CHAPTER 1
INTRODUCTION
OBJECTIVES
RATIONALE
PLAN OF WORK
1.1 INTRODUCTION

With increasing understanding of pain pathophysiology and treatment, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical preparations are the result of such exploration. Developments in topical delivery for inhibition of pain is the first choice treatment and is patient compliant.

1.1.1 Pain

The World Health Organisation defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Harold & Nikolai, 1994). Pain represents an emotional construct and is subjective, hence there exists a dilemma in medical healthcare as many patients do complain about a severe persistent pain, there is an absence of any detectable pathology, thus consuming a large proportion of health care resources. This has resulted in finding and improvising new treatment strategies for pain management.

1.1.2 History of pain

Plato and Aristotle, two giants of Ancient Greece, considered pain to be an emotional experience, and not a sensory one. The word pain is derived from Latin word poena, which means ‘penalty’ (Melzack, 1999).

Market research survey indicates that worldwide that neuropathic pain affects approximately 3- 4.5% of the global population (Global Industry Analysts, Inc., 2011). An estimated one in five of the adult population suffers chronic pain (Breivik, et al., 2006), which therefore appears to be more prevalent than asthma (To, et al., 2012), or diabetes (Federation, 2012) (Sheet, 2011), cancer (Howlader, et al., 2013) and cardiac disease. Studies indicate the financial cost to society being over €200 billion per annum in Europe, and $635 billion per annum in the USA in 2008 (Academics, 2011). In India, there is a higher prevalence of diabetes (4.3%) and study from South India reports 19.1% type II diabetic patients suffer from peripheral neuropathy (Sadikot, et al., 2004). According to an estimate, two thirds of diabetic patients have clinical or subclinical neuropathic pain subsequently (Bansal, et al., 2006).
1.1.3 Classification of Pain

The International Association for the Study of Pain drafted the original classification of pain in 1986 (Pain, 2002). Pain is classified according to four systems based on (Thienhaus & Cole, 2002):
1) pathophysiological mechanism of pain (nociceptive or neuropathic pain);
2) duration of pain (chronic or acute, breakthrough pain);
3) etiology (malignant or non-malignant);
4) anatomic location of pain. (Figure 1.1)

![Classification of Pain](www.PainClinic.org, 2013)

The types of pain are categorized by symptoms/sign constellations based on the classifications proposed by Siddall, Taylor, and Cousins for spinal cord injury (Siddall, et al., 1997).

![Excitatory and inhibitory influences on peripheral nerve activity](Sawynok, 2003)

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**Figure 1.1 Classification of pain** (www.PainClinic.org, 2013)

**Figure 1.2 Excitatory and inhibitory influences on peripheral nerve activity by mediators released by tissue injury and inflammation and by a variety of agents acting on neuroreceptors.** (Sawynok, 2003)
Classification of pain based on duration

Acute pain is of a sudden onset, which is perceived immediately following injury, is severe in intensity, but usually lasts for a short time (Thienhaus & Cole, 2002). Acute pain occurs as a result of tissue injury that stimulates nociceptors and generally disappears when the injury heals. Chronic pain is a continuous or recurrent pain that persists much beyond the expected normal time of healing and may recur due to persistence of noxious stimuli or when there is a repeated exacerbation of an injury. Chronic pain may also occur and persist in the absence of identifiable pathophysiology or medical conditions.

Classification of pain based on pathophysiology

Nociceptive and neuropathic pain are the two major types of pain based on pathophysiological classification.

Nociceptive pain arises when there is a tissue injury that activates specific pain receptors which are called nociceptors, these are sensitive to noxious stimuli (Bennett, 1994).

Neuropathic pain is a heterogeneous group of conditions (Woolf & Mannion, 1999). It differs not only in etiology but also in location (Sindrup & Jensen, 1999).

1.1.4 Neuropathic Pain

Neuropathic pain arises due to a lesion or dysfunction of the normal sensory pathways in either the peripheral or central nervous system (Jensen, 2002;6(Suppl,B)) (Merskey & Bogduk, 1994). Negative sensory functions occur as a result of loss of input, and neuronal hyperexcitability leads to the development of pain and this is followed by neuroplastic changes and reorganization in the nervous system (Baron, 2000).

Neuropathic pain has been redefined by Neuropathic Pain Special Interest Group (NeuPSIG) as “pain caused by a lesion or disease of the somatosensory system” by IASP (The International Association for the Study of Pain), replacing the previous definition “pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system” (Jensen, et al., 2011). This comprises a mixed group of debilitating and difficult conditions (Fields, et al., 1998), mostly resistant to simple analgesics, often requiring additional analgesic approaches (Jenson, et al., 2001). Up to 8% of the general population may suffer from pain, when persistent; it affects significantly the physical, psychological and social functioning of patients (Torrance, et al., 2006).
Known causes of neuropathic pain include syndromes associated with diabetes, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain, and immune deficiencies, traumatic lesions, neoplastic disorders, metabolic, degenerative, toxic and vascular insufficiency (Sarah & Michel, 2008). These may all produce pain that can hardly be distinguished by its clinical features (Jensen & Troels, 2002(Suppl B)).

The incidence of peripheral neuropathy rises from 2.4% in the general population to 8% in subjects older than 55 years of age (RA, 2002 ;Feb 23;) . Clinical and experimental studies have proved that neuropathic pain is related to nociceptive pathway damage (Fields, et al., 1998 Oct, ) (Martyn & Hughes, 1997). Therefore nociceptive pathway function can be obtained only from diagnostic tests that use quantitative tools and measure an objective response (Cruccu G, 2004 Mar;11(3)) with laser evoked potentials (LEPs) and skin biopsy (Lauria, et al., 2005).

1.1.5 Classification of neuropathic pain (Troels, et al., 2001)

Table 1.1 presents a common used scheme for classifying neuropathic pains based on aetiology and anatomy.

Table 1.1: Classification of neuropathic pain  (Nicholson, 2006)

<table>
<thead>
<tr>
<th>Classification of neuropathic pain according to disease and anatomical site</th>
<th>Peripheral</th>
<th>Spinal</th>
<th>Brain</th>
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<td>Spinal stroke</td>
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<td>Trigeminal neuralgia</td>
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A] Diabetic Neuropathy, Commonest Type of Peripheral Neuropathy

Diabetic neuropathy, a microvascular complication of diabetes, develops in 28% to 55% of patients with diabetes mellitus. Patients with existing comorbidities such as dyslipidemia, hypertension, and cardiovascular disease have an increased risk of complications (Elizabeth, et al., 2010). An internationally agreed upon and a simple definition of DPN (Diabetic peripheral neuropathy) is “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” (Boulton , et al.,
Clinically when diabetes is uncontrolled, this leads to progressive demyelination, which results in hyperesthesia and allodynia, and burning, stabbing, or shooting pains which are often worse at night and affected sensory function is distal and symmetric (Rutkove, 2009).

**B] Post Herpetic Neuralgia**

The other common peripheral neuropathy is Post Herpetic Neuralgia which is a complication of herpes zoster (shingles), a secondary infection, caused by the varicella/zoster virus, wherein the virus passes from the skin lesions to the sensory ganglion, remains latent, but has the capacity to revert to full infectivity (Stankus, et al., 2000). Postherpetic neuralgia has been defined as pain persisting for more than 30 days from the formation of the vesicles to pain at six weeks, eight weeks, six months and one year after the initial eruption. Postherpetic neuralgia pain is severe enough to interfere with daily routine, causes disturbances in sleep and is not relieved by simple analgesics. According to reports, pain lasting more than one year has been reported in 48 percent of patients 70 years of age (Alastair, et al., 1996).

**1.1.6 Mechanism Of Neuropathic Pain**

The relationship between symptoms and key cellular and molecular mechanisms provides powerful strategies to direct rational drug therapy. The major cellular mechanisms include ectopic or spontaneous nerve activity and peripheral and central hyperexcitability, phenotypic changes in pain conducting pathways, secondary neurodegeneration, and morphological reorganization (Dray, 2008).

Neuropathic pain probably occurs according to the gate theory of pain wherein a neural mechanism in the dorsal horn of the spinal cord acts like a gate which increases or decreases the flow of nerve impulses from the periphery to the central nervous system (Figure 1.3). (Merskey & Bogduk, 1994).

![Figure: 1.3: Gate control Theory of Neuropathic pain Mechanism](image)
Chapter 1.1: Introduction

The distal part of normal sensory endings are specialized for transducing a mechanical, thermal, or chemical stimulus into a change of transmembrane voltage, the generator potential, whereas at the axon end, is a specialized pacemaker zone where the generator potential is encoded into a propagated impulse train. Electrogenesis is largely a function of Na⁺ channels, large transmembrane proteins that have a central channel (pore) sized to pass Na⁺ ions (only), and voltage-sensitive gates that open and close, permitting the flow of Na⁺ ions or blocking their flow.

At rest, the ion-passing pore of most Na⁺ channels is closed. But when a stimulus is applied, the generator depolarization triggers ion gates of a few sensitive Na⁺ channels to open, permitting Na⁺ ions to flow into the neuron, augmenting the generator depolarization and with more sodium channels open, overwhelming the outward K⁺ current resulting in an action potential (nerve impulse) and cross-over point at which the Na⁺ current overwhelms the K⁺ current is the spike threshold. Having opened, Na⁺ channels rapidly close again, and the membrane potential drifts back toward its initial resting level. Recovery from the post-spike hyperpolarization often includes a brief rebound depolarization, the depolarizing after potential (DAP). DAPs, when present, enhance the cell’s tendency to fire bursts of spikes because the DAP brings the cell rapidly toward the threshold for triggering a second and then a third spike (Chen, et al., 2004).

Peripheral sensitization as a result of tissue injury, sensitization of nociceptors, because of alterations in the brain, or the spinal cord and in the peripheral nerves result in spontaneous discharge activity and hyperexcitability and according to the gate theory of pain wherein the exaggeration of dorsal horn neurons response to afferent stimuli acts like a gate which increases or decreases the flow of nerve impulses from the periphery to the central nervous system and the expansion of their receptive fields occurs by prolonged nociceptor discharge (Figure 1.4). This also leads to severe pain without sensory loss, lead to changes which include upregulation or downregulation of neuropeptides and neurotransmitters which result in pain transmission. As a result of damage to the nervous system, transcription and axonal trafficking of sodium channels increase and potassium channels decrease in number at the site of injury (Gilron, et al., 2006). Sudden and spontaneous sensations of pain result because of hyperexcitable neurons and generation of ectopic activity. Voltage-gated calcium channels can also increase in number following damage to the nerves. Following an increase in calcium channels, calcium entry leads to the release of substance P and glutamate from injured peripheral nerves. Increased expression of the alpha-2-delta subunit of voltage-gated calcium channels within the dorsal root ganglion subsequently leads to allodynia (Rowbotham, et al.,
Peripheral nerve injury results in hypertrophy and activation of glial cells and microglia within the gray matter of the spinal cord. Microglia release interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha) and neurotrophins, including brain-derived neurotrophic factor when activated by adenosine triphosphate (ATP), which exacerbates nociceptive transmission and contributes to the maintenance of neuropathic pain. In PHN, reactivation of the varicella zoster virus results in neural damage and inflammation with subsequent edema (Opstelten, et al., 2004). Other mechanisms for postherpetic neuralgia pain also include neuronal sprouting, and local axons reinnervating previously denervated areas (Head & Campbell, 1900). Neurophysiological responses to injury are decreased in the elderly and moreover the proportion of large fibres to small fibres decreases throughout life and hence there is a tendency for an 'open gate' in the aged (Robinson & Fletcher, 1986). Symptoms of neuropathic pain include a delayed onset of pain after nervous system lesion, pain in an area of sensory loss, spontaneous and different evoked types of pains (Jensen, et al., 2001). Understanding the pathophysiology may help in deciding pharmacological treatment modalities.

![Figure 1.4 Membrane Excitability and Impulse Initiation (Electrogenesis) (Eijkelkamp, et al., 2012)](image)

### 1.1.7 Pharmacological Management Of Neuropathic Pain

Pain is one of the top five reasons for consultations in general practice and is best managed with multi-modal pharmacological and supportive treatments, illustrated by the concept of The World Health Organization (WHO) analgesic ladder proposed in 1986 which has been the cornerstone of cancer pain management, further revised in 1997 and because of its step-by-step concept, the ladder approach is extended to management of acute and chronic pain, (Vargas-Schaffer, 2010) and modified in various specialties (Lawrence, 2012) (Figure 1.5). Analgesics need to be given at regular intervals rather than on demand and therapy should be
individualised according to severity of pain as perceived. Thus the main aim is to relieve as much pain as possible and adjuvant treatment should be added where necessary.

![WHO Analgesic Ladder](image)

**Figure 1.5: WHO Organisation Analgesic ladder** (Anaesthesia, 2006)

According to the International Association for the Study of Pain (IASP) neuropathic pain (NP) is a dysfunction in the nervous system, with evidence-based consensus treatment recommendations being available for neuropathic pain, in patients with PHN and painful diabetic peripheral neuropathy (DPN) (Robert, et al., 2007). Neuropathic pain (NeP) syndromes remain one of the most difficult-to-treat medical entity as therapy remains less than optimal because of insufficient analgesic efficacy coupled with occurrence of pronounced side effects (Dworkin, et al., 2003). Guidelines propose the use of multimodal and balanced pharmacological therapies, focused on the underlying pathophysiological mechanisms (Hans, et al., 2010). A peripheral nerve injury induced due to ectopic activity in peripheral neurons may be mediated by the abnormal expression of sodium channels, which may be responsible for the pacemaker-like activity that is one of the sources of neuropathic pain by increasing the sensitivity of nociceptors and result in peripheral sensitization. These sensitised nerves produce a large evoked potential on activation and resultant transmission to the CNS. Targeting these potential peripheral mechanisms for neuropathic pain, has enabled the development of pharmacotherapies that specifically attack these mechanisms (Dworkin, et al., 2007).

Guidelines for evidence-based treatment of neuropathic pain including PHN and diabetic neuropathy recommendation of the first-, second-, and third-line options of pharmacotherapy consider TCAs, antiepileptics, and topical lidocaine or local anesthetics as first-line analgesics.
for PHN, second line being opioids and tramadol that may be considered for first-line under certain select circumstances with topical capsaicin and valproate being recommended as third-line therapies (Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP., et al., 2007). In circumstances where additive or synergistic analgesia may be required, combination therapy of more than one drug class may prove to be the useful option (Gilron, et al., 2003). Combination therapy provides analgesia more rapidly by combining a drug with a rapid onset of action with one that requires several weeks of treatment before maximum benefit is achieved (de Leon-Casasola, 2007) (Table 1.2).

I) First-line Medications for pain management include tricyclic antidepressants (TCAs) with both Norepinephrine and Serotonin Reuptake Inhibition like duloxetine and venlafaxine found to be efficacious for several different types of NP (Neuropathic pain) according to a large number of placebo-controlled trials (Finnerup, et al., 2005). They may exhibit adverse effects that include dry mouth, orthostatic hypotension, constipation, and urinary retention (Dworkin, et al., 2010). Duloxetine has shown efficacy in the treatment of major depression and generalized anxiety disorder, and its dosing is simple, with 60 mg once daily and most common adverse effect being nausea (McIntyre, et al., 2008). Venlafaxine has been shown to have efficacy in painful DPN and painful polyneuropathies of different origins but is not effective in PHN (Post herpetic neuralgia) (Stacey, et al., 2008).

Venlafaxine should be prescribed with caution in patients with cardiac disease. Withdrawal syndrome can occur with venlafaxine and therefore, venlafaxine should be tapered when treatment is being discontinued (Fava, et al., 1997). Calcium Channel α2-δ ligands (Gabapentin and Pregabalin) (Taylor, 2004) share a similar mechanism of action, binding to voltage-gated calcium channels at the α2-δ subunit and inhibit neurotransmitter release decreasing the release of glutamate, norepinephrine, and substance P, inhibiting calcium influx and subsequent release of excitatory neurotransmitters with evidence base supporting their use for chronic neuropathic pain (Gilron, 2007). For neuropathic pain, a pregabalin oral dosage of 450 mg/day appears to reduce pain comparably to the predicted maximum effect of gabapentin starting at 900 mg/day and gradually increasing (Bockbrader, et al., 2010).

II) Second-line medications that can be used for first-line treatment in select clinical circumstances are opioid analgesics and tramadol with demonstrated clinical efficacy in multiple trials in patients with NP, and when patients do not have a satisfactory response to the first line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications according to the NeuPSIG guidelines recommendation. Tramadol is a weak opioid µ-receptor agonist that also inhibits...
reuptake of serotonin and norepinephrine with proven efficacy in neuropathic pain and provides relatively rapid pain relief, with lesser chances of abuse than that with opioid analgesics. Treatment with tramadol starts at 50 mg once or twice daily and then is increased gradually as needed to a maximum of 400 mg/day (Daniell, 2002).

III) Third-line Medications
The NeuPSIG (The Assessment Committee of the Neuropathic Pain Special Interest Group) guidelines recommend that third line medications should generally be reserved for patients who cannot tolerate or who do not respond adequately to first- and second-line medications. These medications include certain antidepressant medications (eg, bupropion, citalopram, and paroxetine), antiepileptic medications (eg, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid), topical low concentration capsaicin, dextromethorphan, memantine, and mexiletine (Robert, et al., 2007).

IV) Topical Agents
Evidence supporting the use of topical analgesics in the therapy of neuropathic pain is very favourable as part of a multimodal therapeutic program, and is preferred in view of the typical low incidence of side effects and attempts to block pain at peripheral sites. Oral therapy in pain management may have drawbacks of limited efficiency of analgesics, systemic effects, and cognitive impairment due to central effects of drugs (Jorge, et al., 2011). From patients’ viewpoint, the rationale is the application of topical analgesics directly on the site of pain, even if the sensation may be a referred pain as perception that oral treatments can potentially lead to more adverse effects as compared to topical treatment (de Leon-Casasola, 2007).

Among local anesthetics, lidocaine has been used frequently to provide neuropathic pain relief; in Europe, tetracaine and ropivacaine have also been used (Jensen, et al., 2009). The two main topical agents used for neuropathy are capsaicin and lidocaine (Dworkin, et al., 2010). Capsaicin is an alkaloid derived from chili pepper which acts mainly on sensory C fibers to deplete substance P leading to desensitization of afferent sensory nerves, ultimately resulting in pain relief. Main adverse effects include burning, stinging, and erythema (Groninger & Schisler, 2012). Capsaicin needs to be applied 3 to 4 times daily for up to 8 weeks for optimal pain relief to occur, resulting in a major disadvantage have had limited success at providing analgesia for patients with neuropathic pain and professional training is required (Neuroges, 2010).
Topical formulations of capsaicin did not have a demonstrated efficacy in controlled trials of patients with HIV-associated neuropathic pain (Paice, et al., 2000) and painful distal polyneuropathy (Low, et al., 1995). However, studies of patients with diabetic peripheral neuropathy (Group, 1992) and PHN who were treated with 0.075% capsaicin cream reported a benefit (Watson, et al., 1993).

Clonidine, a topical alpha2-adrenergic agonist modifies sympathetic afferent activation, hyperpolarizes nicotinic ganglia and relieves pain which was confirmed in a study where transdermal clonidine was investigated for relief of pain due to diabetic neuropathy (Byas-Smith, et al., 1995). Additionally, ketamine inhibits the effects of substance P and acts as a topical analgesic. Also, several trials have examined a topical ketamine/amitriptyline combination. Topical ketamine may target both peripheral opioid receptors and sodium and potassium channels to reduce pain (Gammaitoni, et al., 2000). Topical opioids target the opioid receptors present on nociceptive fibers and mast cells, bind to them, thereby inhibiting the release of the calcitonin gene-related peptide (CGRP) and substance P from nerves, and prevent the feed-forward mechanism of pain that results in sensitization at the site of injury (primary hyperalgesia) (Gerner, et al., 2003).

Doxepin and amitriptyline, topical tricyclic antidepressants, have demonstrated efficacy in a number of neuropathic pain states (McClean, 2000). Amitriptyline provides pain relief via multiple pharmacologic mechanisms, including inhibiting norepinephrine and serotonin reuptake at the presynaptic level, blocking NMDA and alpha2-adrenergic receptors and partially blocking sodium and voltage-gated potassium and calcium channels (Estebe & Myers, 2004). Transdermal delivery of amitriptyline has resulted in a dose-dependent analgesic effect (Haderer, et al., 2003).

Aspirin, indomethacin, diclofenac, and benzydamine, known topical NSAIDs (Hempenstall, et al., 2005), have also been used to treat neuropathic pain, likely with a rubefacient mechanism of action (Galer, 2001).

Evidence supporting the use of topical analgesics in the therapy of neuropathic pain is very favourable as part of a multimodal therapeutic program, and is preferred in view of the typical low incidence of side effects. In view of strong analgesic effects of amitriptyline/ketamine combinations, based on the current literature, combinations of drugs as multimodal therapies target several receptors, often producing additive or even synergistic effects (de Leon-Casasola, 2007).
A high-concentration capsaicin patch is efficacious in reducing pain from the second week after the capsaicin application throughout a subsequent 8-week period; till observed for 12 weeks in secondary analyses (Backonja, et al., 2008;7(12)) . Application of the high-concentration capsaicin patch in patients with PHN or painful HIV neuropathy was safe and well absorbed (Simpson, et al., 2008) .

In contrast, lidocaine works by inhibiting the voltage-gated sodium channels in the damaged nerves, topical lidocaine reduces discharges of small afferent nerve fibres and is available in gel and transdermal patch formulations (Jensen , et al., 2009). The transdermal patch of lidocaine is approved by FDA in the therapy of PHN (Pharmaceuticals, 2010). The most common adverse effect associated with lidocaine use is skin irritation. According to case reports lidocaine patches have a definite role to play in diabetic neuropathy though randomised controlled trials have not been conducted in diabetic neuropathy (Waknine, 2004).

Table 1.2: Pharmacologic Treatment of Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Max. Dose</th>
<th>Cost-day supply</th>
<th>Duration of treatment</th>
<th>Number Needed</th>
<th>Comments</th>
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Use in local neuropathic pain syndromes. 1 box=10 patches.
V) Role of sodium channel blockers in neuropathic pain

A major focus of analgesic research in the pharmaceutical and biotechnology industry are drugs that block voltage-gated sodium channels (Bhattacharya, et al., 2009), in both injured peripheral and demyelinated neurons, also block the overactivity of sodium channels, an abnormality that can lead to prolonged nociceptive depolarization and result in a supralinear increase in neurotransmitter release. Sodium channel blockers preferentially bind overactive sodium channels that tend to remain in a persistently open conformation (Amir, et al., 2006;). Hence, agents that profoundly reduce neurotransmitter release from nociceptors generating ectopic pulses, such as anticonvulsants, tricyclic antidepressants and topical local anesthetics may relieve neuropathic pain (Fields, et al., 1998). In neuropathic pain like diabetic neuropathy and post herpetic neuropathy, wherein an accumulation of neuronal-specific sodium channels may contribute to pain, local anesthetics applied topically definitely have a role to play in providing analgesia.

1.1.8 Local Anesthetics and their use In Neuropathic Pain

Use of local anesthetics which have ‘membrane-stabilizing activity’ as a topical anesthetic have become widespread in clinical practice since Koller, discovered the local anaesthetic properties of cocaine in 1884. Lofgren developed lidocaine, the most widely used cocaine derivative (1957). There have also been improvements in the understanding of dosing, particularly in combination with other analgesics such as opioids and α2-adrenergic agonists (McLeod & Gallagher III, 2013).

1.1.8.1 Chemistry

Local anaesthetics have a common chemical structure, consisting of a lipophilic aromatic ring, a link, and a hydrophilic amine group, of which most are tertiary amines. They are classified into two groups based on the nature of the link: amides [-NH-CO-] and esters [-O-CO-].

The amide group is the most commonly used and includes lidocaine (Lam DS, Nov 19 2011), prilocaine, (levo-) bupivacaine, mepivacaine and ropivacaine (Grider JS, 2011).

The ester group consists of cocaine, procaine, chloroprocaine and amethocaine. Because these groups are weak bases they are solubilized for injection as strong conjugate acidic hydrochloride salts (pH 3–6).

Amino esters and amino amides differ in several respects. Amino esters are metabolized in the plasma via pseudocholinesterases, whereas amino amides are metabolized in the liver. Amino
esters are unstable in solution, whilst amino amides are very stable in solution. Amino esters have more propensity than amino amides to cause allergic hypersensitivity reactions.

1.1.8.2 Mechanisms of Action

Local anesthetics inhibit the initiation and propagation of nerve impulses. This is achieved by the base form of the drug by penetrating through the axolemma, the outer nerve sheet, and blocking the influx of sodium ions into the nerve cell, thereby dampening the generation of action potential (Guo, et al., 1991).

Local anaesthetics directly block transmission of pain from nociceptive afferents, are applied directly, and their efficacy results from action on the nerve where the inward Na+ current is blocked at the sodium ionophore during depolarisation which prevents propagation of the axonal action potential. Moreover local anesthetics not only block Na+ channels but Ca2+ and K+ channels (Xiong & Strichartz, 1998), transient receptor potential vanniloid-1 receptors (Hollmann, et al., 2005), and other ligand-gated receptors as well and also disrupt the coupling between certain G proteins and their associated receptors, therefore exert potent anti-inflammatory effects and therefore response to injury that can sensitise nociceptive receptors and contribute to pain and hyperalgesia. (Hollmann, et al., 2001) (Figure 1.6). Local anaesthetics can alleviate some types of neuropathic pain, and part of this effect may be related to sensitisation of the antinociceptive pain pathways that occur in the neuropathic pain state; spinal glial cells have been shown to play some part in this as well (Power, 2011).

Figure 1.6: Schematic representation of the four states of sodium ionophore with axonal action potentials
Functional characteristics of local anesthetics

The functional characteristics of local anesthetics are determined by the dissociation constant (pKa), lipid solubility, and protein binding. Local anaesthetic block is more readily achieved when the ionophore is in the activated state compared with the inactivated state and least when in the deactivated or resting state (state-dependent block). The speed of onset of block is related to the concentration of molecules of local anaesthetic that are in the free base or nonionized state. This depends on the initial dose and the dissociation constant (pKa) of the local anaesthetic, and the pH of the tissues.

The pKa is the pH at which a solution of local anesthetic is in equilibrium, with half in the neutral base (salt) and half in the ionized state (cation). Most local anesthetics have a pKa greater than 7.4. The neutral base form of the local anesthetic is more lipophilic, and can penetrate nerve membranes faster. As the pKa of a local anesthetic rises, the percentage in the ionized state increases and the onset of the block is slowed. Once the local anesthetic has passed through the cell membrane, it is exposed to the more acidic axioplasmic side of the nerve, favouring the ionized state. The ionized form of the molecule binds the sodium channel and blocks conduction. Potencies of local anaesthetic agents are related to lipid solubility and are quantified as octanol partition coefficients (Table 1.3).

As lipid solubility increases, the ability of the local anesthetic molecule to penetrate connective tissue and cell membranes increases, causing the increase in potency. The duration of action for local anesthetics is determined by protein binding. Local anesthetics with high affinity for protein binding remain bound to nerve membranes longer, resulting in an increased duration of action. Binding to serum α1-acid glycoproteins and other proteins decreases the availability of free drug in the blood, reducing the potential for toxicity in the primary organs. The free fraction of local anesthetic in the blood is increased in conditions of acidosis or decreased serum protein, thus heightening the potential for toxicity (McLeod & Gallagher III, 2013).

Table 1.3: Physicochemical characteristics of local anesthetics

<table>
<thead>
<tr>
<th>Local anaesthetic</th>
<th>pKa</th>
<th>Octanol partition coefficient</th>
<th>Protein binding (%)</th>
<th>Typical maximum dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine-H⁺</td>
<td>7.8</td>
<td>43.0</td>
<td>64.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Prilocaine-H⁺</td>
<td>7.9</td>
<td>25.0</td>
<td>55.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Bupivacaine-H⁺</td>
<td>8.2</td>
<td>340.0</td>
<td>95.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Levobupivacaine-H⁺</td>
<td>8.2</td>
<td>340.0</td>
<td>93.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Ropivacaine-H⁺</td>
<td>8.2</td>
<td>115.0</td>
<td>96.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Procaine-H⁺</td>
<td>8.9</td>
<td>1.7</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Chloroprocaine-H⁺</td>
<td>9.1</td>
<td>9.0</td>
<td>–</td>
<td>10.0</td>
</tr>
<tr>
<td>Cocaine</td>
<td>8.7</td>
<td>–</td>
<td>–</td>
<td>1.5</td>
</tr>
</tbody>
</table>
1.1.8.3 Pharmacokinetics
Local anaesthetic agents are weak bases, and thus become bound in the plasma to $\alpha_1$-acid glycoproteins. Esters undergo rapid ester hydrolysis by plasma pseudocholinesterases (and other esterases) have a higher incidence of allergic reactions than the amides, owing to the formation of para-amino benzoic acid as a metabolite of hydrolysis. Amides undergo phases I and II hepatic cytochrome P450 metabolism (McLeod & Gallagher III, 2013).

1.1.8.4 Ropivacaine
Ropivacaine comes from a family of molecules known as piperolyxylidines which combine the piperidine ring of cocaine with the xylidine ring of lidocaine, but it is unique in being the first local anesthetic marketed as a pure levorotatory stereoisomer rather than a racemic mixture (i.e., a combination of levorotatory and dextrorotatory molecules) with an efficacy broadly similar to that of bupivacaine and Mepivacaine (Golembiewski, 2007). However, it may be a preferred option because of its reduced central nervous system (CNS) and cardiotoxic potential and its lower propensity for motor block. Ropivacaine has greater lipid solubility than lidocaine, allowing a lower milligram dose to achieve a comparable effect (eg, ropivacaine is prepared as a 0.2% or 0.5% solution, whereas lidocaine is prepared as a 1% or 2% solution) (McClellan & Faulds, 2000). Ropivacaine has a high affinity for plasma proteins (94% bound to plasma proteins), prolonging its duration of action when compared with lidocaine (55% bound to plasma proteins) (Wang, et al., 2011). Agents with a lower pKa, such as lidocaine and mepivacaine, have a greater portion of molecules in the uncharged (active) form, resulting in a more rapid onset of action than an agent with a higher pKa (eg, ropivacaine).

Ropivacaine is the preferred long-acting local anesthetic for providing anesthesia. Ropivacaine is considered the safest long-acting local anesthetic currently available, though all standard precautions should be observed with its use.

1.1.8.5 Mepivacaine
Mepivacaine has pharmacological properties similar to lidocaine, has a pKa of 7.6 but it has a mild vasoconstriction effect which reduces its systemic absorption. In terms of function and toxicity, mepivacaine is often compared to lidocaine. Mepivacaine has been shown to be less cardiotoxic and neurotoxic than lidocaine and has a similar onset to lidocaine but a longer duration. A 3% mepivacaine has quick onset, ideal anesthetic effect and little side effect on cardiovascular system (Ding, et al., 2008). Low toxicity, rapid onset, and dense motor block make mepivacaine attractive for local application (Cox, et al., 2003).
1.1.9 Topical Local Anesthetics

NeuPSIG guideline recommends topical lidocaine as a first-line option for the treatment of localized peripheral neuropathic pain, and the EFNS (European Federation of Neurological Societies) recommends lidocaine as first-line treatment of PHN with allodynia. In neuropathic pain like diabetic neuropathy and post herpetic neuropathy, a peripheral nerve injury induced due to ectopic activity in peripheral neurons may be mediated by the abnormal expression i.e. an accumulation of sodium channels, which may produce a large evoked potential on activation and resultant transmission to the CNS. Targeting these potential peripheral mechanisms for neuropathic pain, has enabled the development of pharmacotherapies that specifically target these mechanisms (Cruccu G, 2004 Mar;11(3)).

Sodium channel blockers inhibit the ectopic activity of sodium channels in both injured peripheral and demyelinated neurons, also block the overactivity of sodium channels. Sodium channel blockers preferentially bind overactive sodium channels that tend to remain in a persistently open conformation (Amir, et al., 2006;). Hence, agents that profoundly reduce neurotransmitter release from nociceptors, such as topical local anesthetics, may relieve neuropathic pain (Fields, et al., 1998). When lidocaine patch 5% is applied to painful skin, lidocaine avidly binds to abnormal sodium channels and suppresses abnormal spontaneous and evoked activity that can initiate neuropathic pain (Lai, et al., 2004).

Lidocaine 5% adhesive has been used in the therapy of PHN pain (Comer & Lamb, 2000) .According to authors Galer et al, lidocaine patch was found to be efficacious. (Galer, et al., 1999) Authors Gammaitoni et al (Gammaitoni, et al., 2003) showed that the lidocaine patch 5% when applied over the area of maximal pain reduced the intensity of moderate-to-severe PHN pain, and patients are responsive to topical lidocaine even if the skin is completely deprived of nociceptors (Meier, et al., 2003).

Adverse effects with the lidocaine patch 5% application are mild skin reactions like erythema and localized rash (Wasner, et al., 2005). Blood levels are minimal thereby enhancing safety with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h (Finnerup , et al., 2005), (Gammaitoni & Davis, 2002). Lidocaine patch may not be available or patient may be intolerant to patch, in such a patient, lidocaine gel formulation has been found to be effective in patients with PHN and allodynia, with better tolerability (Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP,, et al., 2007). NeuPSIG guideline recommends topical lidocaine as a first-line option for the treatment of localized peripheral neuropathic pain, and the EFNS recommends it as first-line treatment of
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PHN with allodynia (Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP., et al., 2007). A maximum of three patches can be applied to the painful area once every 24 hours and left in place for 12 hours. Prior to removing the release liner, the patches can be cut to fit the affected area (Jefferies, 2010).

However, use of the lidocaine patch 5% should be avoided in patients who are on oral Class I antiarrhythmic medications e.g., mexiletine and in patients with severe hepatic dysfunction (Dworkin , et al., 2007).

Several controlled clinical trials have demonstrated the efficacy of the lidocaine patch 5% for relief of pain from PHN. In a randomized, controlled trial, following three weeks of daily therapy, there was a statistically significant difference between the Neuropathic Pain Scale (NPS) scores reported by the treatment and placebo groups (NPS-10; P = 0.043 with a documented 25% improvement in the quality of analgesia for the treatment group from baseline (Galer, et al., 2002). The second effectiveness trial in PHN conducted in 2002 demonstrated that 65.8% of patients had improvements in pain intensity within the first week of therapy and 77% of patients reported an improvement in their quality of life (P = 0.0001). At study completion, after 28 days of therapy, 58% of the patients reported moderate to complete pain relief (Katz , et al., 2002).

Sodium channel blockers inhibit the ectopic activity of sodium channels in both injured peripheral and demyelinated neurons, also block the overactivity of sodium channels, an abnormality that can lead to prolonged nociceptive depolarization and result in a supralinear increase in neurotransmitter release. Sodium channel blockers preferentially bind overactive sodium channels that tend to remain in a persistently open conformation (Amir, et al., 2006;). Hence, agents that profoundly reduce neurotransmitter release from nociceptors generating ectopic pulses, such as topical local anesthetics, may relieve neuropathic pain (Fields, et al., 1998). The authors Gilron et al and de Leon-Casasola in their reviews have emphasised that clinicians have accepted use of combination therapy and provided support for use of topical therapy in neuropathic pain (Gilron, et al., 2009). The authors McCleane et al reported more rapid analgesia from the topical application of a combination of 3.3% doxepin and 0.025% capsaicin than either agent alone (McCleane, 2000).

Hence topical delivery of local anesthetics may provide efficient and painless therapy that may overcome drawbacks of oral or injectable therapy in neuropathic pain.
1.1.10 THE SKIN

The anatomy of the skin guides the delivery of a drug through it as the drug traverses the various barriers in skin, the barrier function, a vital role to prevent the ingress or egress of compounds across it (Bucks & Maibach, 2002). The skin is the largest organ of the body, and accounts for about 15% of the total adult body weight. The skin is continuous, with the mucous membranes, lining the body’s surface entirely (Kanitakis, 2002).

1.1.10.1 Principles of Topical Permeation

Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum - the skin major permeation barrier. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway). In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact stratum corneum becomes the primary pathway for topical permeation.

The release of a therapeutic substance from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, (Figure 1.7) which involves

- Dissolution within and release from the transdermal/topical formulation
- Partitioning into the skin’s outermost layer, the stratum corneum (SC)
- Diffusion through the stratum corneum, principally via a lipidic intercellular pathway, (i.e., the rate-limiting step for most compounds)
- Partitioning from the stratum corneum into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake by the papillary dermis and into the systemic circulation via the capillary network.
1.1.10.2 Skin and its’ functions

Protection: Skin acts as an anatomical barrier against trauma, ultraviolet (UV) radiation, temperature extremes, toxins, and bacteria. Langerhans cells in the skin are part of this adaptive immune system (Proksch, et al., 2008).

Sensation: Skin contains an extensive network of nerve cells that can detect and receptors that respond to heat and cold, touch, pressure, vibration, and tissue injury. Damage to these nerve cells can lead to neuropathy, which results in pain and loss of sensation in the affected areas.

Thermoregulation: Eccrine (sweat) glands and dilated blood vessels (increased superficial perfusion) aid heat loss, while constricted vessels greatly reduce cutaneous blood flow and conserve heat.

Control of evaporation: The skin provides a relatively dry and semi-impermeable barrier to reduce fluid loss.

Storage and synthesis: acts as a storage centre for lipids and water and synthesis of vitamin D.

Absorption: oxygen, nitrogen and carbon dioxide can diffuse into the epidermis in small amounts; drugs can be administered through this route, as topical formulations.

Barrier function: Skin primarily acts as a barrier and protects from mechanical impacts and pressure, variations in temperature, micro-organisms, radiation and chemicals.

Water resistance: The skin acts as a water resistant barrier so essential nutrients aren't washed out of the body.

Excretion: Eccrine sweat glands in the skin eliminate excess metabolic wastes like urea and salts through sweat.
1.1.10.3 Skin and Its Layers

Anatomically the skin is continuous, with the mucous membranes, lining the body’s surface entirely (Kanitakis, 2002). The skin comprises of three layers from inwards out: subcutaneous tissue as the lowermost layer, then the dermis, and the epidermis, which is the uppermost layer.

The subcutaneous tissue, or panniculus tissue contains small lobes of fat cells known as lipocytes and connective tissue that houses larger blood vessels and nerves that reach into the dermal layer. This layer is important is the regulation of temperature of the skin itself and the body and serves as a thermoinsulator. The thickness of this layer varies throughout the body and from person to person.

**Dermis**: The middle layer, the dermis, is basically made up of the fibrillar structural protein: collagen, elastic fibers, blood vessels, sensory structures, and fibroblasts.

The primary function of the dermis is to sustain and support the epidermis. The dermis is a more complex structure and is composed of 2 layers, the more superficial papillary dermis and the deeper reticular dermis. Just below the epidermis is the rich capillary bed, the primary site of drug uptake into the systemic circulation (Figure 1.8).

**Epidermal Appendages**

Epidermal appendages are intradermal epithelial structures, lined with epithelial cells, found deep within the dermis with the potential for division and differentiation. Epidermal appendages include the sebaceous glands, sweat glands, apocrine glands, mammary glands and hair follicles.

**Skin Innervation**

Pain is transmitted through naked nerve endings located in the basal layer of the epidermis. Krause bulbs detect cold, whereas Ruffini corpuscles detect heat.

**The Dermal-Epidermal Junction**

The interface between the epidermis and dermis consists of a porous basement membrane zone containing basal keratinocytes which allow the exchange of cells and fluid and holds the two layers together (James, 2006 10th ed). The dermal-epidermal junction acts as support for the epidermis, establishes cell polarity and direction of growth, provides developmental signals, and functions as a semipermeable barrier between layers (Step, et al., 1990).
Epidermis

The epidermis, outermost layer, consists of a specific constellation of cells known as keratinocytes which comprise over 80% of cells, whose main function is to synthesize keratin, a long, threadlike protein with a protective role and within it also contains pigment-containing melanocytes of neural crest origin, antigen-processing Langerhans cells of bone marrow origin, and pressure-sensing Merkel cells of neural crest origin (Burns, et al., 2004). (Figure 1.9)

The thickness of epidermis varies considerably, depending on the area of the body. The feet soles have the thickest epidermal layer, measuring approximately 1.5 mm.

The epidermis is a continually renewing layer that consists of a stratified, squamous epithelium layer which is composed primarily of two types of cells: keratinocytes and dendritic cells and gives rise to derivative structures, such as pilosebaceous apparatus, nails, and sweat glands (Murphy, 1997). The human skin surface is known to contain, on an
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average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area (Torotora, 2003). The epidermis is a dynamic tissue in which cells are constantly in unsynchronized motion, as differing individual cell populations pass not only one another but also melanocytes and Langerhans cells as they move toward the surface of the skin (Chu, 2008).

The epidermis is basically divided into four layers according to keratinocyte morphology and position as they differentiate into horny cells, from below upwards including the basal cell layer (stratum germinativum), a monocellular, nucleated layer where cells adhere to one another as well as to more superficial squamous cells through desmosomal junctions (desmosomes) (Kolarsick, et al., 2011). This layer undergoes proliferation cycles that provide for the renewal of the outer epidermis, giving rise to stratum germinativum which contains a single layer of basal cells while the next layer, the squamous cell layer (stratum spinosum), layer of the epidermis that is 5–10 cells thick, and the granular cell layer (stratum granulosum) above this is composed of flattened cells holding abundant keratohyaline granules in their cytoplasm that synthesise and modify proteins involved in keratinization (Murphy, 1997). The granular layer is 1-3 cell layers deep, in palms and soles of the feet, the granular layer may be 10 times thicker.

The basal three layers constitute the living, nucleated cells of the epidermis and are known as the stratum malpighii and rete malpighii (Murphy, 1997).

The cornified or horny cell layer (stratum corneum) is the outermost layer (James, 2006 10th ed). Migration of a basal cell from the basal layer to the cornified layer in humans takes at least 14 days, and the transit through the cornified layer to the outermost epidermis requires another 14 days. The final process of maturation resulting in cell death is known as terminal differentiation wherein the keratinocytes, now dead cells form the outermost layer the stratum corneum (James, et al., 2006).

**Cornified Layer**

The natural outcome of keratinocyte maturation is found in layers of hexagonal-shaped, non-viable cornified horny cells (corneocytes) of the (stratum corneum) that provide mechanical protection to the underlying epidermis and a barrier to prevent water loss and invasion by foreign substances. The corneocytes, are rich in water retaining protein, low in lipid content, and are surrounded by continuous extracellular stacks of bilayer lipid matrix, organized as “bricks and mortar” (Chu, 2008). Cells in the middle have a much higher capacity for water-binding than the deeper layers because of the high concentration of free amino acids found in

Shobhaben Prataphbhai Patel School of Pharmacy and Technology Management, Mumbai 23
the cytoplasm of middle layer cells (Haake & Hollbrook, 1999). There are 10-30 layers of stacked corneocytes with maximum number in the palms and soles. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum. The resulting structure provides the natural physical and water-retaining barrier of the skin. The corneocyte layer can absorb three times its weight in water (Figure 1.10).

The corneocytes and the intercellular lamellar lipid bilayers within the stratum corneum, are considered the main structures determining the speed of the transcutaneous exchange of substances. Lipids involved in the composition of SC are 50% ceramides, 25% cholesterol and cholesterol esters, 15% free fatty acids and other lipids are present in low concentrations (Darlenski, et al., 2011).

1.1.10.4 Percutaneous absorption

The anatomy of the skin affects the delivery of a drug through the skin as the drugs must traverse the stratum corneum to reach the site of action as the peripheral transducing terminals of cutaneous sensory fibers are located in the epidermis and dermis (Bucks & Maibach, 2002).

Percutaneous absorption of drug molecules is of particular importance in the case of transdermal drug delivery systems because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general, once drug molecules cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily. Percutaneous drug absorption occurs through the stratum corneum, an almost impermeable barrier that plays a vital role in the absorption of drugs and provides the rate-limiting step in the penetration process (Barry, et al., 1987). The stratum corneum has extremely low permeability to water soluble drugs because of lipid enriched extracellular matrix, including its organisation into a highly controlled and tortuous extracellular pathway imposed by geometrically arranged corneocyte “spacers”. Also the paired bilayer arrangement of extracellular lipids, and their extreme hydrophobicity are further characteristics that provide for barrier function (Prausnitz, et al., 2008).

A drug has to partition from the vehicle into the stratum corneum when applied on skin. As stratum corneum is lipophilic, usually a drug in its base form is ideal candidate for penetration. The viable lower part of epidermis, and the dermis are hydrophilic, and the drug has to be in an ionized state for optimal permeation through these layers. While passing through the layers of the skin, the drug undergoes metabolism by enzymes present in the skin.
to more active or inactive compounds and some of the drug may interact with binding sites forming a depot. The drug on further penetration reaches subcutaneous tissue and muscle which may serve as depot leading to sustained release (Bucks & Maibach, 2002).

### 1.1.10.5 Pathway for skin absorption

Drugs can gain entry through three distinct pathways into the skin: (1) transappendageal pathway, which is across pilosebaceous and eccrine glands like hair follicles and sweat glands, (2) the transcellular pathway, which is through the keratinocytes, and (3) Intercellular pathway, which is through the lipid matrix occupying the intercellular spaces of the keratinocytes.

![Figure 1.11: Routes of Transepidermal penetration](image)

**Figure 1.11: Routes of Transepidermal penetration** (A) across the intact horny layer, (B) through the hair follicles with the associated sebaceous glands, or via the sweat glands

**Transappendageal pathway:** Earlier, skin appendages were not thought of as a major penetration pathway (Hadgraft, 2001), however recent investigations have demonstrated that the transappendageal route is indeed an efficient penetration pathway serving as a reservoir for topically applied substances also appears to be one of the definite pathways in skin permeation.

**Transcellular pathway:** In case of transport through trans-epidermal pathway, drugs have to cross the intact stratum corneum layer wherein two potential micro-routes of entry exist, the transcellular (or intracellular) which is movement of the drug across the epithelial cell and the intercellular pathways.

Drugs with low molecular weight and lipophilicity can traverse intracellularly, by passive diffusion across the epithelial cells wherein these lipid-soluble substances move into the lipid membrane according to their lipid/water partition coefficient. The structural features of drugs
that determine permeability are related to hydrophobicity and molecular volume. In intracellular passive diffusion, the epithelium acts as a simple lipophilic barrier through which drugs can diffuse at a rate correlating with the lipid solubility of the drugs.

**Intercellular pathway:** Drugs may move between cells via intercellular channels. Stratum corneum lipids that exist in bilamellar structures in the extracellular space, each layer separated from the other by a thin water sheet associated with the polar head group of the lipids, play an important role in limiting the diffusion of compounds through the stratum corneum. The intercellular lipids run parallel to the skin surface and are organized into lamellae being required for a competent continuous skin barrier. Chemical penetration enhancers generally exert their action through disruption of the extracellular structure (Lademann, et al., 2008)

When a permeating drug leaves the stratum corneum, it enters into the wet cell mass of the epidermis, and, the drug then diffuses across it to reach the vasculature immediately beneath. The viable lower epidermis, basal layer to granular layer, is considered as a single field of diffusion. It is a permeable field that functions as a viscid fluid to most permeants (Flynn, 1985). The epidermal cell membranes are tightly joined and there is minimal intercellular space for ions and polar nonelectrolyte molecules to diffusionally squeeze through. Permeation through the dermis is through the interlocking channels of ground substance formed between fibres and is without molecular selectivity and are generally considered as a single field of diffusion.

The three pathways are not mutually exclusive and permeation may be determined by the area/volume of the pathway, partitioning, and diffusivity of the drugs in each pathway. Though, for most drugs, transport across the barrier involves intercellular lipid, drugs may also penetrate the corneocytes. The molecular basis for the penetration pathway should be taken into consideration in terms of its morphological structure and material properties. Both the composition and structure of the stratum corneum influences its material properties, which in turn determines the pathway for diffusion as well as the solubility and diffusivity of drug within the barrier.

While studying the extent to which penetration of a drug can be enhanced, knowing the inherent ability of drug to penetrate the stratum corneum can help define the relationship between the structure of a drug and its permeability across the skin and may be directly applicable to the prediction of percutaneous absorption (Murdan, 2002).
The principal pathway taken by a drug is determined mainly by the partition coefficient (log $K$). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic drugs (octanol/water log $K > 2$) traverse the stratum corneum via the intercellular route. Most drugs pass the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs (Fartasch, et al., 1993) (Figure 1.12)

![Figure 1.12: Factors affecting percutaneous absorption](image)

Considering that the skin is a heterogeneous membrane consisting of a lipophilic membrane with a hydrophilic portion, diffusion through the *stratum corneum* is a completely passive process, that takes place along a concentration gradient from higher concentration to lower concentration, simple diffusion laws can be used to describe the passive transport through the skin (Darlenksi, et al., 2011).

Thus conventional transdermal drug delivery is a passive process that is governed by Fick’s law that is, the rate of absorption or flux ($J$) of any substance across a barrier is proportional to its concentration difference across that barrier (Prausnitz, et al., 2008). For topically applied drugs, the concentration difference can be simplified as the concentration of drug in the vehicle, $C_v$, and the proportionality constant relating flux to concentration is the permeability coefficient, $K_p$ (equation 1).

$$J = K_p X C_v$$ (1)
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$K_p$ is composed of factors that relate to both drug and barrier, as well as their interaction. These factors are: $K_m$, the partition coefficient; $D$, the diffusion coefficient; and $L$, the length of the diffusion pathway (equation 2).

$$J = (D \times K_m / L) \times C_v$$  \hspace{1cm} (2)

Thus, four factors control the kinetics of percutaneous drug absorption (equation 2); however, it is of great practical importance that two of the four ($C_v$, $K_m$) are highly dependent on one additional factor, the vehicle.

Fick’s Law of Diffusion defines the rate of drug transport across the stratum corneum which depends not only on its aqueous solubility, but is also directly proportional to its oil/water partition coefficient, its concentration in the formulation vehicle, and the surface area of the skin to which it is exposed; and is inversely proportional to the thickness of stratum corneum. Small surface area has limitations to the amount of drug being absorbed. The stratum corneum is thickest in the soles of feet and palms and is thinnest behind the ear, axillary, and scalp.

Drugs with intermediate partition coefficients (log P octane/water of 1-3) have adequate solubility within the lipid domains of the stratum corneum to permit diffusion through this domain whilst retaining sufficient hydrophilic nature to allow partitioning into the viable tissues of the epidermis. Furthermore, optimal permeability of drug across the SC, according to the equation, is influenced by diffusion coefficient which is related to low molecular size and low melting point, hence the solubility.

1.1.11 Factors affecting transdermal permeation

An adult body surface is covered by approximately $2 \text{ m}^2$ of skin and one third of the blood circulates through the skin. For evaluating the suitability of a drug for the transdermal route of administration, the rationality of drug selection may be based on pharmacokinetic parameters and physicochemical properties of the drug (Chandashekhar & Shoha Rani, 2008).
**Effect of drug characteristics**

Good penetration through the stratum corneum as a property of a drug can be deduced from the equation for steady-state flux. When the cumulative mass of a diffusant, \( m \), passing per unit area through a membrane is plotted, after time \( t \), the graph approaches linearity and the slope yields the steady flux

\[
\frac{dm}{dt}, \frac{D C_0 K}{h}
\]

(Equation 3)

where \( D \) is the diffusion coefficient, \( C_0 \) the constant concentration of drug in donor solution, \( K \) the partition coefficient of solute between membrane and bathing solution, and \( h \) the thickness of the membrane.

For the drug therefore to have good penetration, it should have low molecular mass (high \( D \)), adequate solubility in oil (high \( C_0 \)), and a moderately high partition coefficient (Margetts & Sawyer, 2007).

Factors that affect percutaneous absorption of drugs are physiochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between −1.0 to 4. Biological factors to be taken into consideration are skin irritation and site of application of the drug, i.e. Trans nitro patch applied on the chest.

Drugs with daily dose in few milligrams may be appropriate for delivery by transdermal route. Thus pharmacokinetics of the drug forms a critical factor in deciding its suitability for transdermal formulation. The resulting plasma concentration of drug depends on the clearance; however, a small volume of distribution and relatively long half-life, plasma levels in excess of few micrograms per milliliter are very unlikely. Another important factor is the half-life, (e.g., nitroglycerin \( t_{1/2} \) is 3 min) which provides information on the disposition of a drug in the body. An effective plasma level provides insight into the feasibility of formulation development.

**Occlusion** of the skin enhances the permeation of local anesthetic drugs through the skin. It impairs the passive transepidermal loss of water at the site of application, and increases water content of intercellular areas. This is responsible for increase in the hydrophilic character of the stratum corneum, reducing the stratum corneum–viable epidermis partition coefficient of the penetrant and increases skin temperature by resulting in an increased molecular motion.
and skin penetration (Buchs D, 2005). However occlusion leads to an increased tendency for skin irritation at the site of application as accumulation of water or trapped sweat aggravates irritation. Thus patches working on occlusion mechanism may lead to poor acceptance and justify the need for development of newer transdermal drug delivery systems (TDDS) like sprays with better patient compliance and aesthetics (Paudel, et al., 2010).

1.1.12 Transdermal/Topical Drug Delivery Systems

In the recent years, transdermal drug delivery has emerged as an important delivery route over other routes of drug delivery as the merits of non-invasiveness, better patient compliance, especially when long-term treatment is required and pain-free self-administration for patients and potential for continuous delivery offer a convenient route of administration for many clinical indications including chronic pain treatment like neuropathic pain (Uzor, 2011). Other advantages of topical administration include delivery of conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules and reduction in frequency dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration. Moreover avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another potential advantage of transdermal delivery. Transdermal systems are cost effective when compared with other therapies on a monthly cost basis, and multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems (Backonja, et al., 2008;7(12)). In fact, the transdermal drug delivery market, worth $12.7 billion dollars in 2005 in US, is expected to reach $32 billion in 2015 (Paudel, et al., 2010).

However skin toxicity of the drug or drug excipients, the barrier nature of the skin which limits the number of molecules permeating skin , appropriate physicochemical properties render only few drugs to meet challenges in transdermal drug delivery. The biggest challenge in transdermal drug delivery today is to open the skin safely and reversibly to these high molecular weight hydrophilic drugs. Several technological advances have been made in the past couple of decades to overcome this challenge.

1.1.12.1 Factors affecting transdermal permeability

The factors that may influence transdermal permeability of stratum corneum are1) physicochemical factors associated with the vehicle, 2) factors associated with physiological and pathological conditions of the skin and 3) factors associated with the drug delivery systems.
(A) Physicochemical factors associated with the vehicle

1. **Partition coefficient**- Drugs that possess both water and lipid solubility are absorbed through skin faster. Transdermal permeability coefficient demonstrates linear dependency on partition coefficient wherein a lipid/water partition coefficient of 1 or greater may facilitate optimal transdermal permeability.

2. **pH conditions**- pH of skin surface and of drug delivery system affect the extent of dissociation of ionic drug molecules and their transdermal permeability.

3. **Penetrant concentration**- In mammalian skin transdermal permeability is a passive diffusion process which depends on the concentration of drug on the surface layer of the skin.

**Use of penetration enhancers**, include sulphoxides like dimethylsulphoxide, azones like laurocapram, pyrrolidones, alcohols and alkanols like ethanol, propylene glycol, surfactants and terpenes An ideal enhancer has the properties of being pharmacologically inert, non-toxic, non-irritating or non-allergenic, and a suitable solvent for the drug (Woodford & Barry, 1986) when evaluated for penetration enhancing activity (Barry, 1987). Some of the potential sites of action of penetration enhancers are intercellular lipid matrix in which the accelerants may disrupt intracellular keratin domains or may increase drug partitioning into the tissue by acting as a solvent for the drug within the membrane (Williams & Barry, 2004).

B) Factors associated with the physiological and pathological conditions of the skin:

1. Reservoir effect of horny layer- The stratum corneum especially its deeper layer may act as a depot or reservoir and modify transdermal permeation characteristics of the applied drug.

2. Lipid film- Excretion of sebaceous glands and epidermal cell lipid, may form a lipid film on the skin surface and maintain the barrier function of stratum corneum.

3. Skin hydration- Hydration of stratum corneum can enhance the permeability of the skin by as much as eight fold. Occlusion of the skin enhances the permeation of the anesthetic through the skin by impairing the passive transepidermal loss of water at the site of application, and increases water content of intercellular areas. This is responsible for increase in the hydrophilic character of the stratum corneum, reducing the stratum corneum–viable epidermis partition coefficient of the penetrant (Buchs D, 2005).

4. Skin temperature- An increase in the skin permeation (10 fold) of acetyl salicylic acid and glucocorticoids was observed with increase in skin temperature.

(C) Factors associated with drug delivery systems

Release characteristics: Higher rate of transdermal permeation depends on how easily the drug is released from the delivery system. The mechanism of drug release depends on whether
the drug is dissolved or suspended in the delivery system and on interfacial partition coefficient of the drug from delivery system to the skin tissue.

1.1.12.2 Enhancement of transdermal permeation

Use of penetration enhancers

Penetration enhancers include sulphoxides like dimethylsulphoxide, azones like laurocapram, pyrrolidones, alcohols and alkanols like ethanol, propylene glycol, surfactants and terpenes. An ideal enhancer has the properties of being pharmacologically inert, non-toxic, non-irritating or non-allergenic, and a suitable solvent for the drug when evaluated for penetration enhancing activity. Some of the potential sites of action are intercellular lipid matrix in which the accelerants may disrupt intracellular keratin domains or through increasing drug partitioning into the tissue by acting as a solvent for the drug within the membrane (Williams & Barry, 2004).

Terpene derivatives as well as certain phenols seem to improve transdermal absorption. For example, linalool, alphaterpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine (Valenta, et al., 2001).

Drug delivery systems: The composition of drug delivery system affects percutaneous absorption of a drug, the rate of drug release, also the permeability of stratum corneum by means of hydration, solubility in skin lipids or other absorption promoting effects.

Approaches in overcoming the barrier

Physical Approaches: Active Penetration Enhancement Techniques like iontophoresis, sonophoresis and electroporation are potential adjuvants to the existing passive transdermal systems. Physical methods employed for increasing transport of drug molecules across the skin use some form of mechanical, electrical, magnetic or thermal energy source to promote transport of macromolecules by disrupting the skin membrane.

Iontophoresis involves transferring drugs across the skin by applying an electrical potential difference, and promoting the transfer of charged ionic drugs and high molecular weight drugs such as peptides. Currently iontophoresis has been utilised in intradermal administration of lidocaine as a local anesthetic and dexamethasone for local inflammation (Draper & Coglianese, 2011). Sonophoresis is a low frequency ultrasound treatment and
studies have been carried out to enhance absorption of mannitol, and used as a model for highly hydrophilic drugs (Weinmann, 2004).

Electroporation is a technique which by delivering high voltage pulses of micro-to-millisecond duration to the skin, may alter transiently cell membranes or lipid bilayers. Researchers suggest that pretreatment of the skin by electroporation may enhance the passage of large, polar molecules such as heparin and peptides (Scheindlin, 2004). Other examples of physical approaches include the use of microneedle array (Karande & Mitragotri, 2009) and, ballistic liquid jet (Arora, 2007) and, high velocity particles (Kendall, et al., 2004), ultrasound (Tezel & Mitragotri, 2003) and, electric current, radiofrequency thermal ablation (Sintov, 2003), and thermophoresis (Blank, et al., 1967).

Solid microneedles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, proteins and nanoparticles from an extended-release patch. Alternatively, drug formulations have been coated on or encapsulated within microneedles for rapid or controlled release of peptides and vaccines in the skin. Hollow microneedles have been used to deliver insulin and vaccines by infusion (Karande & Mitragotri, 2009).

**Chemical penetration enhancers**

Penetration enhancers may cause disruption of the stratum corneum lipid bilamellar structure, may interact with intercellular protein, may result in improved partition of the drug, act as coenhancer or solvent into the stratum corneum.

The key to altering the polar pathway is to cause conformational change in protein or solvent swelling. The fatty acid enhancers may increase the fluidity of the lipid protein portion of the stratum corneum. Some enhancers may act on both polar and nonpolar pathway by altering the multilaminate pathway for penetration.

Mitragotri and colleagues have suggested guidelines to design chemical enhancers that may increase skin permeability without causing irritation. Using Fourier transform infrared (FTIR) spectroscopy as a screening tool, they proposed that effective and non-irritating enhancers should alter stratum corneum lipid CH2 symmetric stretching (which correlates with increased skin permeability) and avoid changes in stratum corneum protein amide I band absorption (which correlates with skin irritation). These design principles predicted that optimal chemical structures for enhancing drug delivery would be amphiphiles with long, saturated carbon tails.
or compounds with multiple aromatic rings; the authors went on to validate their predictions experimentally (Karande, et al., 2005).

Enhancers can increase the drug diffusivity through skin proteins. Chemical substances temporarily diminishing the barrier of the skin and known as accelerants or sorption promoters can enhance drug flux.

**Drug/vehicle modification for improved transdermal delivery**

**Drug modification approaches**

Various approaches have been investigated for the modification of the drug molecule for improved drug delivery. Some of them are discussed as follows:

**Vehicle modification approaches/formulations**

In addition to the above methods investigated, a variety of encapsulating/carrier systems have been evaluated for possible delivery of drugs transdermally. These include, among others, vesicular systems like liposomes, niosomes, ethosomes, and solid lipid nanoparticles.

**Vesicles**

Vesicles are colloidal particles that are composed of concentric bilayers formed from self-assembly of amphiphilic molecules. Vesicles have gained prominence as skin permeation enhancing agents as well as drug carrier agents in transdermal drug delivery. Depending on group of molecules that constitute the vesicles, they may be classified in several different categories. The composition of the vesicles influences their physico-chemical characteristics such as, size, charge, thermodynamic phase, lamellarity and bilayer elasticity which in turn have a profound effect on the behavior of the vesicles and hence on their effectiveness in enhancing transdermal delivery. Several mechanisms mediating the vesicle–skin synergistic interactions that occur either at the skin surface or in the deeper layers of the stratum corneum depending upon the elasticity or deformability of the vesicles and may be responsible for the superior skin permeation enhancement of vesicular systems. Vesicles described in the literature include liposomes which are colloidal particles that are formed as concentric molecular multilayers, capable of encapsulating drugs. Addition of cholesterol to the composition stabilizes the structure and imparts rigidity, and incorporating lipids similar to skin lipids increases efficacy. Liposomes readily enter SC lipid lamellae and fuse with endogenous lipids. The other form of vesicle -niosomes are vesicles composed of non-ionic surfactants and have been evaluated as carriers for cosmetic applications and for transdermal delivery of a number of drugs like methotrexate with promising results (Benson, 2005).
Ethosomes are liposomes with high alcohol content and are capable of enhancing penetration to deep tissues and the systemic circulation, as alcohol fluidises the ethosomal lipids and SC bilayer lipids and allows the soft, malleable ethosomes to penetrate. Highly lipophilic molecules such as testosterone, and minoxidil, and cationic drugs such as propranolol, and salbutamol may be incorporated in ethosomes for transdermal delivery.

**Microemulsion and nanoemulsion**

Microemulsions and nanoemulsions are thermodynamically stable, transparent (translucent), colloidal dispersions, based on low interfacial tension composed of oil phase and aqueous phase in appropriate ratios, stabilized by an interfacial film of surfactant and cosurfactant molecules with microemulsion having droplet size of sub micron, usually below 200 nm in diameter and nanoemulsion of the droplet size of less than 100 nm that improve drug solubility and bioavailability. Surfactants are necessary to reduce the hydrophobic interaction between the phases and maintain a stable emulsion and co-surfactants (usually short chain alcohols) may maintain a single phase (Chudasma, et al., 2011). Transdermal permeation of drugs depend on the mobility of a drug in the vehicle, release of a drug from the vehicle, and permeation of a drug into the skin and affect the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum. According to authors Kreilgaard et al, they reported that microemulsions may improve the transdermal delivery of several drugs over the conventional topical preparations, such as emulsions and hydrogels and liposomes (Kreilgaard, 2002). The favourable drug delivery properties of microemulsions appear to mainly be attributed to the small droplet size and large amount of inner phase, excellent solubility properties. The vehicle may also act as penetration enhancer depending on the oil/surfactant constituents, and a few studies have indicated that the internal structure of microemulsions should allow free diffusion of the drug to optimise cutaneous delivery from these vehicles. The dispersed phase may act as a reservoir making possible an almost constant concentration gradient over the skin for a longer time.

When the hydrophilic-lipophilic properties of the surfactant monolayer at the water/oil interface are balanced bicontinuous-type microemulsions are formed. Under these balanced conditions, maximum solubilisation of water and oil with the minimum amount of surfactant is achieved. Concerning dermal application the microemulsions can interact with the stratum corneum changing structural rearrangement of its lipid layers and consequently increasing transdermal drug permeation and so act as penetration enhancer. However, many factors also remain unsolved, such as the effect of the microemulsion droplet size.
Local anaesthetics encapsulated in microemulsions result in fast transdermal penetration and effect (He, et al., 2010). Researchers Changez et al evaluated transdermal flux of tetracaine hydrochloride from lecithin:n-propanol:isopropyl myristate:water microemulsions, and observed that microemulsions enhanced mouse skin permeability to tetracaine hydrochloride by 20- to 25-fold depending upon the composition of the microemulsion (Changez, et al., 2006). Authors Zabka et al investigated in vivo local anaesthetic effects and acute toxicity of carbamate local anaesthetics pentacaine (potent local anaesthetic, gastroprotective) applied in w/o microemulsion vehicles and observed that pentacaine permeated from microemulsion gel through excised rat skin faster than from liquid microemulsion, the reason being higher content of surfactant and isopropylmyristate that can enhance permeation. The lowest flux of pentacaine hydrochloride with high lag time was from the 2 % aqueous dispersion of hydroxyethylcellulose (HEC) used as the reference. The amount of permeated pentacaine from microemulsion vehicles is low and can be convenient for local anaesthetic effect of pentacaine without systemic effect (Zabka & Skoviera, 2003).

**Transdermal patches**

The major products currently marketed for transdermal absorption, provide skin occlusion from water-impermeable backing film of TDDS which further improves systemic efficacy by increasing skin hydration and temperature with a corresponding increase in the rate and extent of skin permeation and maintains relatively uniform concentrations of diffusible drug to ensure relatively constant drug release rates. The scopolamine patch is an example of reservoir type of patch, wherein the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane through which the drug releases. (Figure 1.13) Estradiol patch, the matrix type patch, contains the active ingredient dispersed entirely in the adhesive. Transtec ®, a buprenorphine containing slow-release matrix patch for the treatment of intermediate to severe pain is another example containing a slow release matrix that controls the drug delivery rate and produce stable plasma concentration (Likar, 2006).

![Figure 1.13: Transdermal Patch](image)
Limitations include the potential for skin reactions in 20-50% of patients suffering from allergic contact dermatitis to irritant contact dermatitis (Ale, et al., 2009). Delayed onset of action in comparison with oral and parenteral administration; differing rates of drug absorption, potential for the loss of adhesive properties, which may lead to decreased drug delivery may pose a problem (Durand, et al., 2012).

**Films**

Biodegradable films aim to achieve an optimal and desirable controlled and sustained drug release. An ideal film should be flexible, elastic, and soft, with accepted size and thickness, yet adequately strong to withstand breakage due to stress (Abu-Huwaij, et al., 2007). It must also possess good bioadhesive strength so that it can be retained for a desired duration. It should be nonirritant and be capable of releasing a drug at appropriate rate.

**Eutectic systems**

Eutectic system is a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone. Thus melting point of a drug delivery system can be lowered by formation of a eutectic system. The lower is the melting point, the greater the solubility of a material in a given solvent, including skin lipids, and hence skin penetration. This follows from a regular solution theory. A number of eutectic systems containing a penetration enhancer as the second component have been reported, for example: ibuprofen with terpenes, menthol and methyl nicotinate; propranolol with fatty acids (Benson, 2005).

**1.1.13 Delivery systems with novel applications**

**Metered-dose transdermal spray (MDTS)**

Transdermal Spray (MDTS) is an enhanced, passive TDD system that consists of a volatile: nonvolatile vehicle containing the drug dissolved in a single-phase solution (Manabe, et al., 1996). A finite metered-dose application of the MDTS, by a hand-held applicator can be delivered onto the skin, which results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer, from which the drug may be released into the blood stream in a sustained manner. MDTS relies on the combination of a GRAS
(generally recognized as safe) chemical penetration enhancer and the accurate and precise topical dosing of a volatile: nonvolatile vehicle. Following a once-daily application of the MDTS a sustained and enhanced penetration of the drug across the skin can be achieved from the stratum corneum reservoir. Increases in drug diffusivity are related primarily to stratum corneum lipid fluidization or lipid phase separation. Ethanol, azone and other penetration enhancers have been shown to lower the transition temperature of stratum corneum lipids, which may result in insignificant increases in drug diffusivity across the skin. Clinical experience with estradiol-MDTS to post-menopausal women has shown increased plasma levels of estradiol than the baseline value measured by radioimmunoassay and 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).

Film forming Gels
Gels are a dosage form formed by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substance and the liquid in the formulation, the gels range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water.

Gels are semisolid systems in which a liquid phase is constrained within a three dimensional polymeric matrix of natural or synthetic gums in which a high degree of physical or chemical cross linking has been established (Rhodes & Banker, 1990).

The interaction between the colloidal phase, (inorganic or organic) sets up the ‘structural viscosity’. The type of base used in formulating a topical dermatological product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances provide an emollient effect to dry irritated skin whereas bases made up of non-volatile oleaginous substances (e.g. hydrocarbon bases) can form an occlusive barrier on the skin that prevents escape of moisture from the skin into the environment due to which moisture accumulates between the skin and the ointment layer that cause hydration of the stratum corneum. This results in opening up of the intra and inter-cellular channels and pathway resulting in easier
improved penetration and provides a medium for dissolution of the drug and results in enhanced percutaneous drug absorption (Bharadwaj, et al., 2012).

**Solid Lipid Nanoparticles**

SLN are colloidal drug carrier systems like nanoemulsions, differing in lipid nature and are increasing in significance as alternative drug carriers to polymeric nanoparticles. The liquid lipid used in emulsions is replaced by a lipid solid at room temperature in SLN including high-melting point glycerides or waxes. Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modification of dissolution rate and/or improvement of tissue distribution and targeting of drugs by using SLN, have been reported. SLN due to their small size, large surface area, high drug loading and the interaction of phases at the interface and a stable system may improve performance of a topical pharmaceutical formulation and are biocompatible, have low toxicity and better ability to deliver lipophilic drugs.

SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature.

SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes (Ekambaram, et al., 2012).

SLN and NLC are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system and well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids and patient friendly. Researchers have studied SLN and NLC with vitamin E (Dingler, et al., 1999), tocopherol acetate (Wissing & Mülle, 2003), retinol (Jenning, et al., 2000), ascorbyl palmitate (Uner & Yener, 2007), and a nonsteroidal antiandrogen RU 58841 for topical application (Münster, et al., 2005). The results demonstrate that enhanced skin penetration may be due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN which in turn reduces trans-epidermal water loss (TEWL), penetration might also be affected by the SLN and NLC (nanostructured lipid carriers) themselves, the high specific surface area of nanometer sized SLN and NLC facilitating contact of encapsulated drugs with the stratum corneum. Reports on surface modification of SLN by PEG coating have distinctly increased attention of various research groups with the aim of improving drug bioavailability and is further increasing the importance of SLN among traditional colloidal drug carrier systems (Karande & Mitragotri, 2009).
Topical Local Anaesthetics

Topical delivery systems for LA are composed by a diversity of formulations (viscosity inducing agents, preservatives, permeation enhancers, emollients,) and presentations such as semisolid (gel, creams, ointments), liquid (emulsions, dispersions), and solid (patches) pharmaceutical forms. The proposed formulations aim to reduce the LA concentration used, increase its permeability and absorption, keep the LA at the target site for longer and decrease the clearance, and limit local and systemic toxicity.

Controlled-Release Local Anaesthetic Matrix

Absorbable, controlled-release, local anaesthetic delivery system containing 16% (w/w) lignocaine (Xybrex) is capable of providing up to several days of reversible rat sciatic nerve block in a dose- (mass-) dependent fashion (Wang & Djalali, 2009).

Innovations in topical drug delivery systems may offer substantial clinical advantages resulting in reduction in dosage frequency, improved patient compliance and a minimal fluctuation of the concentration and the maintenance of drug levels within desired range at the site of action.

Film forming topical delivery systems

Topical drug delivery poses challenges due to efficient barrier properties of the skin as with patchless topical delivery systems, there may be lack of retention of the drug and enhancer for the desired duration, at the site of application. This may result in an inadequate therapeutic effect and duration of pharmacological activity for the drug is curtailed. Therefore, an appropriate film-forming polymeric delivery system, that may serve as a matrix for the drug and enhancers, may address these issues. The formed film must be bioadherent and possess viscoelastic properties, breathability, and moisture-vapor permeability keeping in mind various functions of the skin.

The viscosity of the film forming solution should be low enough to enable an application of the dosage form as spray, to obtain an accurate and flexible dosing, and is supposed to dry quickly on the skin. The formed film should be non-sticky to avoid adhesion to the clothes of the patient. Transdermal patches have high visibility which is considered cosmetically unattractive the formed film is supposed to be almost invisible. Moreover, the delivery system must have a certain permanence on the skin, to provide a continuous drug supply over a prolonged period of time. Dermal delivery of drugs requiring significantly higher dosages
may be possible as compared to patches, flexibility of dosing, reduction in skin irritation due to lack of occlusion or from patch components such as adhesives and cosmetic elegance are desired properties from the film forming topical delivery system. Dosage forms may be clear solutions, gels, or emulsions. The criteria of spreadability on skin, drying time, cosmetic feel, and acceptability to users may be taken into account. A mixture of water and alcohol may be a good medium for the preparation of a solution or gel.

For the preparation, key ingredients of such emulsions include oils, waxes, emulsifiers, and emollients and the skin-permeation enhancer, which facilitates delivery of a therapeutically required dosage of the drug. Some of the common enhancers include oleic acid, dimethyl isosorbide, lauryl lactate, dimethyl sulfoxide, decyl methyl sulfoxide, ethoxydiglycol, N-methyl 2-pyrrolidone, and isopropyl myristate. While ensuring drug-permeation enhancement, skin safety is to be taken into consideration in optimizing the formulation.

Other critical issues to be development include the hydrolytic and oonsidered are oxidative stability of the drug in aqueous or hydroalcoholic medium, pH effects, and cosmetic acceptability.

For topical therapy, a few liquid film forming products have been approved, mainly for the therapy of warts and calluses for example, Verrumal® (Hermal oHG, Germany) that contains Fluorouracil and salicylic acid and film forming applications for the nail mycoses therapy are Loceryl® amorolfine (Galderma GmbH, Germany) and Penlac® ciclopirox (Dermik Laboratories, USA).

An et al. investigated a film forming semisolid preparation as a transdermal hydrogel on the basis of polyvinyl alcohol and polyisobutylene which solidified into a substantial film in situ on the skin. The formed film was able to provide a sustained release of testosterone over 24 hours and was removable by peeling due to its cohesive structure.
1.2 OBJECTIVES OF THE INVESTIGATION

To formulate and optimize robust and aesthetic topical formulations of intermediate acting, amide type local anaesthetics like Mepivacaine and/or Ropivacaine for alleviation neuropathic pain.

To explore the capability of different polymers and film forming agents used to prepare various topical formulations.

To develop various topical formulations based on nano-carriers, emulsions, hyrdogels and sprays and to increase the contact time of the formulation with the skin using polymeric carrier systems to alleviate pain for prolonged time.
RATIONALE

Pain can arise from a variety of diseases and conditions, and in many instances, pain originates from a localised point in the body especially the limbs and can benefit from treatments which are administered and act locally as opposed to in systemic delivery of drugs.

Chronic Pain

Chronic pain, whether localized or generalized, is a widespread, often debilitating condition affecting > 25% of adults (Johannes, et al., 2010). Chronic pain continues to be significantly undertreated in many patients, resulting in increased health care utilization costs and poor quality of life outcomes. Increasingly, patients, groups, pain societies, the Joint Commission on Accreditation of Health Care Organizations are highlighting the limitations of pain management and are looking for better options in pain management and therapeutics.

Neuropathic Pain

Neuropathic pain is defined as pain due to a lesion or dysfunction of the normal sensory pathways in either the peripheral or central nervous system (Merskey & Bogduk, 1994) which become extremely sensitive to stimulation and can generate impulses in the absence of stimulation (herpes zoster pain after the rash has healed). Neuropathic pain may be caused by drugs, radiation therapy, surgery, infection, tumor infiltration of peripheral nerve, and diseases. Neuropathic pain can be unrelenting and is characterized by burning, aching or itching with superimposed lancinating pains. Postherpetic neuralgia, painful diabetic neuropathy and painful HIV-neuropathy are examples of neuropathic pain syndromes.

Diabetes affects approximately several million people and about 20% of them suffer from painful diabetic neuropathy, which is a distal, symmetrical neuropathy that usually involves peripheral limbs. Treatment options available for painful diabetic neuropathy are Lyrica® (Pregabalin) and Cymbalta® (Duloxetine) approved by the USFDA of the treatment for this condition.

Postherpetic neuralgia (PHN) is a chronic, debilitating neuropathic pain syndrome that occurs as a complication of herpes zoster infection. In some patients, the pain persists even after healing of the acute lesions and a chronic pain state develops. In PHN, the patient experiences burning, stabbing or aching pains. In US, drugs which are approved to treat PHN
Neuropathic Pain management

While several million people are afflicted with neuropathy, treatment options are limited, thus establishing the need for suitable and effective therapy. Oral therapeutic agents are the cornerstone of chronic pain treatment, but their use may be limited in certain patients, particularly the elderly. With oral therapy, the limitations posed are in the delivery of drugs that are sensitive to degradation due to the pH conditions or enzymatic activity in the gastrointestinal tract and the reliability of the formulation absorption in the gastrointestinal activity such as gastric emptying or disorders such as vomiting and diarrhoea. Furthermore, the hepatic first-pass effect has to be taken into consideration. In consequence with topical delivery systems, the administered drug dose may be reduced and minimal metabolic degradation occurs in the systemic circulation thereby reducing the risk of adverse effects. The plasma levels obtained by the controlled delivery of the transdermal systems are fairly steady. Plasma level peaks or troughs, that are often observed after oral application, are minimized with topical delivery, and assistance of the patient in case of consciousness issues and ability to swallow may be overcome with topical application. Contrary to oral therapy, topical formulations can be instantly removed in case of an emergency. Current treatment of peripheral neuropathic pain involves several drug classes, including gabapentinoids, antidepressants, antiepileptic drugs, local anesthetics, capsaicin and opioids.

With few available treatment options, neuropathic pain represents an area of significant unmet medical need. Many patients have suboptimal relief with monotherapy and treatment is frequently multimodal, involving use of two or more drugs from different pharmacologic classes.

Topical therapies offer advantages over systemically administered medications, including 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. Several types of topical agents have been shown to be useful in the treatment of patients with chronic pain. (Stanos & Galluzzi, 2013)

As an alternative to oral preparations, pain can be treated by topically applying a local anesthetic directly to the painful area to block the nociceptive mechanistic pathway. Local
anesthetics prevent the generation and conduction of nociceptive nerve impulses by decreasing or preventing the large transient increase in permeability of excitable membranes to sodium ions. (Ghosh, et al., 1997)

In patients with neuropathic pain, topical forms of capsaicin, fentanyl patch and lidocaine have been shown to be useful in the treatment of postherpetic neuralgia and diabetic peripheral neuropathic pain. Lidocaine has also demonstrated efficacy in relieving patient pain due to complex regional pain syndrome and may be useful in the treatment of patients with neuropathic pain who have cancer, although clinical trial results have not been consistent. (Fleming & O’Connor, 2009) Data suggest that topical therapies may offer a safe, well-tolerated, and effective alternative to systemic therapies in the treatment of patients with chronic, localized musculoskeletal and neuropathic pain. (Stanos, 2007)

Table 1.3.1 Neuropathic Pain: Approved Therapies

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient</th>
<th>Dosage Form</th>
<th>Postherpetic Neuralgia</th>
<th>Painful Diabetic Neuropathy</th>
<th>Painful HIV Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidoderm*</td>
<td>Lidocaine</td>
<td>Patch</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neurontin*</td>
<td>Gabapentin</td>
<td>Tablet</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lyrica*</td>
<td>Pregabalin</td>
<td>Capsule</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Cymbalta*</td>
<td>Duloxetine</td>
<td>Capsule</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Qutenza*</td>
<td>Capsaicin</td>
<td>Patch</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The use of topical anesthetics (TA) is an important part of the management of neuropathic pain. In a recent study TA were prescribed or used 3.8 million times by physicians over a 5 year study interval (Yentzer, 2009). Worldwide market is estimated at over $5 billion in sale of topical anesthetics with Lidocaine patch being the most commonly used and estimated annual sales valued at more than $1.2 billion, being most prescribed TA by physicians. (Health, 2013) The ideal TA would have the ability to provide a significant anesthetic effect shortly after application (5 – 10 minutes),long lasting action and have an excellent safety profile and be cosmetically aesthetical . Optimized topical drug delivery system can dramatically improve effectiveness of topical drug delivery of local anesthetics for the localized action. (Prabhu & Shirwaikar , 2008) The ideal film forming controlled release topical formulations can achieve dosing at far greater levels than those provided by
conventional topical formulations, leading to dramatic improvements in efficacy and maximized cosmetic acceptability.

Neuropathic pain and chronic pain can sometimes require weeks months, years and even decades of therapy. Consequently, the safety of long-term therapy is of paramount importance. Since local anesthetics may be applied to sites where peripheral nerves are growing or regenerating after injury (e.g., after exposure to chemical injury, mechanical injury, or neurodegenerative disease), their effects on growing neurons are of clinical importance particularly in postsurgical and post-traumatic pain where nerve fibers are regenerating. (Radwan, et al., 2002).

As there are considerable advantages of the topical transdermal application route for some drugs, different dosage forms have been developed for the drug delivery through the skin: polymeric patches and semisolids. Currently, patches still represent the majority of preparations for this application route, however each of the dosage forms is associated with certain drawbacks that can negatively influence the patient compliance or limit the usage of the dosage form. (Moody, 2010)

A limited number of treatments are available for PHN and even fewer have been approved by the FDA. Lidoderm®(Lidocaine) patch was approved in 1999, Neurontin®(Gabapentin) in 2002, Lyrica® (Pregabalin) in 2004 and Qutenza® (Capsaisain) in late 2009. Many patients obtain no relief or incomplete relief from these agents.

The efficacy of Lidoderm patch has been evaluated in post herpetic neuralgia. In addition to very modest efficacy, such studies have suffered from severe design shortcomings, including very short duration of treatment and evaluation, and patient population enrichment (Galer, et al., 2002).

Lidoderm® provides only modest pain relief in patients with PHN, with a lower efficacy response than other drugs, including antiepileptics (NNT=3.2), antidepressants (NNT = 2.1) and OxyContin® (NNT = 2.5). (Rowbotham, et al., 2001)

In addition to a modest efficacy, Lidoderm® patch adheres to skin poorly, particularly over skin surfaces which are highly contoured and hairy. Patients using lidocaine patches may need to apply adhesive tapes, bandages and skin fasteners to secure the patch to skin in place. Additionally, use of a patch may be problematic for the treatment of distal painful neuropathy such as painful diabetic neuropathy and painful HIV-neuropathy which primarily involve the
feet. In patients with neuropathy, or patients who have delayed wound healing, there is a need to have a clear and unobstructed view of the feet for daily inspection, and there is an absence of a large, contiguous flat surface to assure patch adhesion in patients with diabetes who have poor wound healing.

Hence there exists a need for designing alternatives to the conventional transdermal dosage forms, that could be in the form of novel topical film forming sprays and gels and also lipid based delivery systems to further improve the transdermal drug penetration for the patient of neuropathic pain. ((Schroder, 2007)

The film-forming technology plays an occlusive role on the skin, and the skin serves as a reservoir for the sustained release of drug into deeper layers of the skin.

Mepivacaine and Ropivacaine offer a number of potential advantages over lidocaine by their intrinsic vasoconstrictor effects, thereby the rate at which drug is cleared away from peripheral (skin) sites of pain generation is reduced and a the low potential for neurotoxic effects on developing or regenerating primary cultured neurons with lidocaine having shown to exhibit the highest neurotoxic potential in this model (Radwan, et al., 2002)

Ropivacaine is a long-acting, enantiomerically pure (S-enantiomer) amide local anaesthetic with an efficacy broadly similar to that of bupivacaine but is a preferred option because of its reduced central nervous system (CNS) and cardiotoxic potential and its lower propensity for motor block (McClellan & Faulds, 2000). It has high pKa and low lipid solubility which may help in blocking nerve fibres involved in pain transmission to a greater degree than those controlling motor function. The drug is less cardiotoxic than equal concentrations of racemic bupivacaine but more so than lignocaine; it has a significantly higher threshold for CNS toxicity than racemic bupivacaine. Extensive clinical data have shown that epidural Ropivacaine 0.2% is effective for the initiation and maintenance of labour analgesia, and provides pain relief after abdominal or orthopaedic surgery especially when given in conjunction with opioids (Etches, et al., 1997).

Mepivacaine is an effective local anesthetic of rapid onset, intermediate action, and low systemic toxicity. The available formulations have been characterized by immediate release and short duration of action. (McLure & Rubin, 2005)

In any anesthetic topical application, the drug should penetrate the stratum corneum and desensitize the underlying pain receptors within the skin. Local anesthetics are widely used in surgical, obstetric and dental patients for chronic pain therapy and the control of postoperative
pain (Dahm, et al., 2000). To relieve local pain, Mepivacaine, an amide-type local anesthetic characterized by its long action and high therapeutic power, has been commonly used (Bronaugh et al., 1989).

Compared with lidocaine patch, novel formulation of Mepivacaine and Ropivacaine film forming gel, microemulsions, SLN and topical sprays can be expected to provide:

- More suitable dosage form for application to the extremities
- Improved skin contact
- More efficient drug delivery
- Potentially improved efficacy by enhancing permeation of local anesthetics and achieving greater efficacy with reduced dosage
- Improved prescriber and patient acceptance and better aesthetics

With improved delivery systems that would form the basis of current work in the form of film forming gels and sprays of topical mepivacaine and ropivacaine, both local anesthetics with distinct advantages over lidocaine, attempt has been made to develop microemulsions of mepivacaine and ropivacaine, lipid based formulations and topical film forming sprays, and explore the applicability of this modality to deliver drugs to improve penetration and skin substantivity. Moreover, by providing a robust formulation with longer duration of action, better penetrability and enhanced action as a result of film forming ability, and improved cosmetic appeal, patient compliance would be improved.

The microemulsion and solid lipid nanoparticulate formulations of Mepivacaine and Ropivacaine also would go a long way in providing enhanced penetration, therefore result in improved efficacy.

Topical film forming spray formulations of Mepivacaine and Ropivacaine would provide an improved penetration and excellent patient compliance and also a novel method of drug delivery of local anesthetics.

Local anesthetic topical delivery systems using hydrogels and different permeation enhancers, liposomes or lipid nanoparticles (as isolated carrier systems or as their dispersion in their gel base) will be explored as alternatives to available commercial formulations, modifying the release rate of local anesthetics, increasing bioadhesive properties and reducing toxicity, resulting in an improved therapeutic efficacy.
PLAN OF WORK:

The Experimental work was planned as follows

1. Selection of drug candidates based on thorough literature search and Patent review
2. Standardization of drug and polymers
6. Preparation and evaluation of Topical formulations for peripheral neuropathic pain as follows:
   a. Topical Film forming Gels of Mepivacaine and Ropivacaine
   b. Topical Film forming Sprays of Mepivacaine and Ropivacaine
   c. Microemulsion based gels of Ropivacaine
   d. Solid Lipid Nanoparticle based gels of Ropivacaine
7. Evaluation and characterization of developed formulations for parameters like appearance of the formed films on skin, viscosity, particle size of the nano-formulations, in-vitro and ex-vivo drug diffusion studies was performed.
8. Scale up and Pilot Plant studies
9. Stability studies as per ICH guidelines
10. In-vivo pharmacokinetic and pharmacodynamic studies using suitable animal models.
12. Dermatopharmacokinetic evaluations to assess skin penetration
11. Acute toxicity studies and Dermal Irritation Potential of the developed formulations

Based on the proposed plan of work, the developed formulations will be investigated in the present project. Physiochemical characterization and preclinical indications of the formulations will be studied in the following chapters.