3. Drug Profile

3.1. Diclofenac Sodium

Diclofenac Sodium is prototypical NSAID, a phenyl acetic acid derivative structurally related to meclofenamate sodium and mefenamic acid that was developed specifically as an anti-inflammatory agent [1].

3.1.1 General [2]

Name- Diclofenac Sodium

Chemical Formula- C_{14}H_{10}Cl_{2}NO_{2}.Na

IUPAC Name- 2-(2-(2, 6-dichlorophenylamino) phenyl) acetic acid, sodium.

Synonym- 2-[(2, 6-Dichlorophenyl)-amino]-benzeneacetic Acid, Sodium

Chemical Structure-

![Chemical Structure of Diclofenac Sodium]

Average Molecular Weight- 318.1

Melting Range- 281-284°C

Standards- Diclofenac Sodium contains not less than 99.0% and not more than 101.0% of diclofenac sodium.

Loss on Drying- Not more than 0.5% of its weight

Packaging and Storage- Preserve in light resistant containers, and store at controlled room temperature.
3.1.2. Pharmacokinetics Profile [3]

3.1.2.1 Absorption

*Bioavailability:* It is well absorbed following oral administration. It undergoes first-pass metabolism; only 50–60% of a dose reaches systemic circulation as unchanged drug. Peak plasma concentration usually attained within about 1 hour (diclofenac potassium conventional tablets), 2 hours (diclofenac sodium delayed-release tablets), or 5.25 hours (diclofenac sodium extended-release tablets). Absorbed into systemic circulation following topical administration as gel or transdermal system; plasma concentrations generally very low compared with oral administration.

Following application of a single diclofenac epolamine transdermal system to intact skin on the upper arm, peak plasma concentrations occur in 10–20 hours. Following topical application of diclofenac gel, peak plasma concentrations occur in about 10–14 hours.

Moderate exercise does not alter systemic absorption of topically applied diclofenac (transdermal system or 1% gel). Not established whether application of heat following gel application affects systemic absorption as application of a heat patch for 15 minutes before application of the 1% gel did not affect systemic absorption.

*Onset:* Single 50- or 100-mg doses of diclofenac potassium provide pain relief within 30 minutes.

*Duration:* Pain relief lasts up to 8 hours following administration of single 50- or 100-mg doses of diclofenac sodium.

*Food:* Food delays time to reach peak plasma concentration but do not affect extent of absorption following administration as conventional, delayed-release, or extended-release tablets.

3.1.2.2 Distribution

*Extent:* Following oral administration, concentrations in synovial fluid may exceed those in plasma.

*Plasma Protein Binding:* >99%.
3.1.2.3 Elimination

**Metabolism:** Metabolized in the liver via hydroxylation and conjugation. Some metabolites may exhibit anti-inflammatory activity.

**Elimination Route:** Excreted in urine (65%) and in feces via biliary elimination (35%) as metabolites

**Half-life:** Oral preparations: 1–2 hours. Diclofenac epolamine transdermal system: approximately 12 hours.

**Special Populations:**

In geriatric patients, pharmacokinetic profile similar to that in younger adults.

In patients with renal impairment, plasma clearance not substantially altered, although clearance of metabolites may be decreased.

3.1.2.4 Stability and Storage [4,5]

**Tablets:** tight containers at ≤ 30°C.

**Gel:** 25°C (may be exposed to 15 – 30°C). Do not freeze.

**Transdermal System:** 25°C (may be exposed to 15 – 30°C).

3.1.3. Pharmacodynamic Profile [4]

**Drug Category**

- Anti-Inflammatory Agents, Non-Steroidal
- Inhibits cyclooxygenase-1 (COX-1) and COX-2s
- Nonsteroidal Antiinflammatory Agents (NSAIDs)

**Pharmacology:** Diclofenac has analgesic, antipyretic and anti-inflammatory activities. Its potency against cyclooxygenase-1 (COX-1) and COX-2s is substantially greater than that of several other NSAIDs. Diclofenac is used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis.
**Mechanism of Action:** The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis.

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side-effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have, therefore, a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin [6].

The action of one single dose is much longer (6 to 8 hours) than the very short half-life that the drug indicates. This could be partly because it persists for over 11 hours in synovial fluids.

Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A\(_2\) as part of its mechanism of action. These additional actions may explain the high potency of diclofenac – it is the most potent NSAID on a broad basis. There are marked differences among NSAIDs in their selective inhibition of the two subtypes of cyclo-oxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side-effects of NSAIDs like aspirin. In practice, use of some COX-2 inhibitors with their adverse effects has led to massive numbers of patient family lawsuits alleging wrongful death by heart attack, yet other significantly COX-selective NSAIDs such as diclofenac have been well-tolerated by most of the population.

Besides the well-known and often-cited COX-inhibition, a number of other molecular targets of diclofenac that could contribute to its pain-relieving actions have recently been identified. These include:
• blockage of voltage-dependent sodium channels (after activation of the channel, diclofenac inhibits its reactivation also known as phase inhibition).

• blockage of acid-sensing ion channels (ASICs)

• positive allosteric modulation of KCNQ- and BK-potassium channels (diclofenac opens these channels, leading to hyperpolarization of the cell membrane)

Contraindications [7]:

• Hypersensitivity against diclofenac

• History of allergic reactions (bronchospasm, shock, rhinitis, urticaria) following the use of Aspirin or another NSAID

• Third-trimester pregnancy

• Active stomach and/or duodenal ulceration or gastrointestinal bleeding

• Inflammatory intestinal disorders such as Crohn's disease or ulcerative colitis

• Severe insufficiency of the heart (NYHA III/IV)

• Recently, a warning has been issued by FDA not to use to treat patients recovering from heart surgery

• Severe liver insufficiency (Child-Pugh Class C)

• Severe renal insufficiency (creatinine clearance <30 ml/min)

• Caution in patients with preexisting hepatic porphyria, as diclofenac may trigger attacks

• Caution in patients with severe, active bleeding such as cerebral hemorrhage

• NSAIDs in general should be avoided during dengue fever.

• On animals which after death may be eaten by vultures or other scavenging birds.

Adverse Reactions:

• Oral diclofenac: abdominal pain or cramps, constipation, diarrhea, flatulence, GI bleeding, GI perforation, peptic ulcer, vomiting, dyspepsia, nausea, dizziness,
headache, liver function test abnormalities, renal function abnormalities, anemia, prolonged bleeding time, pruritus, rash, tinnitus, edema.

- Diclofenac sodium 1% gel: application site reactions (e.g., dermatitis).
- Diclofenac epolamine transdermal system: application site reactions (e.g., pruritus, dermatitis), nausea, altered taste.
- Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope.
- Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, jaundice.
- Nervous System: anxiety, asthenia, confusion, depression, drowsiness, Insomnia, malaise, nervousness, tremors, vertigo.
- Respiratory System: asthma, dyspnea.

Drug Interactions:

- ACE inhibitors, antacids, anticoagulants (warfarin), aspirin, methotrexate, cyclosporine, diuretics, lithium, quinolones (ciprofloxacin).

3.1.4. Uses [8, 9, 10]

- Orally for symptomatic management of primary dysmenorrhea.
- For relief of mild to moderate pain.
- For relief of the signs and symptoms of symptomatic treatment of osteoarthritis rheumatoid arthritis and ankylosing spondylitis.
- For relief of the signs and symptoms of rheumatoid arthritis.

3.1.5. Dosage Forms

- Tablet, Solution, Injections.

3.1.6. Brand Names

- Arthrotec, Cataflam, Flector, Voltaren
3.2. Paracetamol IP

Paracetamol is analgesic antipyretic derivative of acetanilide. It has weak anti-inflammatory properties and is used as a common analgesic, but may cause liver, blood cell, and kidney damage.

3.2.1 General [11]

**Name**- Paracetamol

**Synonym**- Acetaminofen, Paracetamol, Paracetamolo, Paracetanol

**Chemical Structure**-

![Chemical Structure](image)

**Chemical Formula**- C₈H₉NO₂

**IUPAC Name**- 4- Hydroxy acetanilide.

**Average Molecular Weight**- 151.2.

**Melting Range**- 169-172 °C

**Solubility**- Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

**Standards**- Paracetamol contains not less than 99.0 % and not more then 101.0 % of C₈H₉NO₂ calculated on the dried basis.

**Loss on Drying**- Not more than 0.5 % determined on 1.0g by drying in an oven at 105 °C

**Packaging and Storage**- Protect from light and moisture.

**Description**- White crystals or a white, crystalline powder.
3.2.2. Pharmacokinetics Profile [12]

**Absorption** - rapid and complete from the GI tract. $T_{\text{max}}$ is 0.5 to 2 h; 4 h after over dosage.

**Distribution** - distributed throughout most body fluids. Binding to plasma proteins is variable.

**Metabolism** - primarily metabolized by hepatic conjugation (94%), and about 4% is metabolized by CYP-450 oxidize to toxic metabolite.

**Elimination** - The $t_\frac{1}{2}$ is about 2 hr 90% to 100% is recovered in the urine within the first day, primarily as inactive metabolites. 5% is excreted as unchanged drug.

**Protein binding** - 25%

$pKa$ - 9.51 at 25°C

*Predicted LogP* - 0.51

3.2.3. Pharmacodynamic Profile [13, 14, 15]

**Drug Category** - Nonopioid analgesics, valuable central analgesic but weak peripheral anti-inflammatory agent.

**Pharmacology** - Inhibits prostaglandins in CNS, but lacks anti-inflammatory effects in periphery; reduces fever through direct action on hypothalamic heat-regulating center.

**Mechanism of Action** - Paracetamol is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, Paracetamol does not inhibit cyclooxygenase in peripheral tissues and thus has no peripheral anti-inflammatory affects. Paracetamol indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. The drug selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood [16].
Contraindications -

- Enhances oral anticoagulant activity.
- Alcohol (chronic use) potentiates hepatotoxicity.

Adverse Reactions -

- Hematologic - hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia.
- Hepatic - jaundice.
- Miscellaneous - allergic skin eruptions, hypoglycemia, fever.

Drug Interactions [16, 17, 18]-

- Drug Interaction with acenocoumarol increases the anticoagulant effect.
- Anisindione - acetaminophen increases the anticoagulant effect.
- Dicumarol - acetaminophen increases the anticoagulant effect.
- Dicumarol increases the anticoagulant effect.
- Imatinib increases hepatic toxicity of both agents.
- Isoniazid interaction increases the risk of hepatotoxicity.
- Warfarin acetaminophen increases the anticoagulant effect.

3.2.4. Uses -

- For pain and fever

3.2.5. Dosage Forms -

Capsule, Elixir, Liquid, Solution, drops, Syrup, Tablet, effervescent Tablet, extended release tablet.

3.2.6. Brand Names -

- Anamol, Calpol, Doliprane, Pacimol, etc.
3.3 References


[17] Paracetamol. www.drugbank.ca/drugs/DB00316