Chapter 2

2.1 Non-steroidal anti-inflammatory drugs
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References
2.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs worldwide. These are categorized as 'over-the counter' (OTC) availability, and are also consumed on non-prescription basis as well. The gastrointestinal tract (GIT) is the main target of NSAID toxicity. It is the most frequent organ affected by adverse drug reactions and unfortunately, it is the most common drug-induced toxicity that can be fatal. World over, more than 35 million people consume these drugs on a daily basis and about 30% of users may develop GIT toxicity of sufficient degree requiring a physician's intervention. It has also been estimated that one third of the cost of treating arthritis patients relates to treatment of the side effects of NSAIDs. The conservative calculations estimate that approximately 1,07,000 patients are hospitalized annually for non-steroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications, and at least 16,500 NSAID-related deaths occur each year by arthritis patients alone. The figures for all NSAID users would be overwhelming. Surprisingly, the management of this problem has undergone little change in the last 50 years, and is not only frequently under-diagnosed but also under-treated. Indian studies have shown that NSAIDs are among the most common drugs responsible for
adverse drug reactions seen in clinical practices\(^1\). In general, at least 10 to 20 percent of patients have dyspepsia while taking a NSAIDs and prevalence may range from 5 to 50 percent. Within a six-month period of treatment, 5 to 15 percent of patients with rheumatoid arthritis can be expected to discontinue NSAID therapy because of dyspepsia. Incidence of new ulcers is range from 10-40\% for gastric ulcers and 5-15\% for duodenal ulcers. Most patients are, however, asymptomatic. According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS); 13 of every 1,000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication and the risk of osteoarthritis is 7.3 per 1,000 patients\(^2\)\(^3\).

2.1.1 Mechanisms of NSAIDs-Induced Gi ulcerations
What causes ulceration is precisely unknown. It is believed to occur as the result of a complex interplay of aggravating factors and protective factors. Prostaglandins (PGs) have long been known to be mucoprotective and ulcer healing agents. Prostaglandins protect GI mucosa by forming a cytoprotective layer and increasing the secretion of bicarbonate ions that neutralize the gastric acidity. All therapeutically useful NSAIDs act by inhibiting the synthesis of PGs\(^4\). Gastric damage by these agents can be brought about by at least two distinct mechanisms. Local irritation by orally administered drug, allows back diffusion of acid into the gastric mucosa and induces tissue damage. The parenteral administration also can cause damage and bleeding, correlated with inhibition of the biosynthesis of gastric prostaglandins, especially PGI2 and PGE2 that serve as cytoprotective
agents in the gastric mucosa. These eicosanoids, inhibits acid secretion by
the secretion of cytoprotective mucus in the intestine; inhibition of their
synthesis may render the stomach more susceptible to damage\(^5\)\(^{26}\). Recent
studies have shown that use of multiple NSAIDs; non-use of anti-ulcer
medication, and NSAID use in patients with previous history of peptic ulcers
raises the possibility of developing GI ulcers by 14-17 folds\(^27\).

2.1.2 Classification of NSAIDs

A proposed classification based on their chemical class and plasma half-
lives\(^28\)\(^{29}\).

**Carboxylic Acid**

**Salicylic acids and esters**

Asprin, Diflunisal, Benorylate, Trisalicylate, Sodium salicylate

**Acetic acid**

**Phenylacetic acids**

Diclofenac, Aceclofenac, Fentizac, Fenclofenac

**Carbo and hetrocyclic acids**

Etodolac, Indomethacin, Sulindac, Tolmetin, Tenidep, Zomepirac,
Clopirac, Ketorolac, Tromethamine

**Propionic acids**

Carprofen, Fenbufen, Flurbiprofen, Ketoprofen, Oxaprozin, Suprofen,
Tiaprofenic acid, Ibuprofen, Naproxen, Fenoprofen, Indoprofen,
Benoxaprofen, Pirprofen

**Fenamic acids**

Flufenamic, Mefenamic, Meclofenamic, Niflumic
Inolic acid
Pyrazolones
   Oxyphenbutazone, Phenylbutazone, Azapropazone, Feprazone
Oxicams
   Piroxicam, Sudoxicam, Isoxicam, Tenoxicam, Meloxicam
Nonacidic compounds
   Nabumetone, Proquazone, Fluproquazone, Tiaramide, Befexamac,
   Flunizole, Epirazole, Tinoridine
Diaryl-substituted furanones
   Rofecoxib
Diaryl-substituted pyrazoles
   Celecoxib
Sulfonanilides
   Nimesulide
2.2 Aceclofenac
2.2.1 Description

Nomenclature

Systematic chemical name
   (2-{(2, 6-dichlorophenyl) amino} Phenylacetoxyacetic acid),

Proprietary names
   Aceclo; Acent; Aroff; Dolokind; Dolokind-SR; Hinac; Isiko; Aceclo plus;
   Acenac; Acent-P; Acent-SPD; Aroff-plus; Asten-P; Catrix-P;
   Dolokind-Plus; Dolokind-AA; Dolokind-MR; Zinase-A; Zinase-AP etc.
2.2.2 Formulae

Empirical formula, molecular weight

C16H13Cl2N04 [MW = 354.2]

Structural formula

![Structural formula of Aceclofenac]

2.2.3 Appearance

Aceclofenac is white crystalline powder, which is practically odorless.

2.2.4 Uses and applications

Aceclofenac is a non-steroidal anti-inflammatory drug which acts specifically on inflammatory sites and thereby decreases the inflammation. It is highly effective as an anti-inflammatory drug for various inflammatory conditions.

2.2.5 Physical Properties

Solubility characteristics

It is freely soluble in ethanol, methanol, acetone, dimethylformamide and practically insoluble in water.

2.2.6 Mechanism of action

2.2.6.1 Aceclofenac directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-Beta & TNF in the inflammatory cells (Intracellular Action).

Aceclofenac and 4'- hydroxy aceclofenac are the major compounds in human blood after the administration of aceclofenac. Aceclofenac has demonstrated to inhibit cyclooxygenase (COX) activity and to suppress the
PGE2 production by inflammatory cells, which are likely to be a primary source of PGE2. Inflammatory cells release IL-1 and TNF, which produce PGE2 by induction of COX-2. Aceclofenac and 4'-hydroxyaceclofenac penetrates the inflammatory cells like polymorphonuclears, monocytes and rheumatoid synovial cells. Inside the inflammatory cells aceclofenac and 4'-hydroxyaceclofenac gets hydrolyzed to the active metabolites diclofenac and 4'-hydroxydiclofenac which inhibit IL-1 and TNF released by the inflammatory cells and therefore suppresses production of PGE2 at the site of inflammation\textsuperscript{34, 35}.

2.2.6.2 Aceclofenac stimulates the synthesis of the extracellular matrix of the human articular cartilages

Aceclofenac blocks degeneration and stimulates synthesis of extracellular matrix of cartilages by inhibiting the action of different cytokines.
Aceclofenac and the metabolites inhibit IL-6 production by human chondrocytes. This leads to inhibition of increase of inflammatory cells in synovial tissue, inhibition of IL-1 amplification, inhibition of increased MMP synthesis and thus ensuring proteoglycan production. Aceclofenac also inhibits IL-1 and TNF production by human chondrocytes, inflammatory cells and synovial cells and therefore blocks suppression of GAG and collagen synthesis and stimulates growth factors mediated synthesis of GAG and collagen.

4'-hydroxyaceclofenac a metabolite of aceclofenac inhibits pro MMP1 and pro MMP3 produced by synovial cells (Rheumatoid Synovial Cells) in serum and in synovial fluid and thus inhibits progressive joint destruction by MMPs36-37.
2.2.6.3 Aceclofenac inhibits neutrophil adhesion & accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of neutrophils. It has been recently postulated that some non-steroidal anti-inflammatory drugs (NSAIDs) are able to induce the shedding of L-selectin in neutrophils, an adhesion molecule that plays an essential role in the inflammatory responses. Aceclofenac is a molecule with diphenylamine as its structural core. Diphenylamine is the core structure responsible for the anti-L-selectin activity seen with aceclofenac. Aceclofenac induces proteolytic-shedding of L-selectin in neutrophils leading to inhibition of transmigration of neutrophils into inflamed tissue and therefore blocks adhesion and accumulation of neutrophils in inflamed tissue. This property contributes to the anti-inflammatory action of aceclofenac\(^{38}\).
2.2.6.4 Aceclofenac is also an NSAID with greater COX-2 specificity when compared to diclofenac sodium. Recent studies have shown aceclofenac to have the highest COX-1: COX-2 IC50 ratio a range of agents, including rofecoxib, celecoxib, nimesulide, diclofenac and tenoxicam39-40.

<table>
<thead>
<tr>
<th>COMPARISON : COX-SPECIFICITY</th>
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<tr>
<td><strong>ACECLOFENAC</strong></td>
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<tr>
<td>COX-1 IC50 = 100 micro M</td>
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<tr>
<td>COX-2 IC50 = 0.77 micro M</td>
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<tr>
<td>Ratio = 129</td>
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2.2.7 Pharmacokinetics and bioavailability

2.2.7.1 Pharmacokinetics

After oral administration, aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak plasma concentrations are reached approximately 1.25 to 3 hours following ingestion. T_{max} is delayed with concomitant food intake whereas the degree of absorption is not influenced. Distribution: Aceclofenac is highly protein-bound (>99.7%). Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 60% of those in plasma. The volume of distribution is approximately 30 L.

The mean plasma elimination half-life is 4 - 4.3 hours. Clearance is estimated to 5 litres per hour. Approximately two-thirds of the administered dose is excreted via the urine, mainly as conjugated hydroxymetabolites. Only 1% of an oral single dose is excreted unchanged. Aceclofenac is
probably metabolized via CYP2C9 to the main metabolite 4-hydroxyaceclofenac whose contribution to the clinical activity probably is negligible. Diclofenac and 4-hydroxydiclofenac have been detected amongst many metabolites.

Characteristics in patients: No changes in the pharmacokinetics of aceclofenac have been detected in the elderly. A slower rate of elimination of aceclofenac has been detected in patients with decreased liver function after a single dose of aceclofenac. In a multiple dose study using 100 mg once daily, there was no difference in the pharmacokinetic parameters between subjects with mild to moderate liver cirrhosis and normal subjects. In patients with mild to moderate renal impairment no clinically significant differences in the pharmacokinetics were observed after a single dose.\textsuperscript{41-44}

2.2.7.2 Clinical studies

Aceclofenac is a novel NSAID indicated for the symptomatic treatment of pain and inflammation in acute, sub-chronic and chronic inflammatory conditions. Aceclofenac is rapidly and efficiently absorbed after oral administration, with an associated half-life of 4 hours.

Aceclofenac because of its analgesic and anti-inflammatory properties with excellent safety profile has been widely studied for providing symptomatic relief in a variety of painful conditions.

Numerous double-blind, randomized, comparative clinical trials are established the efficacy and tolerability of aceclofenac compared with diclofenac, ketoprofen, indomethacin, naproxen, piroxicam and tenoxicam in the treatment of Ankylosing Spondylitis, Osteoarthritis and Rheumatoid
arthritis. Aceclofenac has shown to be also effective in acute painful conditions as well as conditions involving dental and gynaecological pain.

Large experience studies in everyday practice enable validation of the drug's clinical profile of efficacy and tolerability in clinical settings that reflect how physicians and patients actually use the drugs. The European Observational Cohort study, a pan European study involving 23,407 patients with pain due to various inflammatory or degenerative rheumatic diseases (Post traumatic pain, Low back pain, Cervical pain, Ankylosing spondylitis, Rheumatoid arthritis and Osteoarthritis) was undertaken to validate the efficacy and patient acceptability of aceclofenac. The study was performed to provide practical experience with aceclofenac, observing a large number of patients with acute and chronic inflammatory pain, and to evaluate patient and physician satisfaction with aceclofenac therapy.

Recent systematic reviews of randomized clinical trials have concluded that they are effective for short term symptomatic relief of acute low back pain, and that the various types of NSAIDs were equally effective. However, NSAIDs are associated with high incidence of GI side effects, which may lead to discontinuation of treatment. Newer NSAIDs, such as aceclofenac do however, exhibit better safety and tolerability profiles than older formulations.

2.2.8 Toxicity

The relative gastrointestinal toxicity of NSAIDs in normal clinical practice showed that individual risks for each NSAID were dose dependent. Ketorolac was associated with the highest risk estimate (24.7; 95% CI 8.0, 77.0). For newer NSAIDs, the risks were as follows: aceclofenac 1.4 (95% CI
0.6, 3.3), celecoxib 0.3 (95% CI 0.03, 4.1), dexketoprofen 4.9 (95% CI 1.7, 13.9), meloxicam 5.7 (95% CI 2.2, 15.0), nimesulide 3.2 (95% CI 1.9, 5.6) and rofecoxib 7.2 (95% CI 2.3, 23.0). The risk was significantly increased in patients with a history of peptic ulcer and/or upper gastrointestinal bleeding, and in those taking antiplatelet drugs. Other side effects of aceclofenac are indigestion, heartburn, dyspepsia, diarrhoea, nausea, abdominal pain and flatulence.

Aceclofenac is contraindicated in the following situations:

- Patients previously sensitive to aceclofenac.
- Patients in whom substances with a similar action (e.g. aspirin, or other NSAIDs), precipitate attacks of asthma, bronchospasm, acute rhinitis or urticaria or patients hypersensitive to these drugs
- Patients with active or suspected peptic or duodenal ulcer or history of recurrent peptic or duodenal ulcer or who have gastrointestinal bleeding or other active bleedings or bleeding disorders
- Patients with severe heart failure or severely impaired hepatic or renal organ function - during the last three months of pregnancy.$^{45-55}$

2.2.9 Special warnings and special precautions for use

Aceclofenac should be administered with caution and under close medical surveillance to patients suffering from gastro-intestinal disease and to those with a history of peptic ulceration, cerebro-vascular bleeding, ulcerative colitis, Crohn's disease, SLE, porphyria, hematopoietic- or coagulation-disorders. Caution should be exercised in patients with mild to moderate impairment of hepatic, renal or cardiac function as well as in patients with
other conditions predisposing to fluid retention. In these patients, the use of NSAIDs may result in deterioration of renal function and fluid retention. Caution is also required in patients with diuretic treatment or otherwise at risk of hypovolemia. Caution should be exercised in the treatment of elderly patients, who are generally more prone to adverse reactions. The consequences, e.g. gastrointestinal bleeding and/or perforation, are often more serious and may occur without warning symptoms or previous history, at any time during treatment. Elderly patients are more likely to be suffering from impaired renal, cardiovascular or hepatic function. All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts).

2.2.10 Interaction with other medicinal products

No pharmacokinetic interaction studies have been performed, except with warfarin. Aceclofenac is metabolized through cytochrome P450 2C9 and a risk of pharmacokinetic interaction is therefore possible with phenytoin, digoxin, cimetidine, tolbutamide, phenylbutazone, amiodarone, miconazole and sulphaphenazole. As with other products within the NSAID-group, there also exists a risk of pharmacokinetic interactions with other drugs eliminated by active renal secretion, such as methotrexate and lithium. Aceclofenac is bound practically completely to plasma albumin and consequently the possibility of displacement interactions with other highly protein bound drugs must be borne in mind. Due to the lack of pharmacokinetic interaction studies the following is based upon knowledge from other NSAID’s.
2.3 Tizanidine hydrochloride

2.3.1 Description

Nomenclature

Systematic chemical name
5-chloro-4-(2-imidazolin-2-ylamino)-2, 1, 3-benzothiazole\textsuperscript{62}

Proprietary names
Sirdalud; Tizan; Tizpa; Zatru, Astnim-MR; Avolide T; Bestogesic MR;
Bionim-MR; Brutiz; Bruzen-MR; Canmet MR; Citantz; Combidin.

2.3.2 Formulae

Empirical formula, molecular weight
\[ \text{C}_9\text{H}_8\text{ClN}_2\text{S} \cdot \text{HCl}, (290.2) \]

Structural formula\textsuperscript{62,63}

\begin{center}
\includegraphics[width=0.5\textwidth]{structural_formula.png}
\end{center}

2.3.3 Appearance

Tizanidine HCl is a white to off-white, fine crystalline powder, odorless or
with a faint characteristic odor. It is slightly soluble in water and methanol;
solubility in water decreases as the pH increases\textsuperscript{62,63}.

2.3.4 Uses and applications

Tizanidine is a relatively new treatment for spasticity, indicated for use in
spasticity associated with multiple sclerosis or spinal cord injury or disease.
Evidence is now emerging that tizanidine may also have a role to play in the
treatment of other conditions associated with muscle spasm.
2.3.5 Solubility characteristics

It is slightly soluble in water and methanol; solubility in water decreases as the pH increases.

2.3.6 Mechanism of action

The imidazoline derivative, tizanidine, is a centrally acting muscle relaxant that reduces muscle tone in conditions associated with spasticity, such as multiple sclerosis, stroke and spinal cord injury. An agonist at spinal and supra-spinal alpha 2 receptors, its actions include directly reducing motor neuron excitation by inhibiting the release of excitatory amino acids from spinal neurons, and indirectly reducing spinal transmission by inhibiting facilitatory noradrenergic descending pathways.

At doses effective in animal models of spasticity, tizanidine exerts a dose-dependent inhibition of polysynaptic spinal reflexes, with little effect on monosynaptic reflexes. Tizanidine has no direct effect on skeletal muscle or the neuromuscular junction. Tizanidine has also been found to have dose-dependent activity in animal models of pain. Its mechanism of action is central and may involve the same central inhibitory effects that reduce spasticity: noradrenergic pathways that descend from the locus coeruleus also regulate the transmission of pain impulses. The effects of tizanidine appear to be mediated by alpha2 receptors, not opioid receptors. This action may involve inhibition of the release of the amino acid neurotransmitters, glutamate and aspartate, or inhibition of the release of Substance P, a transmitter in afferent pain neurons. Although tizanidine is structurally related to clonidine it has substantially less activity on the cardiovascular system\textsuperscript{64,65}. 
2.3.7 Pharmacokinetics and clinical efficacy

Tizanidine is rapidly absorbed after oral administration. It undergoes first-pass hepatic metabolism and its bioavailability is 34 per cent. Maximum plasma concentrations are achieved after approximately one hour. Tizanidine readily crosses the blood-brain barrier and is only 30 per cent protein-bound. Its elimination half-life is two to four hours; the metabolites, none of which are pharmacologically active, are largely excreted in the urine. The clearance of tizanidine is reduced up to three-fold in elderly patients.76,77

2.3.8 Clinical studies

In clinical trials, tizanidine significantly reduced muscle tone and improved spasticity and clonus without impairing muscle strength.63 A meta-analysis of 10 randomised double-blind trials, involving 270 patients with multiple sclerosis or cerebrovascular lesions, showed that tizanidine (4-32mg daily) was as effective as baclofen (10-90mg daily) and diazepam (5-40mg daily) in improving muscle tone; the greatest improvements in muscle strength occurred in patients treated with tizanidine.68 This analysis confirmed the findings of a pooled analysis of 20 comparative studies involving 777 patients.68 The effects were sustained in long term non-comparative studies of up to 36 months.63 In patients with spasticity secondary to stroke, treatment with tizanidine reduced muscle tone in 81 per cent of patients without impairing muscle strength.69 There was a significant improvement in pain scores, although the reduction in pain frequency was not statistically significant. Several published uncontrolled studies, as well as ongoing clinical trials, suggest that tizanidine may be effective in relieving pain.
associated with a range of disorders, including myofascial pain, refractory pain and neuropathic pain, chronic tension-type headache and chronic daily headache. Tizanidine may also be a useful adjunct to NSAIDs in the treatment of analgesic rebound headache.

2.3.9 Toxicity

Tizanidine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

2.3.9.1 More common

Chest pain or discomfort, fever, loss of appetite, nausea and/or vomiting, lower back or side pain, nervousness, pain or burning while urinating, painful or difficult urination, sores on the skin, tingling, burning, or prickling sensations, unusual tiredness, yellow eyes or skin

2.3.9.2 Less common

Black, tarry stools, bloody vomit, blurred vision, chills or sore throat, coldness, convulsions (seizures), cough or hoarseness, dark urine, dry, puffy skin, eye pain, fainting, influenza (flu)-like symptoms, irregular heartbeat, kidney stones, persistent anorexia, pruritus, right upper quadrant tenderness, seeing things that are not there, shortness of breath, slow or irregular heartbeat, unusual tiredness or weakness, weight gain.

2.3.9.3 Incidence not known

Continuing vomiting, general feeling of tiredness or weakness, headache and light-colored stools
2.3.9.4 Symptoms of overdose
Blurred vision, change in consciousness, chest pain or discomfort, confusion, decreased awareness or responsiveness, difficult or troubled breathing, dizziness, faintness or light headedness when getting up from a lying position, irregular, fast or slow, or shallow breathing, lightheadedness, dizziness or fainting, loss of consciousness, pale or blue lips, fingernails, or skin; severe sleepiness, shortness of breath, sleepiness or unusual drowsiness, slow or irregular heartbeat, sweating and unusual tiredness or weakness.

2.3.10 Drug interactions\(^66\)

2.3.10.1 Oral contraceptives
One potentially important pharmacokinetic interaction has been identified to date. The clearance of tizanidine is reduced by 50 per cent in women using oral contraceptives; therefore, these patients may require lower doses.

2.3.10.2 Pharmacodynamic interactions
The pharmacodynamic interactions reported with tizanidine include potentiation of the hypotensive effects of antihypertensive drugs (including diuretics) and possible additive effects with alpha\(_2\) agonists or digoxin that may cause bradycardia or hypotension. Care should be taken if tizanidine is taken concurrently with drugs known to prolong the QT interval.

2.3.10.3 Alcohol and sedatives
The sedative effects of tizanidine may be enhanced by alcohol and sedatives. Concurrent use of centrally acting drugs with hallucinogenic
potential, such as antidepressants, increases the risk of hallucinations during treatment with tizanidine.

2.4 Nimesulide

2.4.1 Description

Nomenclature

Systematic chemical name

4'-Nitro-2'-phenoxyethanesulphonanilide

N-(4-Nitro-2-phenoxyphenyl)ethanesulfonamide

4-nitro-2-phenoxyethanesulfonanilide

(Methylsulfonyl)(4-nitro-2-phenoxyphenyl)amine

Nonproprietary names

Nimesulide

Proprietary names

Algolider; Antifloxil; Aulin; Eudolene; Fansidol; Flogovital; FlOLID; Guaxan; Laidor; Ledoren, Ledoven; Mesid; Mesulid; MFNide; NIDOL; Nimedex; Nimesulene; Nims; Nimulid; Nisal; Nisulid; Remov; Resulin;

2.4.2 Formula

Empirical formula, molecular weight

C13H12N2O5S [MW = 308.31]

Structural formula

![Structural formula image]
2.4.3 Elemental analysis

The calculated elemental composition is as follows:

- Carbon: 50.64%
- Hydrogen: 3.92%
- Oxygen: 25.95%
- Nitrogen: 3.92%
- Sulfur: 10.40%

2.4.5 Appearance

Nimesulide is a light yellow crystalline powder, which is practically odorless.

2.4.6 Uses and applications

Nimesulide has analgesic, anti-inflammatory, and antipyretic properties, acting as an inhibitor of prostaglandin synthetase and platelet aggregation. It is given in doses of up to 200 mg twice daily by mouth for inflammatory conditions, fever, and pain.

2.4.7 Physical properties

2.4.7.1 Ionization constants

Nimesulide is characterized by a single ionization constant associated with dissociation of the -NH proton of the sulfonanilide group. Various pKa values have been reported in the literature: 5.984, 6.4685, 6.5086, and 6.5687. These values clearly indicate the acidic nature of the drug.

2.4.7.2 Solubility characteristics

Nimesulide is soluble in moderately polar solvents such as dichloromethane and acetone. The solubility is diminished in solvents of high polarity such as methanol. The solubility of Nimesulide in water is reported to be...
0.01 mg/mL\textsuperscript{68,69}, which becomes enhanced by an increase in the pH of the aqueous solution. This is essentially due to deprotonation and ionization of the sulfonanilide group.

2.4.7.3 Partition coefficient

The octanol/water partition coefficient of Nimesulide is 238, corresponding to a log P value of 2.376\textsuperscript{60}. A value of this magnitude clearly demonstrates the lipophilic character of the drug.

2.4.8 Pharmacokinetics and bioavailability

2.4.8.1 Pharmacokinetics

The pharmacokinetics of Nimesulide has been extensively investigated\textsuperscript{91-104}. Studies have been carried out following oral or rectal administration in healthy volunteers, pediatric patients, patients with predisposition for altered pharmacokinetics, and in the elderly. Bernareggi\textsuperscript{97} has carded out a detailed clinical pharmacokinetic study of Nimesulide, and has reported that oral administration of Nimesulide tablet, granule, or suspension form in healthy human volunteers resulted in a rapid and extensive absorption of the drug. The mean peak concentration of 2.86 to 6.50 mg/L was reached within 1.22 to 2.75 hours of administration. The presence of food did not reduce either the rate or extent of absorption. Nimesulide is rapidly distributed and has an apparent volume of distribution ranging between 0.18 and 0.39 L/kg. The established mean terminal elimination half-life varied from 1.80 to 4.73 hours.

Excretion of the unchanged drug in urine and feces is reported to be negligible. It is largely eliminated via its metabolites 50.5 to 62.5% in the
urine and 17.9 to 36.2% in feces. The total plasma clearance of Nimesulide is reported to be 31.02 to 106.16 mL/h/kg, reflecting almost exclusive metabolic clearance. The pharmacokinetic profile of the drug in children and the elderly is not different from that of young healthy individuals. However, hepatic insufficiency is reported to remarkably reduce the rate of elimination of the drug necessitating a dose reduction (4 to 5 times) in patients with hepatic impairment. Moderate renal failure does not alter the pharmacokinetic profile of the drug. Pharmacokinetic interaction between Nimesulide and other drugs given in combination such as glibenclamide, cimetidine, furosemide, theophylline, warfarin, digoxin, and antacids were reported to be absent or of no apparent clinical relevance. In another study Gandini et al. have carried out first dose and steady state pharmacokinetics of Nimesulide and its 4-hydroxy metabolite in healthy volunteers. After a single dose of 200 mg, peak plasma concentration of Nimesulide (9.85 μg/mL) were reached at 3 to 7 hours and the half-life during the elimination phase was 4.95 hours. Plasma concentration on the seventh day, predicted from the results of the first day, was similar to the measured values. The study pointed out that pharmacokinetics of Nimesulide or its metabolite after single or repeated dose were not time or dose dependent.

Sengupta et al. studied the analgesic efficacy and pharmacokinetics of topical Nimesulide gel in healthy human volunteers and carried out a double-blind comparison with piroxicam, diclofenac, and placebo. Nimesulide exhibited better efficacy than did diclofenac, piroxicam, and placebo. The
superior analgesic activity of Nimesulide as gel formulation correlated with its pharmacokinetic profile. The study concluded that the topical route of administration may be a safe and effective alternative to the presently used oral or related routes. Study of the pharmacokinetic profile of a parenteral formulation of Nimesulide demonstrated that Nimesulide intramuscularly administered may be superior to other routes of administration when fast onset of action is required\(^{105}\). A summarized version of the pharmacokinetic profile of Nimesulide in different dosage forms has been presented by Singla and coworkers\(^{106}\). In a review, Rainsford\(^{107}\) analyzed the relationship of Nimesulide safety to its pharmacokinetics and concluded that Nimesulide is associated with a relatively low occurrence of adverse drug reactions, especially in the gastrointestinal tract. The reactions in the liver are within or below the general incidence with other NSAIDs'.

2.4.8.2 Bioavailability

The bioavailability of Nimesulide has been studied in healthy volunteers\(^{97,108}\). A single 100-mg oral dose of nimesulide was given to the volunteers in the form of conventional tablets, mouth-dissolving tablets or as a suspension in randomized crossover study by scientists Jovanovic D et al.\(^{109}\). The plasma concentration of Nimesulide was assayed by high performance liquid chromatography. Only a 90% confidence interval for the relative differences of log-transformed AUC (0-infinity) values of nimesulide absorbed from mouth dissolving tablets vs. suspension was included in the 80% to 125% interval proposed by the Food and Drug Administration (FDA). On that basis,
mouth-dissolving tablets (Nimulid-MD) were considered bioequivalent to Nimulid suspension according to the extent of drug absorption. Concerning the comparable amounts of nimesulide available in the systemic circulation after application of these formulations the one might not expect therapeutic failure after switching the patient from one to another.

Bernareggi\textsuperscript{97} has reported that when Nimesulide was administered in suppository form, the Cmax was lower and occurred later than after oral administration. The bioavailability of Nimesulide via suppository administration ranged from 54 to 64% relative to that of orally administered formulations.

2.4.9 Protein binding

Bree et al.\textsuperscript{110} have carried out a detailed equilibrium dialysis study of the binding of Nimesulide within human serum to isolated proteins and to erythrocytes. Within the range of therapeutic concentrations, Nimesulide was 99% bound to serum involving a non-saturated process (NKA = 91). This binding was almost identical to binding of Nimesulide to serum albumin (NKA=95). Binding of Nimesulide to serum albumin was not affected by physiological concentrations of free fatty acids. The retention of Nimesulide by erythrocytes suspended in buffer was moderate (67%), although in whole blood no erythrocyte binding was observed because of the greater affinity of this drug for serum. Over the range of therapeutic concentrations (25 to 63 pmol/L) the free fraction of Nimesulide in serum remains constant. Serum binding was decreased in samples obtained from patients with renal failure or hepatic cirrhosis associated with hypoalbuminemia and
hyperbilirubinemia, respectively. The binding of Nimesulide at therapeutic concentrations was unaffected by warfarin, cefoperazone, furosemide, glibenclamide, tamoxifen, or digitoxin. However, valproic acid\textsuperscript{110}, fenofibrate\textsuperscript{108, 110}(80 gmoi/L), salicylic acid\textsuperscript{108}, tolbutamide\textsuperscript{108} may displace Nimesulide on concurrent administration. It was reported that the principal metabolite of Nimesulide 4-hydroxy- Nimesulide, significantly increased the free fraction of the drug. Although methotrexate had no effect on the free fraction of Nimesulide, the free fraction of methotrexate was significantly increased in the presence of Nimesulide. It was also demonstrated by the study that there are two distinct Nimesulide binding sites, site I and site II, on serum albumin (10 gmoi/L) with different affinities: site II \( K_A = 3.57 \times 10^5 \) L/tool and site I \( K_A = 1.24 \times 10^5 \) L/tool. It was indicated that Nimesulide binds to site II with higher affinity and to a lesser extent to site I. Bernareggi\textsuperscript{97} has also reported that Nimesulide is extensively bound to albumin; the unbound fraction in plasma being 1%. The unbound fraction increased to 2 and 4% in patients with renal or hepatic insufficiency.

2.4.10 Toxicity

Nimesulide is the leading molecule of a new class of sulfonanilides among non-steroidal anti-inflammatory drugs that has shown a significant inhibitory selectivity towards cyclooxygenase-2 without affecting cyclooxygenase-1. This results in equivalent efficacy against pain and inflammation but with a better safety profile\textsuperscript{111}. Nimesulide appears to be particularly useful for patients who have allergic hypersensitivity to aspirin or NSAIDs. Studies have suggested Nimesulide as an alternative treatment in NSAIDs intolerant
patients. There are very few reports of toxicity or adverse effects of Nimesulide. Though well-documented cases of acute hepatitis have not yet been reported with this drug, there is one report on a 54-year-old Arabic woman treated with nimesulide for chronic low back pain was admitted to the hospital with acute hepatitis confirmed by biopsy. Her liver function test results returned to normal within one month after nimesulide discontinuation. From clinical and histological data, it appears that both immunological and metabolic idiosyncratic reactions can be invoked as pathogenic mechanism of Nimesulide-induced liver disease. Although thrombocytopenia is a common feature in patients infected with HIV, one group of workers considered that thrombocytopenia in one of their patients was related to the use of Nimesulide. A study has provided evidence that atopy and history of allergic reactions to antimicrobial drugs increase the likelihood of intolerance of Nimesulide in subjects allergic to NSAID's.

2.5 Ethylcellulose

2.5.1 Description

**Synonym**: Ethocel, ETS, Cellulose ethyl.

**Nonproprietary Names**

BP: Ethylcellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose
2.5.2 Formula

Structural formula

2.5.3 General properties

2.5.3.1 Description

Tasteless, free-flowing, white to light tan powder.

2.5.3.2 Solubility

Insoluble in water, glycerin and propylene glycol. Soluble in varying degrees in certain organic solvents depending upon the ethoxyl content. The addition of 10-20% of a lower aliphatic alcohol to solvents, such as ketones, esters and hydrocarbons, can improve the solubility.

2.5.3.3 Grades

Ethocel is available in six grades from standard 4 to 100. The numbers representing viscosity of 5% w/v solutions in toluene: ethanol (80:20) in CP.

2.5.4 Physical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethoxy content</td>
<td>47 – 48%</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.14</td>
</tr>
<tr>
<td>Glass transition temperature</td>
<td>120°C</td>
</tr>
<tr>
<td>Specific volume in solutions</td>
<td>23.9 (in³/lb)</td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.47</td>
</tr>
</tbody>
</table>
2.5.5 Incompatibilities

Incompatible with paraffin wax and microcrystalline wax\(^{117}\).

2.5.6 Health and safety:

Toxicity data

Oral-rat LD\(_{50}\) > 5gm/Kg

Skin-rabbit LD\(_{50}\) > 5gm/Kg

Irritation data

Skin-rabbit LD\(_{50}\) 500mg/24 hour mild.

2.5.7 Stability and storage conditions

It is resistant to alkalis, both dilute and concentrated, and to salt solutions. It is more sensitive to acidic materials than are cellulose esters. However, the material can withstand dilute acids for a limited period of exposure. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by use of an antioxidant and a compound with light absorption properties between 230-340 nm. Ethyl cellulose should be stored between 7° and 32°C in a dry area away from all sources of heat. Store in a well-closed container\(^{118}\).

2.5.8 Applications

2.5.8.1 Binder in tablets

Ethyl cellulose may be blended dry and wet-granulated with a solvent such as alcohol. Tablets made with ethyl cellulose as a binder tend to exhibit extended release of drugs.
2.5.8.2 Coating material for tablets
Ethyl cellulose by itself forms a water-insoluble film coating. It is commonly used with hydroxypropyl methyl cellulose to alter the solubility of the film.

2.5.8.3 Coating material for stabilization:
Ethylcellulose coated microcapsules were used for the enhancement of stability of drugs like alkannin, shikonin against photo-oxidation\textsuperscript{119,120}.

2.5.8.4 Coating to prevent unpleasant taste
Microencapsulation not only renders sustained-release, but also decreases gastric irritation and masks the bitter taste of drugs. Ethyl cellulose may be used to mask the bitter taste of sparfloxacin, Bacampicillin hydrochloride and theophylline\textsuperscript{121-123}.

2.5.8.5 Coating for drug microcapsules
Ethyl cellulose has been extensively used for the reduction of extent and rate of drug absorption of drugs like diltiazem hydrochloride, bioadhesive microspheres of metronidazole encapsulation of a fungal lactase, controlled release of diltiazem hydrochloride, microspheres of oral vaccines of Actinobacillus pleuropneumoniae antigens, ketoprofen microspheres, Microencapsulation of aspirin, prolonged release of alachlor, slow the release of zidovudine, microencapsulation of the bacteria Pseudomonas fluorescens-putida\textsuperscript{124-132}.

2.5.8.6 Thickness agents in creams, lotions or gels
Ethyl cellulose may be used in these types of formulations, provided an appropriate solvent is used\textsuperscript{133}.
2.6 Cellulose acetate

2.6.1 Description

Nonproprietary Names

BP: Cellulose acetate
PhEur: Cellulosi acetas
USPNF: Cellulose acetate

Synonyms

Acetyl cellulose; cellulose diacetate; cellulose triacetate.

2.6.2 Formula

Structural Formula

\[ R \cdot H, COCH_3 \]

2.6.3 General properties

2.6.3.1 Description

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

2.6.3.2 Solubility

In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and
dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower-acetyl materials\(^{134}\).

### 2.6.3.3 Grade

Filtered and unfilteres. Also graded by percent combined acetic and content: Plastic 52-54%, lacquer 54-56%, film 55.5-56.6%, water resisting, 56.5-59%, triacetate 60.0-62.5%.

### 2.6.4 Physical properties

Good toughness, deep gloss, high impact strength, easy of fabrication, high transparency, a feel that can be described as 'natural'.

- **Specific gravity**: 1.32
- **Melting point**: 260°C
- **Density**: 1.27-1.34
- **Softening temperature**: 60-97°C

### 2.6.5 Incompatibilities

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.

### 2.6.6 Health and safety

Cellulose acetate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic and nonirritant material.

### 2.6.7 Stability and storage conditions

Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse
conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid\textsuperscript{135}.

\textbf{2.6.8 Applications in pharmaceutical formulation or technology}

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking. It is used as a semi-permeable coating on tablets, especially on osmotic pump-type tablets and implants. This allows for controlled, extended release of actives. Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems. Cellulose acetate and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics.

Cellulose acetate films are used in transdermal drug delivery systems and also as film coatings on tablets or granules for taste masking. For example, acetaminophen granules have been coated with a cellulose acetate-based coating before being processed to provide chewable tablets. Extended-release tablets can also be formulated with cellulose acetate as a directly compressible matrix former. The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to be insensitive to cellulose acetate molecular weight and particle size distribution. Therapeutically, cellulose acetate has been used to treat cerebral aneurysms, and also for spinal perimedullary arteriovenous fistulas\textsuperscript{136-146}.


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