4.1 SELECTION OF DRUG

The pain has been defined as a characteristic sensation arising from a noxious stimulus, which includes its neurophysiological aspect. Sherrington, in his classic definition has further included the reactive component of pain, i.e. the "psychical adjuvant of an imperative protective reflex". This indicates that pain also has a survival value for the species. There are two main classes of pain superficial and deep. Some pain receptors in the body are probably chemoreceptor’s, as a wide variety of compounds, including autacoids like bradykinin, and several of the prostaglandins, can elicit the pain. Drugs can alter the pain experience in three ways (Pain reception, perception, and reaction) the first that can be intercepted is peripheral pain reception at the nerve endings. This modality is susceptible to non-narcotic analgesic and local anesthesia. The second step, which can be modified, is pain perception at the level of the CNS. Both, narcotic and non-narcotic analgesics interfere with this level of pain integration. The third step, which can be influenced, is pain reaction.

WILLOW BARK (SALIX ALBA) had been used for many centuries. Salicylic acid was prepared by hydrolysis of the bitter glycoside obtained from this plant. Sodium salicylate was used for fever and pain in 1875; its great success led to the introduction of acetylsalicylic acid (aspirin) in 1899. Phenacetin and Antipyrine were also produced at that time. The next major advance was the development of Phenylbutazone in 1949 having anti-inflammatory activity almost comparable to corticosteroids. The term Nonsteroidal anti-inflammatory drug (NSAID) was coined to designate such drugs.

Role of Non-Steroidal Anti inflammatory drugs in pain (NSAIDs)

NSAIDS play an important role in symptomatic management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and other acute pain conditions. In general, they produce their anti-inflammatory and analgesic effects by inhibiting cyclooxygenase and this preventing the production of prostaglandins from arachidonic acid. It has been suggested that some NSAIDS inhibit leukotriene production via lipooxygenase inhibition.
The major groups of NSAIDS are as follows:

A. Nonselective COX inhibitors (conventional NSAIDS)

1. SALICYLATES: Aspirin, Diflunisal
2. PYRAZOLONE DERIVATIVES: Phenylbutazone, Oxyphenbutazone
3. INDOLE DERIVATIVES: Indomethacin, Sulindac
4. PROPIONIC ACID DERIVATIVES: Ibuprofen, Naproxen, ketoprofen, flurbiprofen
5. ANTHRANILIC ACID DERIVATIVES: Mefenamic acid
6. ARYL-ACETIC ACID DERIVATIVES: Diclofenac, Aceclofenac
7. OXICAM DERIVATIVES: Piroxicam, Tenoxicam

PYRROLO-PURROLE DERIVATIVE: Ketorolac

B. COX-2 inhibitors (non-selective)

Nimesulide, Meloxicam, Nabumetone

C. Selective COX-2 inhibitors

Celecoxib, Rofecoxib, Valdecoxib

4.2 DRUG SELECTED: ACECLOFENAC

4.2.1 WHY ACECLOFENAC?

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joint space which involves synovial proliferation and cartilage destruction.

In patients with osteoarthritis of the knee, the drug decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam and naproxen. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to Acelofenacprofen, diclofenac, indomethacin and tenoxicam in these patients.
The duration of morning stiffness and pain intensity are reduced, and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis, with improvements being similar to those observed with indomethacin, naproxen or tenoxicam. **Aceclofenac** is also effective in other painful conditions (e.g. dental and gynecological). In contrast to some other NSAIDs, Aceclofenac has shown stimulatory effects on cartilage matrix synthesis.

Aceclofenac is well tolerated, with encouraging reports of improved general and GI tolerability relative to other NSAIDs from a meta-analysis of double-blind trials and from large nonblind studies.

Because Diclofenac has very poor gastrointestinal (GI) tolerability, it is not particularly well suited for formulation. By contrast, because of lesser side effects than diclofenac, Aceclofenac has been proposed for injectable formulation.

Furthermore, two studies have demonstrated that aceclofenac is at least as effective as Acelofenacprofen and better tolerated, in terms of fewer drop-outs, in the long-term treatment of RA. In some comparative studies in joint diseases, there was a tendency for aceclofenac to be better tolerated than diclofenac or Acelofenacprofen, with fewer patients being withdrawn from treatment due to gastric intolerance.

Unfortunately, attempts to formulate Aceclofenac as a ready-to-use solution for injection have heretofore been complicated by the fact that Aceclofenac, when in solution and especially in presence of certain excipients, is unstable, and undergoes degradation which may precipitate out injection unsuitable for making use.

These side effects, barriers to oral drug administration as well as for longer treatment demand for sustained release of drug for therapeutic use in RA. One approach to overcome the problems includes the formulation of biodegradable polymeric microsphere entrapping Aceclofenac for parenteral drug delivery. Considering above facts current project is focused on design of Aceclofenac encapsulated PLGA microsphere that can be used for pain management.
4.3 DRUG PROFILE

4.3.1 Structure  
ACECLOFENAC

\[
\text{Cl} \quad \text{H} \quad \text{Cl} \\
\text{O} \quad \text{O} \quad \text{COOH}
\]

4.3.2 Physicochemical properties

- Molecular formula: \( C_{16}H_{13}Cl_2NO_4 \)
- Chemical Name: \( 2-[(2, 6-	ext{Dichlorophenyl}) \text{ amino}] \text{ phenyl} \text{ acetyl}] \text{ oxy} \text{ acetic acid.} \)
- Molecular weight: 354.2
- \( pK_a \): 4.7
- Melting point: 149-153ºC
- Appearance: white or almost white, crystalline powder.
- Solubility: practically insoluble in water, freely soluble in acetone, soluble in alcohol.

4.3.3 Structure Activity Relationship:

Structure-activity relationship in this series, have not been extensively studied. It does appear that the function of the two o-chloro groups is to force the anilino-phenyl ring out of the plane of the phenylacetic acid portion, this twisting effect being important in the binding of NSAIDs to the active site of the cyclooxygenase
enzyme.

4.3.4 PHARMACOLOGY

4.3.4.1 Pharmacodynamics

Aceclofenac relieves pain and inflammation through a variety of mechanisms and in addition exerts stimulatory effects on cartilage matrix synthesis.

Anti-inflammatory activity: The anti-inflammatory effects of Aceclofenac have been shown in both acute and chronic inflammation. It inhibits various mediators of pain and inflammation including:

- PGE2 via cyclooxygenase inhibition (COX-1 & COX-2) after intracellular metabolism to 4’hydroxy-aceclofenac and diclofenac in human rheumatoid synovial cells and other inflammatory cells
- IL-1β, IL-6 and tumor necrosis factor in human osteoarthritic synovial cells and human articular chondrocytes.
- Reactive oxygen species (which plays a role in joint damage) has also been observed in patients with osteoarthritis of knee.
- Expression of cell adhesion molecules (which is implicated in cell migration and inflammation) has also been shown in human neutrophils.

Stimulatory effect on cartilage matrix Synthesis:-

Aceclofenac stimulates glycosaminoglycan synthesis in human osteoarthritic cartilage by inhibition IL-1β and suppresses cartilage degeneration by inhibiting IL-1β mediated promatrix metalloproteinase production and proteoglycan release.

In patients with osteoarthritis of the knee, aceclofenac decrease pain reduces disease severity and improves the functional capacity of the knee. It reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis.
4.3.5 Pharmacokinetics

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (> 99%). Aceclofenac circulates mainly as unchanged drug. 4’- Hydroxyketo is the main metabolite detected in plasma. Approximately two thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. No changes in the pharmacokinetics of aceclofenac have been detected the elderly.

4.3.6 Clinical Efficacy

In large trials of 2 to 6 months duration, aceclofenac significantly reduced pain and improves functional capacity and mobility relative to baseline in patients with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis and reduces inflammation in patients with rheumatoid arthritis. No head to head comparison between aceclofenac and coxibs have been performed, nor for efficacy neither for tolerance.

Aceclofenac in osteoarthritis.

In patients with osteoarthritis of the knee, aceclofenac decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam, and naproxen.

Aceclofenac in rheumatoid arthritis

The anti-inflammatory and analgesic efficacy of aceclofenac is similar to that of Acelofenacprofen, indomethacin, tenoxicam and diclofenac in patients with rheumatoid arthritis. In randomized, double blind trials in 169 to 261 patients, aceclofenac (100 mg twice daily for 3 or 6 months) significantly reduced relative to baseline joint inflammation, pain intensity and the duration of morning stiffness and improved handgrip strength.
Aceclofenac in ankylosing spondylitis

The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis, with improvements being similar to those observed with indomethacin, naproxen or tenoxicam. These effects were observed after aceclofenac 100 mg twice daily for 3 months in randomized, double blind trials involving 104 to 308 patients.

Aceclofenac in dental pain

The analgesic efficacy as single doses of aceclofenac has been assessed in patients with moderate to severe tooth pain and in extraction of impacted third molars. The analgesic efficacy of single doses of aceclofenac 50, 100 and 150 mg was greater than that of placebo in patients with moderate to severe tooth pain or pain caused by extraction of impacted third molars.

Aceclofenac in postoperative pain

The analgesic efficacy of aceclofenac has been shown in comparisons with paracetamol in women undergoing episiotomy. Aceclofenac 100 mg was superior to paracetamol 650 mg in providing relief from post episiotomy pain, particularly 3 to 5 hours after ingestion.

Aceclofenac in Dysmenorrhoea

In a more recent noncomparative study in 1338 women with dysmenorrhea treated for first 3 days of 2 consecutive cycles.

Aceclofenac in acute lumbago

Aceclofenac (150 mg intramuscularly for 2 days, then 100 mg, both twice daily) was superior to diclofenac in alleviating functional impairment in a 7 days study in 100 patients with acute lumbago. Aceclofenac 100 mg twice daily was associated with symptomatic relief of acute low back pain in a non-comparative study in 67 patients.
Aceclofenac in musculoskeletal trauma

Aceclofenac 100 mg twice daily has also been assessed in patients with musculoskeletal trauma, although only non-comparative studies are available.

Aceclofenac Gonalgia (Knee pain)

A controlled double blind study was performed with aceclofenac comparing it with diclofenac in 40 patients with acute or chronic gonalgia. The results of the trial indicate slightly superior activity, although there was no statistically significant difference between two drugs.

4.3.7 Clinical toxicity

Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrhea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%), and pancreatitis (0.1%).

Dermatological complaints including pruritus and rash and abnormal hepatic enzyme and serum creatinine levels have also been reported. If serious side-effects occur, Aceclofenac should be withdrawn.

Although the incidence of gastro intestinal adverse events with aceclofenac was similar to those of comparator NSAIDS in individual clinical trials, withdrawal rates due to these events were significantly lower aceclofenac than with Acelofenacprofen and tenoxicam.

4.3.8 Dosage regimens

Adults

The recommended dose is 200 mg daily, taken as two separate 100 mg doses, in the morning and in the evening.
**Children**

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children.

**Elderly**

The pharmacokinetics of Aceclofenac is not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency. As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of elderly patients, who are at increased risk of the serious consequences of adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The elderly should be monitored regularly for GI bleeding during NSAID therapy.

**Renal insufficiency**

There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised (see also Precautions).

**Hepatic insufficiency**

There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

### 4.3.9 Contraindications

- Hypersensitivity to any of the constituents.
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Severe hepatic and cardiac failure (See section Special warnings and precautions for use).
✓ Moderate to severe renal failure.
✓ During the last trimester of pregnancy (See section - Pregnancy and lactation)
✓ Active or previous peptic ulcer.
✓ History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
✓ Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors.

4.3.10 Special warnings and precautions for use[91]

Undesirable effects may be minimized by using the minimum effective dose for the shortest possible duration.

_Elderly:_

✓ The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

_Respiratory disorders:_

✓ Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

/Cardiovascular, Renal and Hepatic Impairment:_

✓ The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

✓ If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac should be discontinued. Hepatitis may occur without prodromal symptoms.

✓ Use of Aceclofenac in patients with hepatic porphyria may trigger an attack.
Caution in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

**Gastrointestinal bleeding, ulceration and perforation:**

- GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
- Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
- Caution should be advised in patients receiving concomitant medications which could increase the risk of gastro toxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin.
- When GI bleeding or ulceration occurs in patients receiving Aceclofenac the treatment should be withdrawn.
- NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) as these conditions may be exacerbated.
- Close medical surveillance is imperative in patients with bleeding diathesis or hematological abnormalities.

**SLE and mixed connective tissue disease:**

- In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

**Female fertility:**

- The use of Aceclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Aceclofenac should be considered.
Hypersensitivity reactions:

✓ As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Hematological:

✓ Aceclofenac may reversibly inhibit platelet aggregation

Long-term treatment:

✓ All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts.

4.3.11 Interactions with other medicinal products and other forms of interaction

Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentrations of lithium.

Cardiac Glycosides: Through their renal effects, NSAIDs may increase plasma glycoside (including dioxins) levels, exacerbate cardiac failure and reduce the glomerular filtration rate in patients receiving glycosides.

Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendroflumethiazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: Like other NSAIDs, Aceclofenac may enhance the activity of anticoagulants such as warfarin close monitoring of patients on combined anticoagulant and Aceclofenac therapy should be undertaken.
Ant diabetic agents: Clinical studies have shown that diclofenac can be given together with oral ant diabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycemic and hyperglycemic effects. Thus with Aceclofenac, consideration should be given to adjustment of the dosage of hypoglycemic agents.

Methotrexate: Caution should be exercised if NSAIDs and Methotrexate are administered within 24 hours of each other, since NSAIDs may increase methotrexate plasma levels, resulting in increased toxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Cyclosporine: Cyclosporine nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving a NSAID.

Other analgesics: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Anti-hypertensive: Reduced anti-hypertensive effect.

Corticosteroids: Increased risk of GI bleeding

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

4.3.12 Pregnancy and lactation
**Pregnancy:**

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some foetuses.

**Lactation:**

There is no information on the secretion of Aceclofenac to breast milk; there was however no notable transfer of radio-labeled (14C) aceclofenac to the milk of lactating rats. In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

**4.3.13 Overdose**

There are no human data available on the consequences of Aceclofenac overdose.

**a) Symptoms**

Symptoms include headache, nausea, vomiting, epigastria pain, gastrointestinal bleeding, rarely diarrhea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally and convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

**b) Therapeutic measure**
Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

Table-2: List of Oral Marketed Preparation of Aceclofenac

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Company</th>
<th>Dosage form</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>Ind Swift</td>
<td>Tablet</td>
<td>100 mg</td>
</tr>
<tr>
<td>Dolokind</td>
<td>Mankind</td>
<td>FC-Tablet</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hifenac SR</td>
<td>Intas</td>
<td>SR-Tablet</td>
<td>200 mg</td>
</tr>
<tr>
<td>Hinac</td>
<td>Intas</td>
<td>Tablet</td>
<td>100 mg</td>
</tr>
<tr>
<td>Dolokind SR</td>
<td>Mankind</td>
<td>SR-Tablet</td>
<td>200 mg</td>
</tr>
<tr>
<td>Movexx</td>
<td>Cipla</td>
<td>FC-Tablet</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

4.4 DRUG PROFILE [92, 93, 94, 96, 97, 98]:

Indomethacin is an indole derivative. It is an Anti-inflammatory drug used in Rheumatoid arthritis.

Category: - Potent anti-inflammatory drug with prompt antipyretic action.

Structure:
**Chemical Name:** 2-[(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-indole-3yl) acetic acid.

(diphenylmethyl)-4-(3-phenyl-2-propenyl) piperazine

**Description:**

- **CAS Number:** 53-86-1
- **Molecular formula:** C19H16NO4Cl
- **Molecular Weight:** 357.79 g/mol

**Physical Properties:**

- **Solubility:** solubility in water: insoluble (0.937 mg / L)
- **Melting Point:** 158-165°C
- **pKa Value:** 4.5

**Metabolism and Excretion:**

Indomethacin is partly metabolized in liver to inactive product and excreted by kidney.

**Pharmacokinetics:**

- **Plasma Protein Binding:** 95 %
The peak plasma levels  :  1 to 2 hours after intake
Half-life  :  3-3.5 hours

**Pharmacological Properties:**

It has anti-inflammatory, antipyretic action. It is used in treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other rheumatic disorders.

**Mechanism of Action:**

Indomethacin is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. The Drugs inhibits synthesis of the inflammatory cytokines interleukin.

**Side-Effects:** -

The most common side-effect of indomethacin are nausea, vomiting, diarrhea, stomach discomfort, heartburn, rash, headache, dizziness and drowsiness.

**Contraindication:**

It is contraindicated in machinery operators, drivers, psychiatric patient and epileptics and in pregnant women.

**4.4.1. Pharmacokinetic Aspects of Indomethacin:**

Indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered Indomethacin are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of Indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25
or 50 mg t.i.d., the steady-state plasma concentrations of Indomethacin are an average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as Indomethacin and its glucuronide), and 33 percent is recovered in feces (1.5 percent as Indomethacin).

About 99% of Indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta.

4.4.2. Indications:

Indomethacin has been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

4.4.3. Dosage and Administration:

a) Pediatric Use

Indomethacin generally should not be prescribed for pediatric patients 14 years of age and under.

b) Adult Use

Dosage Recommendations for Active Stages of the Following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis. In patients who have persistent night pain and/or morning stiffness, the giving of a large
portion, up to a maximum of 100 mg, of the total daily dose at bedtime, either orally or by rectal suppositories, may be helpful in affording relief. The total daily dose should not exceed 200 mg.

2. Acute painful shoulder (bursitis and/or tendinitis).
   Initial Dose: 75-150 mg daily in 3 or 4 divided doses.

   The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

3. Acute gouty arthritis.

   Indomethacin 50 mg t.i.d. until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

4.4.4. Past work done on Indomethacin:

   Indomethacin is practically insoluble in water, soluble in 1 in 50 of ethanol, 1 in 30 of chloroform, and 1 in 40-45 of ether and soluble in acetone. Converting crystalline state to amorphous state in most of the cases improves the solubility of compound. Solid Dispersion is one of the most promising techniques for converting compound structure from crystalline to amorphous state. Mastummoto and Taylor\textsuperscript{[99]} investigated the physical properties of Indomethacin with several water polymer carriers like PVP and Poly co-vinyl acetate stating that drug is present in amorphous form in Indomethacin -PVP Solid Dispersion system. Phase characterization of Indomethacin in Solid Dispersion was reported as the initial $\square$-form which in crystalline form of Indomethacin get converted into amorphous |3- form of Indomethacin in Solid Dispersion process. Later Solid Dispersion of Indomethacin with PVP was prepared by solvent free Solid Dispersion process (Supercritical Fluid Process)\textsuperscript{[100]} for checking the impact on process change related to physical characterization of Solid Dispersion. Crystallization of Indomethacin from its amorphous state below and above its glass transition temperature was explained by Yoshioka Hirofumi\textsuperscript{[101]} prepared the Solid Dispersion of Indomethacin with two different
types of silica, nonporous silica (aerosil 200) and porous silica (sylsia 350) by spray drying method and they observed the increase in dissolution rate of Indomethacin Solid Dispersion with porous material. Wantable \cite{102,103} reported the stability of amorphous Indomethacin when it compounded with silica.

SECTION 4.5: EXCIPIENT PROFILES

CHITOSAN \cite{104}

**Nonproprietary names:**

BP/PhEur: Chitosan Hydrochloride

**Synonyms:** 2-Amino-2-deoxy-(1,4)-b-D-glucopyranan; Chitosani hydrochloridum deacetylated chitin; Deacetylchitin; b-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-b-D glucopyranosamine)

**Chemical name:** Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose

**Empirical Formula and Molecular Weight:**

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. A clear nomenclature with respect to the different degrees of N-deacetylation between chitin and chitosan has not been defined and as such chitosan is not one chemical entity but varies in composition depending on the manufacturer. In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight by 10000–1000000, and vary in degree of deacetylation and viscosity.

**Structure of Chitosan:**

![Structure of Chitosan](image-url)
**Description:**

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may looks as like cotton.

**Typical Properties:**

- pK:\( \text{H} \): 4.0–6.0 (1% w/v aqueous solution)
- Density : 1.35–1.40g/cm
- Glass transition temperature: 203 °C
- Moisture content: Chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.
- Solubility: Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic solvent.

**Functional Category:**

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

**Applications in Pharmaceutical Formulation or Technology:**

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications use as a component of mucoadhesive dosage forms, rapid release dosage forms improved peptide delivery, colonic drug delivery systems, and use for gene delivery. Chitosan has been processed into several pharmaceutical forms including gels, films, beads, micro-spheres,
tablets, and coatings for liposome’s. Furthermore, Chitosan may be processed into drug delivery systems using several techniques including spray-drying, coacervation, direct compression, and conventional granulation processes.

**Stability and Storage Conditions:**

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 6.5 specifies that chitosan should be stored at a temperature of 2–8°C.

**HYDROXY PROPYLMETHYL CELLULOSE-15cps**

**Nonproprietary names:**

BP: Hypromellose  
USP: Hydroxypropylmethylcellulose  

**Synonyms:** Benecel MHPC, Cellulose, Methocel  

**Chemical name:** Cellulose, 2-Hydroxy propyl methyl ether  

**Molecular weight:** 10,000-1,500,000  

**Structure of hypromellose (HPMC):**

![Structure of hypromellose](image)  

where \( R \) is \( H, CH_3, \) or \( CH_3CH(OH)CH_3 \)

**Description:** Hydroxypropylmethylcellulose is an odorless, tasteless, white or creamy-white colored porous or granular powder.

**Typical properties**

- **Acidity/Alkalinity:** pH: 5.5-8.0 (1% w/w aqueous solution)  
- **Density (bulk):** 0.341 g/cm\(^3\)  
- **Density (tapped):** 0.557 g/cm\(^3\)
Melting point: softens at 150°C

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether.

**Functional category:** Coating agent, rate-controlling polymer for sustained release, film former, Stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

**Applications in pharmaceutical Formulation or Technology:** In oral products, Hydroxypropylmethylcellulose is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentration of between 2-5%w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drug from a matrix at levels 10-80%w/w in tablets and capsules. Depending upon the viscosity grade, concentrations between 2-20%w/w are used as film-forming solutions for film-coat tablets.

**Stability and storage conditions:** Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions. Hydroxy Propyl methyl cellulose powder should be stored in a well closed container, in a cool, dry place.

**HYPROMELLOSE ACETATE SUCCINATE**

**Nonproprietary Names:**

USP-NF: Hypromellose Acetate Succinate

**Synonyms:** Aqoat, Aqoat AS-HF/HG, Aqoat AS-LF/LG, Aqoat AS-MF/MG; Cellulose, 2-hydroxypropyl methyl ether, acetate succinate; HPMCAS.

**Chemical Name:** Cellulose, 2-hydroxypropylmethyl ether, acetate hydrogen butane dioate.

**Empirical Formula and Molecular Weight:**

The USP32–NF27 describes Hypromellose acetate succinate as a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose. It is available in several grades, which vary in extent of substitution, mainly of acetyl and succinoyl groups, and
in particle size (fine or granular). When dried at 105 °C for one hour, it contains 12.0–28.0% of methoxy groups; 4.0–23.0% of hydroxypropoxy groups; 2.0–16.0% of acetyl groups; and 4.0–28.0% of succinoyl groups. The molecular weight of Hypromellose acetate succinate is approximately 55000–93000Da, measured by gel permeation chromatography using polyethylene oxide as a relative reference standard.

**Structural Formula:**

![Structural Formula Image]

**Description:**

Hypromellose acetate succinate is a white to off-white powder or granules. It has a faint acetic acid-like odor and a barely detectable taste. Hypromellose acetate succinate is available in several grades, according to the pH at which the polymer dissolves (low, L; medium, M; and high, H) and its predominant particle size (cohesive fine powder or free-flowing granules).

**Typical properties:**

- Density: 1.27–1.30g/cm
- Glass transition temperature: 113± 2°C
- Equilibrium moisture content: 2–3% w/w at ambient temperature and humidity (25 °C, 40% RH).
- Solubility: Practically insoluble in ethanol (95%), hexane, un buffered water, and xylene. On the addition of acetone, or a ethanol (95%) and dichloromethane (1:1), a clear or turbid viscous solution is produced.
Functional Category:
Controlled-release agent; solubility enhancing agent; enteric coating agent; film-forming agent; sustained-release agent.

Applications in Pharmaceutical Formulation or Technology:
- Hypromellose acetate succinate is commonly used in oral pharmaceutical formulations as a film coating, as well as an enteric coating material for tablets or granules.
- It is a solubility enhancing agent via solid dispersion. Hypromellose acetate succinate is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. For aqueous film-coating purposes, a dispersion of Hypromellose acetate succinate fine powder and triethyl citrate (as a plasticizer) in water is commonly utilized.
- Organic solvents can also be used as vehicles for applying this polymer as a film coating. Hypromellose acetate succinate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent. Dispersions of poorly soluble drugs with hypromellose acetate succinate are prepared using techniques such as mechanical grinding, solvent evaporation, and melt extrusion.

Stability and Storage Conditions:
Hypromellose acetate succinate should be stored in a well-closed container, in a cool, dry place. In such storage conditions, hypromellose acetate succinate is a stable material. Hypromellose acetate succinate is hygroscopic. It is hydrolyzed to acetic acid and succinic acid, and the hypromellose polymer starts to form if dissolved in 1mol/L sodium hydroxide for more than two hours.

The hydrolysis is the main degradation pathway that is responsible for increasing amounts of free acids in storage, especially upon exposure to moisture.

POLYETHYLENE GLYCOL 4000 [104]

Nonproprietary Names:
BP: Macrogols,
JP: Macrogol 4000,
PhEur: Macrogols,
USP-NF: Polyethylene Glycol

Synonyms: Carbowax; CarbowaxSentry; Macrogola; PEG; Pluriol; Polyoxyethylene glycol.

Chemical Name: α-Hydro-ω-hydroxypropyl (oxy-1,2-ethanediyl)

Empirical Formula and Molecular Weight:

\[ \text{HOCH}_2 (\text{CH}_2 \text{OCH}_2) \text{mCH}_2 \text{OH} \]

where \( m \) represents the average number of oxyethylene groups. Alternatively, the general formula \( H(\text{OCH}_2 \text{CH}_2)n \text{OH} \) may be used to represent polyethylene glycol, where \( n \) is a number \( m \) in the previous formula.

Average molecular weight: 3000-4800

Structural Formula:

\[
\begin{array}{c}
\text{HO} \\
\hline
\text{CH}_2 \quad \text{CH}_2 \quad \text{O} \\
\hline
\text{H}
\end{array}
\]

\( n \)

Description: The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Typical Properties:

- Density: 1.080
- Melting point: 69.0-84.0 °C
• Moisture content: Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades e.g. PEG 4000 and above, are not hygroscopic.

• Solubility: All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol. They are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

**Functional Category:** Ointment base; plasticizer; solvent; suppository base; tablet and Capsule lubricant.

**Applications in Pharmaceutical Formulation or Technology:**

• Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

• Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin.

• They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.

• Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of poly ethylene glycol.

**Stability and Storage Conditions:**

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous
polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation