INTRODUCTION
Local anaesthetics produce loss of sensation and motor activity in circumscribed areas of the body by reversibly blocking conduction in nerve fibres. They stabilize the nerve membrane and thus prevent transmission of nerve impulses. They reversibly depress impulse transmission in nerves. They bind to a specific receptor site within the pore of the sodium channels in nerves and block ion movement through this pore. In general, their action is restricted to the site of application and rapidly reverses upon diffusion from the site of action in the nerve. When applied locally to nerve tissue in appropriate concentrations, local anaesthetics reversibly block the action potentials responsible for nerve conduction. They act on any part of the nervous system and on every type of nerve fibre. Thus, a local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. Local anaesthetics could also be described as analgesics as they are frequently used to prevent pain in surgical procedures, dental manipulations, injury and disease without loss of nervous control. (William Catterall, 1988)

The local anesthetic agents are useful chemical tools for the temporary relief of localized pain in dentistry and minor surgical procedures, as well as for producing a state of nonresistance without general anesthesia. Many over the counter agents are used topically for temporary relief of pain and itching caused by minor burns, insect bites, allergic response, hemorrhoids, and other minor conditions. (Zipf, H. F. et al, 1971). An ideal local anesthetic has not yet been discovered, but several desirable properties may be stated:

1. Nonirritating to tissue and not causing permanent damage. Most clinically available agents fulfill this requirement.
2. Low systemic toxicity because it is eventually absorbed from its site of application. Most local anesthetics are rapidly metabolized after absorption.
3. Effective whether injected into the tissue or applied locally to skin or mucous membranes. Intact skin is resistant generally to the action of most local anesthetics and requires high concentrations for prolonged periods. This is probably due to a slow rate of penetration and a rapid vascular diffusion following penetration. Thus, insufficient drug accumulates at the nerve ending in the dermis.
4. Rapid onset of anesthesia and a short duration of action must last long enough to allow time for the contemplated surgery, yet not so long as to entail an extended period of recovery.

1.1.1 HISTORY

Acupuncture, hypnotism, refrigeration, and nerve compression are known to have been used for many years to alleviate surgical pain before the development and utilization of local anesthetic drugs, and the anesthetic and central nervous system (CNS) stimulant effect derived from the leaves of the Erythroxyylon coca bush. It had been recognized by Peruvians, the natives of Peru learned to chew the leaves of the coca bush to stimulate the general feeling of well being and to prevent hunger. Although no early literature citation is available to substantiate it, the suggestion is often made that the Incas produced local anesthesia for surgical procedures by chewing a cud of the leaves and allowing the saliva to drop upon the site of incision. In 1860, the alkaloid cocaine was isolated from the coca leaf by Niemann. He like, many chemists of that era, tasted his newly isolated compound and noted that it caused a numbing of the tongue. In 1884, Carl Koller, studied cocaine (derived from the leaves of Erythroxyylon coca) with Sigmund Freud, and introduced the drug as topical the organic amine bases classified as esters or amides, as they differ from each other in their onset and duration of action, metabolism and toxicity. Shortly thereafter, Halstead popularized its use in infiltration and conduction block anesthesia. However, Cocaine was found to be extremely toxic and addictive, and the search for a suitable substitute culminated in the synthesis of procaine in 1904 by Einhorn. Procaine the prototype amino ester local anesthetic was first used clinically in 1905. Numerous other amino ester local anesthetics were introduced subsequently including tetracaine in 1932 and 2- chloroprocaine in 1955. In 1943, lidocaine was synthesised by Lofgren and its clinical introduction 1 year later marked the first use of a new class of local anesthetics, the amino amides. Several additional amide local anesthetics have been developed, including pivaclaine (1956), bupivacaine (1957), prilocaine (1959), and etidocaine (1971), and they have subsequently been placed (Covino, B.G.: 1972)
1.1.2 CHEMISTRY OF LOCAL ANESTHETICS

The structure of typical local anesthetics contains hydrophilic and hydrophobic domains that are separated by an intermediate ester or amide linkage. A broad range of compounds containing these minimal structure features can satisfy the requirements for action as local anesthetics. The hydrophilic group usually is a tertiary amine, but it is also may be a secondary amine; the hydrophobic domain must be an aromatic moiety. The nature of the linking group determines certain of the pharmacological properties of these agents. For example, local anesthetics with an ester link are hydrolyzed readily by plasma esterase. (J.P. Howe, 1996)

The Local Anesthetics Molecule to understand and predict the differences in biologic activity of local anesthetic agent, it is necessary to appreciate both the general structure of the local anesthetic molecule and the properties of each of subunits. The typical clinically employed local anesthetic molecule is weakly basic in nature containing an amine residue that contributes water solubility in its quaternary form and that is separated from lipophilic domain by an intermediate alkyl chain. The intermediate chain connecting the lipophilic head and the hydrophilic tail contains either an ester or amide linkage, thus subdividing the clinically useful local anesthetic into two main groups: the aminoesters, which are metabolized by plasma cholinesterase, and the aminoamides, which are metabolized in the liver. The lipophilic portion of the molecule is usually an aromatic residue, contributed by a derivative of benzoic acid in the case of the aminoester anesthetic or by a derivative of aniline in the case of the aminoamides.

1.1.3 STRUCTURE-ACTIVITY RELATIONSHIPS

In its tertiary form, the local anesthetic molecule is poorly soluble in water, but because of its basic nature, it combines readily with acids to form water-soluble salts. Thus, for clinical utility, local anesthetic are usually prepared as their salts form, most often as hydrochlorides. In aqueous solution, the hydrochlorides salt ionizes to yield a positively charged quaternary amine and a chloride anion. The exact percentage of local anesthetic molecules in each of the two form depends on the pKa, or dissociation constant, of the local anesthetic and the pH of the surrounding medium.
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The basic properties of a local anesthetic can be manipulated through alternations in its molecular structure. For example, increasing the degree of alkyl substitution on the aromatic ring or on the tertiary amine increases lipid solubility and produces greater local anesthetic potency but at the expenses of increasing toxicity. Compounds containing ethyl ester, such as procaine and chloroprocaine, are more easily metabolized and produce less systemic toxicity. Molecular changes that lead to increased protein binding result in prolongation of the duration of local anesthetic action. Finally, when local anesthetic molecules contain asymmetric carbon atoms and thus can be resolved into optical isomers, an enantiometric preparation of the local anesthetic may possess differing therapeutic and/or toxic qualities when compared with the racemic mixture.

The most widely used agents today are procaine, lidocaine, bupivacaine, and tetracaine. To understand and predict the differences in biologic activity of local anesthetic agents, it is necessary to appreciate both the general structure of the local anesthetic molecule and the properties of each of its subunits. The typical clinically employed local anesthetic molecule is weakly basic in nature containing an amine residue that contributes water solubility in its quaternary form and that is separated from a lipophilic domain by an intermediate chain connecting the lipophilic head and the hydrophilic tail contains either an ester or an amide linkage, thus subdividing the clinically useful local anesthetic into two main groups; the aminoesters which are metabolized by plasma cholinesterase, and the aminoamides which are metabolized in the liver. The lipophilic portion of the molecule is usually an aromatic residue, contributed by a derivative of benzoic acid in the case of aminoesters anesthetics or by a derivative of aniline in the case of aminoamides.
1.1.4 ABSORPTION, FATE, AND EXCRETION

Absorption of various local anesthetics depends on the site of injection, the degree of vasodilation caused by the agent itself, the dose, and the presence of vasoconstrictor in the solution. Epinephrine added to a procaine hydrochloride solution greatly increases its duration of action as an infiltration agent.

Local anesthetics of the ester type are hydrolyzed by plasma pseudocholinesterase. Those having the amide linkage are largely destroyed in the liver. In human beings, procaine is broken down to p-aminobenzoic acid, 80% of which is excreted in the urine, and diethylaminoethanol, 30% of which is excreted in the urine. Only 2% is excreted unchanged in the urine. Only 10% to 20% of lidocaine appears unchanged, the rest being metabolized, presumably mainly in the liver.

Procaine is hydrolyzed in spinal fluid 150 times more strongly than in plasma, there being very little esterase present. The hydrolysis results from the alkanity of spinal fluid and is approximately the same as with a buffer having the same pH. Lidocaine is metabolized in the liver by removal of one or both ethyl groups from the molecule. The resulting metabolites, monoethylglycinexylidide (MEGX) and glycinexilidine (GX), still have pharmacological activity and may contribute to CNS toxicity.

Local anesthetics exert their effect largely on a circumscribed area. Nevertheless, they are absorbed from the site of injection and may exert systemic effects, particularly on the cardiovascular system and the CNS, particularly when an excessive dose is administered.

1.1.5 CLINICAL USES OF LOCAL ANESTHETICS

Local anaesthetic requirements and activity vary considerably. Selection of an appropriate agent in a specific situation requires knowledge of the clinical needs and pharmacological properties of the various anaesthetic drugs currently available.

1.1.6 TYPES OF ANESTHESIA

Topical Anaesthesia

Local anesthetics may be applied to the skin, the eye, the ear, the nose and the mouth as well as other mucous membranes. In general, cocaine, amethocaine, lignocaine
and prilocaine are the most useful and effective local anesthetics for this purpose. When used to produce topical anaesthesia, they usually have a rapid onset of action (5-10 mins) and a moderate duration of action (30-60 mins). Cocaine is a potent vasoconstrictor and is useful in the reduction of bleeding as well as topical anaesthesia. Other local anaesthetic agents may be absorbed in significant amounts particularly after topical application to the more vascular areas, and fatalities have occurred after application of these agents to mucosal surfaces.

Absorption of local anaesthetics through intact skin is usually slow and unreliable and high concentrations (e.g. 20% benzocaine or 40% lignocaine) are required.

EMLA cream is a eutectic mixture of local anaesthetics which may be used to provide surface anaesthesia of the skin (particularly in paediatric practice). It is a mixture of the base forms of lignocaine and prilocaine in equal proportions in an emulsion. Cutaneous contact (usually under an occlusive dressing) should be maintained for at least 60 minutes prior to venepuncture.

1.1.7 INFILTRATION ANAESTHESIA

Infiltration techniques are used to provide anaesthesia for minor surgical procedures. Amide anaesthetics with a moderate duration of action are commonly used (lignocaine, prilocaine and mepivacaine). The site of action is at unmyelinated nerve endings and onset is almost immediate. The duration of local anaesthesia is variable. Procaine has a short duration of action (15-30 min), while lignocaine, mepivacaine and prilocaine have a moderate duration of action (70-140 min). Bupivacaine has the longest duration of action (approximately 200 min). The addition of adrenaline (1 in 200,000) will increase the quality and prolong the duration of anaesthesia.

1.1.8 CONDUCTION ANAESTHESIA

Conduction anaesthesia can be divided into minor nerve blockade (e.g. ulnar, radial or intercostal), and major blockade of deeper nerves or trunks with a wide dermatomal distribution (e.g. brachial plexus blockade). For each individual agent the
duration of anaesthesia will be determined more by the total dose of the drug rather than
the volume or concentration of drug used.

When amide local anaesthetics are used to produce minor nerve blockade, they
have a relatively rapid onset of action (5-10 min). Lignocaine, mepivacaine and prilocaine
have a moderate duration of action (1-2 hr), while bupivacaine and etidocaine produce
local anaesthesia for 2-6 hrs.

In major nerve blockade the onset is more variable, mainly due to anatomical
factors which can delay or restrict the access of the local anaesthetic to its site of action.
In general lignocaine, mepivacaine and prilocaine have a moderate duration of action (1-2 hr),
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**1.1.9 EXTRADURAL ANAESTHESIA**

Local anaesthetic solutions are deposited in the epidural space between the dura
mater and the periosteum lining the vertebral canal. The epidural space contains adipose
tissue, lymphatics and blood vessels. The injected local anaesthetic solution produces
analgesia by blocking conduction at the intradural spinal nerve roots.

The quality and extent of the blockade produced by each agent is determined by
the volume as well as the total dose of the drug. The spread of local anaesthetic solutions
may be more extensive in pregnant women as the volume of the potential space is
reduced by venous engorgement in the epidural space. Enhanced effects may also be seen
in the elderly and in patients with arteriosclerosis due to impairment of vascular
absorption from the epidural space.

Bupivacaine (0.5%) or lignocaine (1.5-2.0%) are usually used to produce
extradural anaesthesia. Repeated administration of lignocaine or mepivacaine into the
epidural space may result in a diminished response with each subsequent dose
(tachyphylaxis). This may be due to local changes in pH due to the relative acidity of
these solutions. The reduction in pH may reduce the amount of free base available for
diffusion across the neuronal membrane. (Carpenter et al., 1992)
1.1.10 SPINAL ANAESTHESIA

The introduction of local anaesthetic solutions directly into the cerebrospinal fluid (CSF) produces spinal anaesthesia. The local anaesthetics do not have to cross tissue or diffusion barriers and also the central attachments of the ventral and dorsal nerve roots are unmyelinated, which allows rapid uptake of the free base. There is a faster onset of action and a smaller dose is required. Spinal anaesthesia produces a similar clinical effect with a dose approximately ten times smaller than that needed for extradural anaesthesia.

Solutions of amethocaine (0.2%), lignocaine (5%), prilocaine (5%) bupivacaine (0.5%) and mepivacaine (4%) are commonly used to produce spinal anaesthesia. Prilocaine and mepivacaine have a slightly longer duration of action than lignocaine; bupivacaine has the longest duration of action.

In pregnancy, compression of the inferior vena cava by the pregnant uterus leads to distension of the vertebral venous plexus and reduces the volume of the subarachnoid space. Consequently the degree of blockade is enhanced and reduced doses are required. (Greene,N.M et al.,1993)

1.1.11 Effects of local anesthetics

(a) Cardiovascular Effects: Since lidocaine is widely used as an antiarrhythmic drug, much have been learned about its effect on the heart, and this information is generally also applicable to the other local anesthetics. At nontoxic concentrations, lidocaine alters or abolishes the rate of slow diastolic depolarization in Purkinje’s fibers and shortens the effect in refractory period as well as the duration of the action potential. In toxic doses lidocaine decreases the maximal depolarization of purkinje’s fibers and reduces conduction velocity. Such doses may also have direct negative inotropic effect.

The local anesthetics tend to relax the vascular smooth muscle, but cocaine can cause vasoconstriction by blocking the reuptake of norepinephrine.

(b) CNS effects: Although the usual local anesthesia produces no CNS effects, increased doses may cause excitatory effects resulting in convulsions and eventually respiratory
depression it is believed on the basis of animal experiments that the local anesthetics may block inhibitory and facilitory neurons, leading to depression.

(c) Vasoconstrictors and local anesthetics: Vasoconstrictors, particularly epinephrine, are commonly added to local anesthetic solutions that are to be used for infiltration or nerve block. The purpose is to prevent absorption of the drug and thereby prolong its action locally and reduce systemic reaction. Concentrations of epinephrine used for this purpose in local anesthesia vary from 2 to 10 μg/ml, or 1:500,000 to 1:100,000.

Although the addition of epinephrine to such drugs as procaine is sound, other drugs such as lidocaine, prilocaine, mepivacaine, and bupivacaine may be used without the addition of vasoconstrictors.

Epinephrine may contribute to the systemic effects of local anesthetics and may be responsible for symptoms such as anxiety, tachycardia, and hypertension.

(d) Miscellaneous effects Although the usual local anesthetics have few additional effects, they may depress ganglionic transmission and neuromuscular transmission. These actions are unimportant unless some other potent agent is used concomitantly. For example, lidocaine may enhance the action of neuromuscular blocking agents.

1.1.12 TOXICITY

The ester-type local anesthetics, such as procaine and tetracaine, may produce true allergic reactions manifested as skin rashes or bronchospasm. Allergic reactions to the amides, such as lidocaine, are very rare.

The majority of toxic reactions are a result of overdosage. In general the true pharmacological signs of toxicity from local anesthetics are CNS stimulation followed by depression and peripheral cardiovascular depression. Salivation and effective tremor, convulsion, and coma, associated with hypertension and tachycardia and followed by hypotension, all occurring in a few minutes.

The treatment is symptomatic and essentially involves restoration of normal ventilation and circulation. Barbiturates in doses greater than hypnotic are in the prevention of CNS stimulation caused by local anesthetics. Diazepam (Valium) is being used increasingly for the same purpose. (Alper, M.H. 1976)
1.1.13 Commercial Preparations

Because the free-base form of most local anesthetics is poorly soluble in aqueous solution, they are prepared as hydrochlorides salts dissolved in sterile water or normal saline. The solution is acidified to a pH of 4.4-6.4 to favor existence of the water-soluble, cationic, quaternary amine form of the local anesthetic molecule. Unfortunately, this decreases the potency of the local anesthetic, and although increasing the pH of the local anesthetic solution may shorten the onset and increase the duration of blockade, this also increases the risk of precipitation of the local anesthetic out of solution, the action of local anesthetics may also be potentiated by carbonation, with the suggested mechanism of action being a direct depressant effect of carbon dioxide on the axon, an increased conversion of the local anesthetic to the active cation form at the site of action inside the axon, and/or direct modification of local anesthetic binding sites in the Na\(^+\) channel.

Because of their antibacterial and antifungal and antimicrobial activity, antimicrobial preservatives are added to local anesthetic solutions contained in multidose vials. Preservative-containing local anesthetic solutions should not be used in spinal, epidural, or caudal anesthesia because of their potentially cytotoxic effects. The most frequently used antimicrobials are parabens derivatives of para-hydroxy benzoate, such as methyl paraben, ethyl paraben, and propyl paraben. The paraben derivatives are potent allergens and have been implicated in allergic reaction initially attributed to local anesthetic. Because of this, preservative containing local anesthetic are not recommended for intravenous use.

Proper handling and storage of local anesthetics are important. Because of the possibility of small pieces of glass falling into single-dose ampules when they are opened, some manufactures prefer to prepare single dose local anesthetic solutions in rubber-stoppered vials. These solution autoclaved only once, and they should not remain in the autoclave any longer than necessary. Ampoules of local anesthetic should never be sterilized by soaking in an antiseptic solution because of the potential for contamination through unnoticed cracks in the ampules. Any local anesthetic solution containing a free aromatic amino group, such as 2-chloroprocaine or procaine, may be discolored by prolonged exposure to light. Similarly, epinephrine oxidizes with prolonged exposure to light.
1.2 INTRODUCTION OF NONSTEROIDAL ANTIINFLAMMATORY COMPOUNDS

The inflammatory, analgesic and antipyretic are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and side effects. The prototype is aspirin; hence these compounds are often referred to as aspirin-like drugs. They are also frequently called nonsteroidal antiinflammatory drugs or NSAIDs.

1.2.1 History. The medicinal effect of the bark of willow and certain other plants has been known to several cultures for centuries. The active ingredient in the willow bark was a bitter glycoside called salicin. First isolated in a pure form in 1829 by Leroux, who also demonstrated its antipyretic effect. On hydrolysis, salicin yields glucose and salicylic alcohol. The later can be converted into salicylic acid, either in vivo or by chemical manipulation. Sodium salicylate was first used for the treatment of rheumatic fever and as an antipyretic in 1875, and the discovery of its uricosuric effects and of its usefulness in the treatment of gout soon followed. The enormous success of this drug promoted Hoffman, a chemist employed by Bayer, to prepare acetylsalicylic acid based on earlier, but forgotten, work of Gerhardt in 1853. After demonstration of its antiinflammatory effects, this compound was introduced into medicine in 1899 by Dreser under the name of aspirin. The name is said to have been derived from Spiraea, the plant's species from which salicylic acid was once prepared.

The synthetic salicylate soon displaced the more expensive compounds obtained from natural sources. By the early years of this century the chief therapeutic benefits of aspirin were known. Toward the end of the nineteenth century, other drugs were discovered that shared some or all of these actions; among these, only derivatives of para-aminophenol (e.g., acetaminophen) are used today. Beginning with indomethacin, a host of new agents has been introduced into medicine in various countries during the past 30 years.
1.2.2 Chemical classification of Analgesic, Antipyretic, and Nonsteroidal Antiinflammatory Drugs (Paul A. Insel; 1996).

Salicylic acid derivative

Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicyl salicylic acid, sulfasalazine olsalazine

Para-aminophenol derivatives

Acetaminophen

Indole and indene acetic acids

Indomethacin, sulindac, etodolac

Heteroaryl acetic acids

Tolmetin, diclofenac, ketorolac

Arylpromionic acids

Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin

Anthranilic acids (fenamates)

Mefenamic acid, meclofenamic acid

Enolic acids

Oxicams (piroxicam, tenoxicam)

Pyrsolidinediones (phenylbutazone, oxyphenbutazone)

Alkanones

Nabumetone

Table I: Marketed Formulations of Specific Nonsteroidal Antiinflammatory Drugs

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>Generic Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascriptin, Bayer, Anacin &amp; many others</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Ansaid</td>
<td>Naproxen sodium</td>
</tr>
<tr>
<td>Celebrex</td>
<td>flurbiprofen</td>
</tr>
<tr>
<td>Clinoril</td>
<td>Sulindac</td>
</tr>
<tr>
<td>Daypro</td>
<td>Oxaprozin</td>
</tr>
<tr>
<td>Disalcid</td>
<td>Salsalate</td>
</tr>
<tr>
<td>Dolobid</td>
<td>Diflunisal</td>
</tr>
<tr>
<td>Feldene</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Indocin</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Lodine</td>
<td>Etodolac</td>
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</table>
1.2.3 Mechanism of Action of NSAIDs

Although NSAIDs had been known to inhibit a wide variety of reactions in vitro, no convincing relationship could be established with their known antiinflammatory, antipyretic and analgesic effects until 1971, when Vane and associates and Smith and Willis demonstrated that low concentrations of aspirin and indomethacin inhibited the enzymatic production of prostaglandins. There was, at that time, some evidence that prostaglandins participated in the pathogenesis of inflammation and fever, and this reinforced the hypothesis that inhibition of the biosynthesis of these autacoids could explain a number of the clinical actions of the drugs. There are differences of opinion as to whether or not NSAIDs may have other actions that contribute to their effects.

Considerable research has continued in an effort to find new nonsteroidal antiinflammatory agents (NSAIA). (Wong, S et al; 1975) Long term therapy with the corticosteroids is often accompanied by various side effects. Although several new agents have been introduced for use in rheumatoid arthritis, aspirin appears to remain as one of the agents of choice.

Of considerable interest is the observation that prostaglandins appear to play a major role in the inflammatory processes (Collier, H.O et al 1971). Of particular significance are reports that drugs, such as aspirin and indomethacin, inhibit prostaglandin synthesis in several tissues. Furthermore, almost all classes of nonsteroidal antiinflammatory agents strongly inhibit the conversion of arachidonic acid into prostaglandin E2 (PEG2). This has been shown to occur at the stage of conversion of arachidonic acid, released by the action of phospholipase on damaged tissues, to the cyclic endoperoxides, PGG2 and PGH2, by prostaglandin synthetase. These are known to cause
vasoconstriction and pain. They, in turn, are converted in part to PEG$_2$ and PEG$_{2d}$, which can cause pain and vasodilation. This effect of the nonsteroidal anti-inflammatory agents parallels their relative potency in various tests and is stereospecific (Shen, T.Y et al., 1972). The search for specific inhibitors of prostaglandin synthesis has opened a new area of research in the field.

1.2.4 Therapeutic activities and side effects of Non Steroidal Antiinflammatory Therapeutic Effects. All NSAIDs are antipyretic, analgesic, and antiinflammatory, but are different in their activities. The reasons for such differences are not known, but differential sensitivity of enzymes in tissue environments may be important. NSAIDs find their chief clinical application as antiinflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease and do not arrest the progression of pathological injury to tissue during severe episodes.

1.2.5 Side effects of NSAIDs Therapy. In addition to sharing many therapeutic activities, NSAIDs share several unwanted side effects, those are: (Borda and Koff, 1992)

- Gastrointestinal ulceration and intolerance
- Blockade of platelet aggregation (inhibition of thromboxane synthesis)
- Inhibition of uterine motility (prolongation of gestation)
- Inhibition of prostaglandin-mediated renal function
- Hypersensitivity reactions

Other side effects of these drugs that probably depend upon blockade of the synthesis of endogenous prostaglandins include disturbances in platelet function, the prolongation of gestation or spontaneous labor, and changes in renal function (Graham et al., 1993)
1.3 MUCO-ADHESIVE DRUG DELIVERY SYSTEM

Muco-Adhesion

In recent years considerable attention has been focussed on developing drug delivery systems which utilize the principle of bioadhesion for optimum delivery of drugs from the device. The principle of bioadhesion has been exploited for various routes of administration with the scope of both topical and systemic drug delivery.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or it can be the mucous coat on the surface of a tissue. Bioadhesive is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended periods of time (Park, K. et al. 1990). The goal of development of bioadhesive is to duplicate, mimic or improve biological adhesives, which are both durable where required and degradable where necessary and not toxic at all. If the adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion (Jimenez, C. et al. 1993b). Mucoadhesion is described as the interaction between a mucin surface and a synthetic or natural polymer.

Mucoadhesion could resolve several problems of controlled release systems (Gandhi, R.B. et al. 1988)

• It localizes drug in a particular region, thereby improving and enhancing bioavailability for those drugs with bioavailability problems,
• The strong interaction between a polymer and the mucus lining of a tissue helps increase contact time and permits localization when modification of tissue permeability is important for delivery,
• It inhibits the metabolizing of enzymes in a localized area and frees agents locally for the purpose of modulating antigenicity.

1.3.1 MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration (Nagai, T. 1985) and hence
can be used for targeting a drug to a particular region of the body for extended periods of time (Kamath, K.R. et al; 1994).

The mucosal layer lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose and eye. These represent potential sites for attachment of any bioadhesive system and hence, the mucoadhesive drug delivery systems may include the following (Jimenez, C. et al. 1993b; Smart, J.D. 1992; Ahuja, A. et al. 1997).

i. Buccal delivery system

ii. Sublingual delivery system

iii. Vaginal delivery system

iv. Rectal delivery system

v. Nasal delivery system

vi. Ocular delivery system

vii. Gastro intestinal delivery system.

1.3.2 MECHANISM OF BIOADHESION

For bioadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevice of the tissue surface or interpenetration of the chains of the bioadhesive with those of the mucous takes place. Low chemical bonds can then settle (Duchene, D. et al. 1988).

One of the most important factors for bioadhesion is tissue surface roughness (Jimenez, C. et al. 1993b). Adhesive joints may fail at relatively low applied stresses if cracks, air bubbles, voids, inclusions or other surface defects are present. Viscosity and wetting power are the most important factors for satisfactory bioadhesion.

On a molecular level, mucoadhesion can be explained on the basis of molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from Vander Waals forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For muco-adhesion to occur, the attractive interaction should be larger than nonspecific repulsion (Kamath, K.R. et al. 1994).
1.3.3 THEORIES OF BIOADHESION

Several theories have been proposed to explain the fundamental mechanisms of adhesion (Nagai, T. 1985; Duchene, D. et al. 1988; Gandhi, R.B. et al. 1988; Mikos, A.G. et al. 1990b; Jimenez, C. et al. 1993b). In a particular system, one or more theories can equally well explain or contribute to the formation of bioadhesive bonds.

I. Electronic theory: According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

II. Adsorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as:

1) Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.

2) Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vander waals forces and hydrogen and hydrophobic bonds.

III. Wetting theory: Wetting theory is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behaviour in terms of the ability of a liquid or a paste to spread over a biological system.

The work of adhesion (expressed in terms of surface and interfacial tension, \( \gamma \)) is defined as the energy per cm\(^2\) released when an interface is formed. The work of adhesion is given by:

\[
Wa = YA + YB - YAB
\]

where 'A' and 'B' refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:
For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by:

\[ SB/A = YA - (YB + YAB) \]

\( SB/A \) should be positive for a bioadhesive material to adhere to a biological membrane.

IV. Diffusion theory: According to this theory, the polymer chains and the mucous mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucous depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between crosslinks and decreases significantly as the crosslinking density increases.

V. Fracture theory: This theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory equivalent to adhesive strength is given by

\[ G = (E \varepsilon/L)^{1/2} \]

where

- \( E \) is the Young’s modulus of elasticity
- \( \varepsilon \) is the fracture energy and
- \( L \) is the critical crack length when two surfaces are separated.

1.3.4 FACTORS IMPORTANT TO BIOADHESION

I. Polymer related factors

a) Molecular weight: Numerous studies have indicated that there is a certain molecular weight at which bioadhesion is at a maximum. The interpenetration of polymer molecules is favourable for low molecular weight polymers whereas entanglements are favoured for high molecular weight polymers. The optimum molecular weight for maximum bioadhesion depends on the type of polymers. Their nature dictates the degree of swelling in water which inturn determines interpenetration of polymer molecules within the mucous (Bodde, H.E. et al. 1992).

b) Concentration of active polymer: There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous. For solid dosage forms such as tablets, it was showed that higher the polymer concentration the stronger is the bioadhesion (Duchene, D. et al. 1988).

c) Flexibility of polymer chains: It is important for interpenetration and entanglement. As water soluble polymers become cross linked, the mobility of the individual polymer chain decreases. As the cross linking density increases, the effective length of the chain which can penetrate into the mucous layer decreases even further and muco adhesive strength is reduced.

d) Spatial conformation: Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to that of polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.
II. Environment related factors

a) pH: pH was found to have a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross linked with COOH groups. pH influences the charge on the surface of both mucous and the polymers. Mucous will have a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone. The pH of the medium is critical for the degree of hydration of highly crosslinked polyacrylic acid polymers, increasing between pH 4 and pH 5, continuing to increase slightly at pH 6 and pH 7 and decreasing at more alkaline pH levels. This behaviour is attributed to differences in charge density and the different pHs (Ch'ng, H.S. et al. 1985).

b) Applied strength: It is necessary to apply a defined strength to place a solid bioadhesive system. Whatever the polymer, poly (acrylic acid/divinyl benzene), poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, upto an optimum (Duchene, D. et al. 1988). The pressure initially applied to the muco-adhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become muco-adhesive even though they do not have attractive interactions with mucin.

c) Initial contact time: The initial contact time between mucoadhesives and the mucous layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases. It can be easily controlled when mucoadhesives are applied to exposed areas such as eye, nose or mouth. For the application of mucoadhesives to the GI tract, however, the initial contact time cannot be controlled, which is one of the difficulties in applying mucoadhesives to the GI tract (Kamath, K.R. et al. 1994).
d) Selection of the model substrate surface: The handling and treatment of biological substrates during the testing of mucoadhesives is an important factor, since physical and biological changes may occur in the mucous gels or tissues under the experimental conditions. The viability of the biological substrate should be confirmed by examining properties such as permeability, electrophysiology or histology. These studies may be necessary before and after performing the in-vitro tests using tissues.

e) Swelling: Swelling depends both on polymer concentration and on water presence. When swelling is too great, a decrease in bioadhesion occurs. Such a phenomenon must not occur too early, in order to lead to a sufficient action of the bioadhesive system. Its appearance allows easy detachment of the bioadhesive system after the discharge of the active ingredient.

III. Physiological variables

a) Mucin turnover (Kamath, K.R. et al. 1994): The natural turnover of mucin molecules from the mucous layer is important for at least two reasons. The mucin turnover is expected to limit the residence time of the mucoadhesives on the mucous layer. No matter, how high the mucoadhesive strength, mucoadhesives are detached from the surface due to mucin turnover. Mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they have a chance of interaction with the mucous layer. Mucin turnover may depend on other factors such as the presence of food. Mucin turnover time has been found to be of 47-270 minutes. The ciliated cells in the nasal cavity are known to transport the mucous to the throat at a rate of 5 mm/min. The mucociliary clearance in the tracheal region has been found to be in the range of 4-10 mm/min.

b) Disease states: The physicochemical properties of the mucous are known to change during the disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female
reproductive tract and inflammatory conditions of the eye. Mucoadhesive property should be evaluated under these conditions (Kamath, K.R. et al. 1994).

1.3.5 ANATOMY AND PHYSIOLOGY OF THE ORAL CAVITY

The oral cavity is lined by a relatively thick, dense and multi-layered mucous membrane of a highly-vascularized nature. The multi-layered structure of the oral mucosa is formed by cell divisions, which occur mainly in the basal layer (Merkle, H. P. et al. 1990; Chidambaram, N. et al. 1995; Rathborne, M. J. et al. 1991).

The epithelium of the oral cavity is in principle similar to that of the skin, with interesting differences regarding keratinization and the protective and lubricant mucous spread across its surface. The total area is about 100 sq.cm. The buccal part with about one third of the total surface is lined with an epithelium of about 0.5 mm thickness and rest by 0.25 mm thickness (Merkle, H. P. et al. 1990; Squier, C. A. 1992).

The mucosa of the oral cavity can be divided into three functional zones (Siegel, I. A. et al. 1971):

a) The mucous-secreting regions (consisting of the soft palate, the floor of the mouth, the under surface of the tongue, and the labial and buccal mucosa) have a normally non-keratinized epithelium.

b) The hard palate and the gingiva are the regions of the masticatory mucosa and have a normally keratinized epidermis.

c) Specialized zones are the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

These oral mucosal sites differ greatly from one another, in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time (Khanna, R. et al. 1998). According to its natural function, the oral mucosa is routinely exposed to a multitude of different external compounds and therefore is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form, its drug, excipient or additives. Transport of drugs through the oral mucosa is most likely to occur mainly through the non-keratinized sections. The mucosae of the soft palate and the sublingual buccal regions are not keratinized (Merkle, H.P. et al. 1990; Harris, D. et al. 1992).
MUCOUS LAYER

The tissue layer responsible for formation of the adhesive interface is mucous. The mean thickness of this layer varies from about 50-450 (m in humans (Duchene, D. et al. 1988; Marriott, C. et al. 1990; Bodde, H.E. et al. 1992; Kamath, K.R. et al. 1994). The composition of mucous varies widely depending on animal species, anatomical location and the normal or pathological state of the organism (Gandhi, R.B. et al. 1988). It is secreted by the goblet cells lining the epithelial or by special exocrine glands with mucous cells acini. The lubrication properties of mucous secretions are a result of their viscous and gel forming properties and general stickiness (Jimenez, C. et al. 1993b). It has the following general composition (Duchene, D. et al. 1988).

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>95.0%</td>
</tr>
<tr>
<td>Glycoproteins and lipids</td>
<td>0.5-5.0%</td>
</tr>
<tr>
<td>Mineral salts</td>
<td>1.0%</td>
</tr>
<tr>
<td>Free proteins</td>
<td>0.5-1.0%</td>
</tr>
</tbody>
</table>

Mucous glycoproteins are high molecular proteins possessing attached oligo-saccharide units. These units contain an average of about 8-10 mono-saccharide residues of five different types. They are a) L-fucose b) D-galactose c) N-acetyl-D-glucosamine d) N-acetyl-D-galactosamine and e) sialic acid.

At physiological pH, the mucous network may carry a significant negative charge because of the presence of sialic acid and sulfate residues and this high charge density due to negative charge contributes significantly to bioadhesion.

SALIVARY SECRETION

Besides the mucous, the mucosal layer of the oral cavity is kept moist by the saliva secreted mainly by three pairs of salivary glands namely the submaxillary, the parotid and the sublingual glands. Minor salivary glands are situated in the buccal, palatal and retromolar regions of the oral cavity. The pH of the salivary secretion ranges from about 6.2 to 7.4 with an average of 6.6. The quantity of saliva produced each day ranges
from 0.5-1.5 litres (Afronsky, D. et al. 1961). There is a considerable variation in the individual's saliva flow rate. It ranges from 0.21 to 1.18 ml/min with a mean of 0.65 ml/min under the resting condition (Schneyer, L.H. et al. 1955b) and 0.56 to 2.70 ml/min with a mean of 1.63 ml/min under exogenously stimulated conditions (Schneyer, L.H. et al. 609-613, 1955a).

1.3.6 BUCCAL DRUG DELIVERY SYSTEMS

Drug delivery via the membranes of the oral cavity can be subdivided as follows (Bodde, H. E. et al. 1992; Martini, A. et al. 1995; Merkle, H. P. et al. 1990; Harris, D. et al. 1992):

I. **Sublingual delivery** which is the administration of drug via the sublingual mucosa to the systemic circulation. The sublingual mucosa is relatively permeable giving rapid absorption and acceptable bioavailabilities of many low molecular weight drugs, and is convenient and accessible. The delivery systems evaluated clinically for sublingual delivery have been rapidly disintegrating tablets and liquid filled soft gelatin capsules which are crushed open in the mouth. The concentrations are sustained for a relatively short period of time.

II. **Buccal delivery** which is administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation. The buccal route is better suited to the use of retentive systems such as mucoadhesive tablet or patch system, in that it has an expanse of smooth and relatively immobile surface for placement of such systems. Hence it is suitable for sustained delivery applications, delivery of less well permeating molecules and perhaps drugs (Hoogstrate, A.J. et al. 1996).

III. **Local delivery** for the treatment of conditions of the oral cavity by application of the bioadhesive system either to the palate, the gingiva or the cheek (Bouckaert, S. et al. 1996; Bouckaert, S. et al. 1993a; Nagai, T. et al. 1990). Local delivery of drugs to tissues of the oral cavity has a number of applications including the treatment of toothache (Ishida, M. et al. 1982), periodontal diseases (Deasy, P.B. et al. 1989; Agarwal, R.K. et

Conventional formulations for local oral delivery are principally lozenges, troches, mouth paints, mouth washes, oral gels, pastes and suspensions that give high drug levels in the oral cavity, but for only a short time (Harris, D. et al. 1992; Anders, R. et al. 1989; Zegarelli, D. J. et al. 1991). Release of drug from these preparations involves an initial burst of activity, whose level rapidly declines to subtherapeutic concentrations. A conventional lozenge formulation produces effective levels of drug locally in the mouth for a period of less than one hour and repeated administration is usually limited to a maximum of less than 10 units per day because of the systemic toxicity of the large quantity of drug swallowed. Apart from compliance problems involved in frequent administration such products are unsuitable for effective therapy overnight. Also conventional lozenges tend to increase salivary flow when sucked, thereby reducing local drug concentration and residence time in the mouth (Collins, A.E. et al. 1990). Mouth washes have an even more transient effect than lozenges, while oral gels, pastes and suspensions are difficult to be retained in the mouth and have poor patient acceptability. Moreover, administration of conventional buccal and sublingual tablets and capsules does not go along with drinking and eating and is, at least, a handicap for speaking, so any administration is restricted to rather limited periods of time and controlled release is not within the scope of such formulations (Anders, R. et al. 1989). Although it is feasible to design delivery systems that improve localization, few of these have seen commercial success.

1.3.7 Advantages of mucoadhesive buccal drug delivery systems

Ease of administration.

i. Termination of therapy is easy.

ii. Permits localisation of the drug to the oral cavity for a prolonged period of time.

iv. Can be administered to unconscious patients.

v. Offers an excellent route for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.

vi. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.

vii. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionised species can be achieved.

viii. Drugs which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestines can be administered by this route.

ix. It offers a passive system for drug absorption and does not require any activation.

x. The oral mucosa lacks prominent mucous secretion goblet cells and therefore there is no problem of a diffusion limited mucous build up, beneath the applied dosage form.

xi. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.

### 1.3.8 Limitations of bioadhesive drug delivery systems


i. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.

ii. Drugs which are unstable at buccal pH cannot be administered by this route.
iii. Only drugs with a small dose requirement can be administered.

iv. Drugs contained in the swallowed saliva follow the per oral route and advantages of buccal route are lost.

v. Only those drugs which are absorbed by passive diffusion can be administered by this route.

vi. Eating and drinking may become restricted.

vii. There is an ever present possibility of the patient swallowing the tablet.

viii. Over hydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.

ix. The related impermeability and small surface area coupled with metabolism of some drugs are other realistic problems with this route of delivery.