgan, et al., carried out this study to determine if a novel metered-dose topical aerosol (MDTA) formulation containing the new dermal penetration enhancer, padimate O, can enhance the transdermal delivery of estradiol to an extent that would result in clinically relevant plasma concentrations. In this trial, the estradiol MDTA (with padimate O) was applied once daily to postmenopausal women for 9 days, and plasma estradiol and estrone was measured daily (24 h post-application) by radioimmunoassay. The topical dose administered was as three 1 mg doses of estradiol, each applied as a single spray over 10 cm² which were placed adjacent to each other on the subject's ventral forearm. In the entire study period none of the subjects tested showed any sign of skin irritation at the application site using the Draize irritation score while in four postmenopausal women (age 54-63 years, weight 67-93 kg) the mean estradiol level 24 h post-application over the 9 day study period was 53 pg/mL which was significantly greater (p < 0.001) than the baseline value of 13 pg/mL with the mean estradiol/estrone ratio rising significantly (p < 0.04) from a baseline value of 0.2 up to 0.8. The authors concluded that this novel MDTA formulation significantly enhanced the transdermal delivery of estradiol to allow a clinically relevant dose of estradiol to be delivered in postmenopausal women with once daily dosing (Morgan, et al., 1998).

Wangding, et al., developed a Metered Dose Transdermal Spray (MDTS) formulation for transdermal delivery of testosterone and characterized its efficacy. Testosterone release from
a series of formulations was assessed *in vitro*. Skin from hairless mice was used in permeation experiments with Franz diffusion cells. The spray pattern, pump seal efficiency, average weight per metered dose and dose uniformity were evaluated. An optimized formulation containing 10% (w/v) testosterone, 9% (v/v) azone and 91% (v/v) ethanol was based on good skin permeation and acceptable drug concentration and permeation enhancer (PE) content. A skin irritation study indicated that the formulation was non-irritating in a rat model. An *in vivo* pharmacokinetic study indicated that the optimized formulation showed a different plasma concentration-time profile from that of the commercially available product Testopatch®. The Testopatch® product demonstrated a more sustainable drug release. The evaluation of the testosterone MDTS indicated that it could deliver reproducible amounts of the formulation per actuation. The results obtained showed that the MDTS was a potential alternative therapeutic system for transdermal testosterone delivery (Wangding, et al., 2013).

*Bakshi, et al.*, developed a metered dose spray formulation for transdermal delivery of oxybutynin and carried out the in vitro characterization of the optimized formulation. Oxybutynin release from a series of ethanol/acetone/methanol based formulations was assessed *in vitro* and the developed formulation was used for delivery from a metered dose spray. Various qualitative and quantitative parameters like spray pattern, particle size distribution, pH, evaporation time, pump seal efficiency test, average weight per metered dose, content per spray and content uniformity were evaluated. The different film forming agents were assessed and carbopol (0.5%) and lutrol (0.1%) were found to give good clarity of solution, evaporation rate, spray pattern and tackiness of the film. Diffusion studies of the optimized formulations through the semipermeable membrane showed the release of drug to the extent of almost 50% over a period of 24 h. Stability studies were conducted as per ICH guidelines and indicated that formulations were stable. Skin irritation studies were performed using rabbit as an animal model. The results obtained show that the metered dose transdermal spray formulation can be a promising and innovative therapeutic system for the transdermal administration of oxybutynin (Bakshi, et al., 2008).

*Gohel et al.*, fabricated modified transport fluconazole transdermal sprays using ethyl cellulose and Eudragit RS100 as film-forming polymers. Eudragit RS100 (X(1)) and ethyl cellulose (X(2)) were selected as independent variables in 3(2) full factorial design, whereas drug transport in first hour (Y (1)) and the time required for 50% drug transport (Y(2)) were selected as dependent variables. Eutectic blend of camphor and menthol was used as permeation enhancer cum solvent for film-forming polymers. The pH, viscosity, volume of
solution delivered upon each actuation, spray angle, ex-in vivo physical evaluation and in vitro drug transport of the formulated products were evaluated. The optimized batch B16 containing 5.25% w/w ethyl cellulose and 10.6% w/w Eudragit RS100 was formulated by overlapping the contour plots of Y(1) and Y(2). The pH, viscosity, volume of solution sprayed upon each actuation and spray angle of was 6.3, 52.9 cPs, 0.24 ml and 82.6 degrees respectively. The film of optimized batch was flexible and dermal-adhesive. The kinetics of drug transport was best explained by the Korsmeyer and Peppas model. The eutectic mixture consisting of equal parts of camphor and menthol showed improved drug permeation through shed snake skin. Short-term stability study demonstrated insignificant changes in performance characteristics (Gohel & Nagori, 2009).

Leichtnam, et al. identified a suitable penetration enhancer-containing formulation for the transdermal delivery of testosterone from a spray. The first step involved in vitro measurement of drug flux from a 1:1 ethanol/water saturated solution across hairless rat skin, which had been pre-treated with a series of penetration enhancers. Isopropyl myristate (IPM) was found to be the most efficient excipient, increasing testosterone transport by more than a factor of 5. The enhancing ability of IPM was also apparent when the drug was formulated in 3:1 ethanol/propylene glycol, a more compatible vehicle for use in a spray. IPM was then incorporated into this formulation directly (as opposed to being used to pre-treat the skin) over a range of concentrations from 10-25% v/v, and testosterone transport was evaluated when delivered from either a solution, or from a mechanical spray, or from an aerosol (which also contained 50% v/v propellant). At the highest level of enhancer, the flux was improved 2.5-fold from both the spray and the aerosol, relative to a control. However, these formulations were far from optimally conceived, in that the amount of drug which eventually contacted the skin represented only approximately 10% of the pulverized quantity from the spray, and approximately 40% of that from the aerosol (Leichtnam, et al., 2006).

The literature survey supported the development and execution of the research project.
Pharmacology of Mepivacaine:

Pharmacodynamics:

Mepivacaine, a local anesthetic of the amide type has a reasonably rapid onset and medium duration. Mepivacaine is known by the proprietary names as Carbocaine and Polocaine. Mepivacaine has been used in local infiltration and regional anesthesia. Systemic absorption of local anesthetics act on the cardiovascular and central nervous systems and at serum concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are found to be minimal.

Mechanism of Action:

Local anesthetics like Mepivacaine block the generation and the conduction of nerve impulses, by increasing the threshold for electrical excitation in the nerve, and also slow the propagation of the nerve impulses, and reduce the rate of rise of the action potential. The progression of anesthesia with Mepivacaine is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, after a Mepivacaine infiltration anesthesia, the order of loss of nerve function is as follows: pain, temperature, touch, proprioception, and skeletal muscle tone.

Pharmacokinetics

Absorption: Mepivacaine is absorbed locally. The rate of systemic absorption of local anesthetics depends upon the total dose, concentration of drug being administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution to be infiltrated.

Metabolism and excretion: Mepivacaine is rapidly metabolized, with only a small percentage of the local anesthetic (5 percent to 10 percent) being excreted unchanged in the urine. The principal site of metabolism is in the liver, with over 50% of the administered dose being excreted into the bile as metabolites.

Half Life: The half-life of Mepivacaine in adults is 1.9 to 3.2 hours and in neonates 8.7 to 9 hours.
Adverse effects

Reactions to Ropivacaine may result from hypersensitivity, idiosyncrasy or diminished tolerance to normal dosage on the part of the patient. Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision, or tremors have been observed. Drowsiness, convulsions, unconsciousness, and possible respiratory arrest rarely have been reported.

Pharmacology of Ropivacaine:

Pharmacodynamics: Studies in humans with ropivacaine have demonstrated that, the presence of epinephrine has no major effect on either the time of onset or the duration of action of Ropivacaine, unlike most other local anesthetics.

Mechanism of Action

Ropivacaine is an intermediate acting local anaesthetic of the amino amide class and is available as the pure S-(−)-enantiomer. Ropivacaine is known to cause reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres. This action is potentiated by dose-dependent inhibition of potassium channels. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres; therefore, it has selective action on the pain-transmitting A β and C nerves rather than Aβ fibres, which are involved in motor function

Pharmacokinetics

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy Ropivacaine. After a single IV dose approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy Ropivacaine. Urinary excretion of the 4-hydroxy Ropivacaine, and both the 3-hydroxy N-de-alkylated (3-OH-PPX) and 4-hydroxy N-de-alkylated (4-OH-PPX) metabolites account for less than 3% of the dose. An additional metabolite, 2-hydroxy22 methyl-Ropivacaine, has been identified but not quantified in the urine. The N-de23 alkylated metabolite of Ropivacaine (PPX) and 3-OH-ropivacaine are the metabolites excreted in the urine during epidural infusion. Unbound PPX, 3-hydroxy and 45 hydroxy ropivacaine, have a pharmacological activity in animal models less than that of Ropivacaine. There is no evidence of in vivo racemization in urine of Ropivacaine.
Elimination: The kidney is the main excretory organ for most local anesthetic metabolites. In total, 98.6% of the Ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. After intravenous administration Ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1 h after epidural administration.

Half Life: Approximately 4.2 hours

Adverse effects: Systemic absorption of local anesthetics may affect the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Adverse effect noted are hypotension, nausea, urinary retention, back pain, chest pain, pain, oliguria, insomnia, dizziness, rigors, headache, temperature elevation, paraesthesia, bradycardia, hypertension, tachycardia and vomiting. Other adverse effects that have been noted include anxiety, hypoaesthesia, syncope, dyspnoea, hypothermia.