CHAPTER II

REVIEW OF LITERATURE

The aetiology and pathogenesis of rheumatoid arthritis are still obscure, despite the immense efforts that have been made to elucidate them in both experimental and clinical researches. Endeavours to improve pharmacotherapy in this and other rheumatic diseases are therefore being concentrated mainly on a search for substances which markedly inhibit the inflammatory process and its consequences with the least undesirable effects. During the course of investigations, a very large number of o-aminophenyl-acetic acids were synthesized and evaluated for their pharmacological activities.

In the implementation of this broad programme of synthesis, care was taken to ensure that the basic principle of the molecule met the following requirements :

1. An acidity constant (pK_a) of 4-5
2. A partition coefficient P (n-octanol/aqueous buffer, pH 7.4) of approximately 10
3. Two aromatic rings twisted in relation to each other

The selection of these criteria were based on the structural and physico-chemical properties common to phenylbutazone, mefenamic acid, and indomethacin, all of which have proved clinically effective in the control of inflammation and pain.

Out of more than 200 analogues, it was diclofenac sodium that was found to exhibit the most interesting pharmacological properties. This compound fulfils the physico-chemical target criteria. (Menasse *et al.*, 1978)

Review of Diclofenac Sodium

Diclofenac sodium is a non-steroidal anti-inflammatory drug advocated for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. It was manufactured and marketed by Ciba-Geigy under the proprietary name Voltaren ®.

Physicochemical Properties

(Windholz *et al.*, 1983; Menasse *et al.*, 1978)

Chemically, diclofenac sodium is a phenylacetic acid derivative. The chemical name of diclofenac sodium is sodium[o-[(2,6-dichlorophenyl) amino] phenyl] acetate (Small, 1989) or sodium [2-[(2,6-dichlorophenyl] amino] benzene acetate. The chemical structure is shown in figure 1.

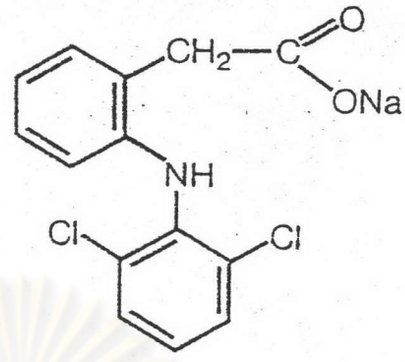

Figure 1 Diclofenac Sodium : sodium [O-[2,6-dichlorophenyl) amino]phenyl]acetate.

Description	:	White crystalline powder
Empirical Formula	:	$C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight	:	318.13
Melting Point	:	283-285°C
Chemical Properties	:	Diclofenac sodium has a pKa of 4.0 and a partition coefficient of 13.4; and the two aromatic rings are twisted in relation to each other (angle of torsion = 69°). The two chlorine atoms in the ortho-position of one of the phenyl rings cause maximum twisting of this ring.
Solubility	:	Diclofenac sodium is soluble in water, methanol and ethanol and insoluble in chloroform and acetone.

UV spectroscopy : Diclofenac sodium 1 mg% in 0.01 N sodium hydroxide in methanol has maximum absorption at wavelenght 281±1 nm.

Mode of Action and Pharmacology

Diclofenac acts within the cyclo-oxygenase pathway, as shown in Figure 2.

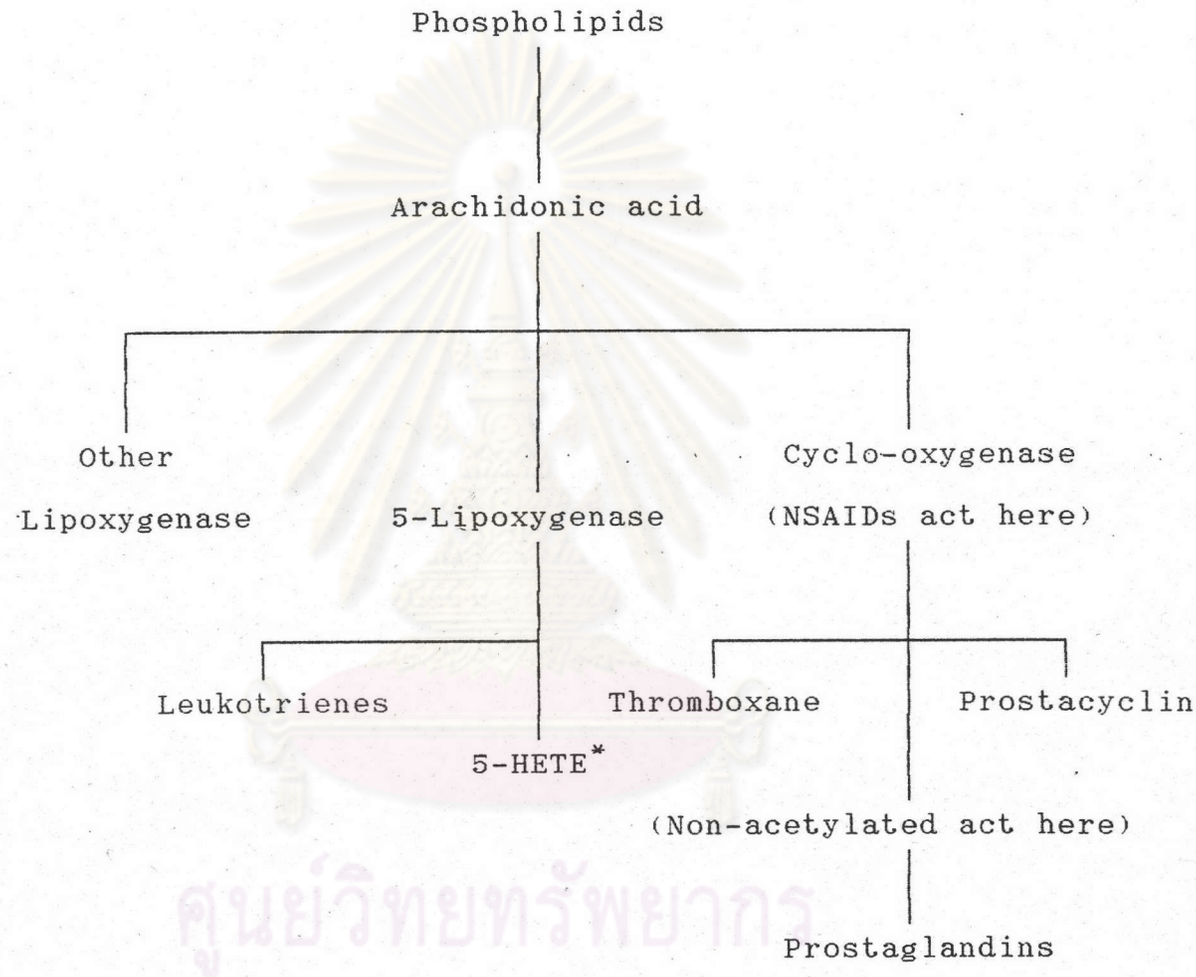

Figure 2 Arachidonic acid cascade

(*5-HETE = 5-hydroxyeicosatetranoic acid)

It competes with arachidonic acid in vitro and in vivo in a dose-dependent manner for binding to cyclo-oxygenase, which results in decreased formation of prostaglandin E_2, prostaglandin $F_{2\alpha}$, prostacyclin,

and thromboxane A_2. By inhibiting the production of these prostaglandins, diclofenac reduces the inflammation, swelling, and pain that accompany arthritis. The ability of diclofenac to reversibly inhibit platelet cyclo-oxygenase activity, as indicated by a reduction in serum thromboxane B_2 levels, is compared with that of other NSAIDs in Table 2. Thromboxane inhibition parallels serum drug concentrations and is reversible as a function of drug elimination.

Table 2 Reversible Inhibition of Platelet Cyclo-oxygenase Activity by Single Oral Doses of Nonsteroidal Anti-inflammatory Drugs in Humans.

Drug	Dose (mg)	% of Initial Enzyme Acitivity*		
		1 hr.	3 hr.	24 hr.
Indomethacin	75	2 ± 2	2 ± 1	50 ± 23
Naproxen	250	11 ± 3	12 ± 3	22 ± 12
Diclofenac Sodium	50	19 ± 7	34 ± 6	57 ± 3
Sulindac	200	38 ± 16	22 ± 2	62 ± 33
Piroxicam	20	68 ± 22	41 ± 16	27 ± 18
Ibuprofen	300	33 ± 14	12 ± 4	59 ± 39

* As reflected by changing in serum thromboxane E_2 concentration values are mean ± S.D. of five determinations.

In vitro, diclofenac is a potent reversible inhibitor of the secondary phase of platelet aggregation induced by adenosine diphosphate; however, at therapeutic doses in humans, it has little effect on bleeding time, platelet count, platelet adhesiveness, spontaneous platelet aggregation or activated partial thromboplastin time. The drug also affects polymorphonuclear leukocyte function in vitro, thereby reducing chemotaxis, superoxide toxic radical production, and neutral protease production.

Diclofenac has negligible effects on 5- and 15-lipoxygenase but still prevents the formation of 5-hydroxyeicosatetranoic acid and leukotrienes, which cause inflammation. Reduced availability of arachidonic acid due to its enhanced reincorporation into triglycerides has been identified as a mechanism that may be responsible for the reduced formation of leukotrienes.

Diclofenac has antipyretic and analgesic activities. It is active in suppressing inflammation in animal models, including paw edema induced by mustard, croton oil, kaolin, and carrageenan (Takashima *et al.*, 1972; Menasse *et al.*, 1978; Noguchi *et al.*, 1984). It also suppresses ultraviolet-induced erythema in guinea pigs and vascular permeability induced by human plague and cotton pellet granuloma formation in rats. (Peters *et al.*, 1977; Dorietto de Menezes and Catanzaro-Guimaraes, 1985) Diclofenac is effective in reducing

primary and secondary inflammation in adjuvant-induced arthritis in rats. In these animal studies, diclofenac demonstrated anti-inflammatory potency (weight for weight) equal to that of indomethacin, greater than that of ibuprofen, aspirin, and naproxen, and less than that of piroxicam.

Diclofenac is an effective analgesic that inhibits writhing induced by acetic acid, ethacrynic acid, phenylbenzoquinone, and yeast in rats and mice. It is also effective in raising the pain threshold of adjuvant-induced arthritis in rats. Diclofenac's analgesic activity in these tests is equal to that of indomethacin and piroxicam but greater than that of aspirin, ibuprofen, and naproxen. Plasma β-endorphin concentration in patients given diclofenac were increased nearly fourfold, while placebo had no effect; (Martini *et al.*, 1984) this effect may contribute to the drug's potent analgesic activity. In rats with yeast-induced fever, body temperature was reduced by 1.5°C with lower doses of diclofenac than required for aspirin, ibuprofen, indomethacin, and naproxen. Diclofenac has antipyretic activity similar to that of other commonly used NSAIDs. (Small, 1989)

Pharmacokinetic Properties

Absorption :

Bioavailability studies with single doses of oral and intravenous ^{14}C-labelled diclofenac indicate that the orally administered drug is almost totally absorbed (John, 1979; Kendall *et al.*, 1979; Riess *et al.*, 1978). However, diclofenac undergoes "first-pass" metabolism, with about 60% of the drug reaching systemic circulation in an unchanged form (John, 1979). Single doses of commercially available preparations are equally well absorbed whether administered orally as solution or enteric-coated tablets or rectally as suppositories. Diclofenac is also absorbed percutaneously and reaches systemic circulation when administered as an emulsified gel formulation.

Absorption is rapid after administration of the drug as an oral solution, rectally or intramuscularly, with peak plasma concentrations occurring within 10 to 30 minutes. With enteric-coated tablets peak concentrations are delayed until about 1.5 to 2.5 hours after ingestion in fasting subjects (Geiger *et al.*, 1975; Willis *et al.*, 1981). Food delays the absorption of diclofenac with the enteric-coated formulation, as passage of the drug to the site of dissolution, the small intestine, is slowed : peak plasma concentrations were attained 2.5 to 12 hours after ingestion (Willis *et al.*, 1981).

The mean peak plasma concentration (C_{max}) of unchanged drug was about 1 mg/L after administration of a single plain tablet of diclofenac 50 mg (John, 1979). This compares with about 1.5 mg/L with a 50 mg enteric-coated tablet (Willis and Kendall, 1978; Willis *et al.*, 1980; 1981) and 0.7 mg/L with a 50 mg film-coated tablet (Kozatani *et al.*, 1972). In vitro tests showed that complete dissolution of a 100 mg slow release diclofenac tablet takes as long as 17 hours. Thus, after administration to volunteers no clear peak plasma concentrations were observed, although at 2 hours after administration the plasma concentration was 0.09 mg/L (Dittrich and Brunner, 1981).

The peak plasma concentration and area under the plasma concentration-time curve (AUC) are linearly related to dose over the range of 25 to 150 mg after oral, rectal or intramuscular doses, indicating no saturation of distribution or metabolic processes at therapeutic dosages (John, 1979). Repeated doses of a 25 mg diclofenac, 3 times daily for 15 days had no significant effect on the pharmacokinetic behaviour of the drug relative to that of single doses (John, 1979; Willis *et al.*, 1981).

Distribution

Animal studies have shown that the highest concentrations of diclofenac are found, in descending order, in the liver, bile, kidneys, blood, heart and lungs (Reiss *et al.*, 1978). Diclofenac passes into the synovial fluid of patients with osteoarthritis and rheumatoid arthritis and is then eliminated over a longer period than that from plasma (Benson *et al.*, 1985; Fowler *et al.*, 1983). The peak concentration in synovial fluid is lower than that in plasma and is not achieved until about four hours after administration. After four hours, concentrations are much higher in synovial fluid than in plasma. Even though diclofenac has a relatively short elimination half-life in plasma (1.5 hours), the drug persists in synovial fluid (Willis and Simkin, 1983). Since this fluid is at the site of inflammation, persistence of drug may explain the extended duration of therapeutic effect after plasma concentrations have decreased.

Diclofenac, like all NSAIDs, is > 99.5% bound to human serum proteins, specifically albumin (Chamouard *et al.*, 1985). The drug binds to a high-affinity site, the benzodiazepine-binding site, and a low-affinity site, the warfarin site, on human serum albumin the volume of distribution of diclofenac is 0.12 to 0.17 L/kg (Willis *et al.*, 1979).

Diclofenac is metabolized in the liver by conjugation. The principal metabolite in humans, 4′-hydroxydiclofenac, has about 1/40 th of the activity of the parent compound against adjuvant-induced arthritis.

Diclofenac is eliminated by urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites (Sterlin and Faigle, 1979). Urinary excretion of 4′-hydroxydiclofenac accounts for 20-30% of the dose; biliary excretion of this metabolite accounts for 10-20%. The other metabolites excreted in urine 10-20% each; smaller amounts are excreted in bile. About 90% of an oral dose of diclofenac is excreted within 96 hours. The mean elimination half-life of unchanged drug is 1.2 to 1.8 hours.

Adverse Reaction

Gastrointestinal effects were the only common adverse effect frequently occured in patients taking diclofenac. Willkens reported in 1985 that appoximately 12.5% and 1.5% of patients had to discontinue the drug. Gastrointestinal reactions, CNS symptoms, allergic or local reactions, visual and hearing disturbances, and edema were also reported.

Diclofenac is contraindicated in patients who are hypersensitive to the drug. It should not be used in

patients who have had allergic reactions, including asthma or urticaria, after taking aspirin or other NSAIDs. Diclofenac should be used with caution in patients with a history of peptic ulcer disease, hypertension or congestive heart failure, liver dysfunction, impaired renal function, patients who are taking diuretics, and elderly patients.

Diclofenac has been shown to cross the placenta in rats and mice, but reproduction studies produced no evidence of teratogenicity. It should be safe to avoid this drug during the later stages of pregnancy and not recommended for use in nursing women (Small, 1979).

Drug Interactions

Concomitant administration of diclofenac and aluminum or magnesium hydroxide antacids may delay the absorption of diclofenac but does not affect the total amount of drug absorbed (Schumacher *et al.*, 1982).

Diclofenac inhibits renal prostaglandins, leading to a decrease in renal function. This may increase the renal toxicity of cyclosporine (Deray *et al.*, 1987), decrease the antihypertensive and diuretic effects of hydrochlorothiazide or furosemide (Koopmans *et al.*, 1987), decrease renal clearance of lithium (Reimann and Frolich, 1981), increase serum digoxin levels, and

decrease renal elimination of methotrexate (Daly *et al.*, 1986; Gambrielli *et al.*, 1987). Caution should be exercised when prescribing these drugs together, and serum drug concentrations should be monitored when appropriate.

Dosage and Administration

For rheumatoid arthritis, the dosage of diclofenac sodium is 150 to 200 mg daily administered as 50 mg t.i.d. or q.i.d. or 75 mg b.i.d.

For osteoarthritis, the dosage is 100 to 150 mg daily administered as 50 mg b.i.d. or t.i.d. or 75 mg b.i.d.

For ankylosing spondylitis, the dosage is 100 to 150 mg daily administered as 25 mg q.i.d. or 50 mg t.i.d. Doses should be administered with meals.

In children, the usual daily dosage is 2 to 3 mg per kg administered as 25 mg b.i.d. (15 to 30 kg), 25 mg t.i.d. (31 to 45 kg), or 50 mg b.i.d. (>45 kg). Diclofenac is not recommended for children under the age of 18 months.