CHAPTER 3
MONOGRAPH AND ANALYTICAL PROFILE OF DRUGS

3.1 SELECTION OF DRUGS

The non steroidal anti inflammatory drugs belong to a variety of chemically differing groups but they obstruct the inflammatory process by similar mechanism. The NSAIDs selected in the present study are Aceclofenac (AC), Mefenamic acid (MA) and Dexamfetamine (Dex), which suffer from gastrointestinal side effects.

3.2 STANDARDIZATION OF DRUGS

Tests were carried out on the selected drug samples to establish their identity and purity as per specifications of British Pharmacopoeia.

3.3 PROFILE OF ACECLOFENAC 162, 163

![Fig 3.1 Structure of aceclofenac](image)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name</td>
<td>2-[(2, 6-dichlorophenylamino) phenylacetyloxy acetic acid</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{16}H_{13}Cl_{2}NO_{4}</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>354.2 g/mol</td>
</tr>
<tr>
<td>Colour</td>
<td>White or almost white crystalline powder</td>
</tr>
<tr>
<td>Odour</td>
<td>Odourless</td>
</tr>
<tr>
<td>Melting point</td>
<td>149-150°C</td>
</tr>
<tr>
<td>Pk_{a} value</td>
<td>4.65</td>
</tr>
<tr>
<td>Log P</td>
<td>1.87 at pH 1.2 (n-octanol vs. acidic buffer)</td>
</tr>
</tbody>
</table>
Protein binding : 92 
Half life : 4 h
Excretion : Renal

3.3.1 General Characteristics

Aceclofenac, a phenyl acetic acid derivative, is a non steroidal drug with marked anti inflammatory and analgesic properties. Aceclofenac displays a high degree of enantio-selectivity in its inhibitory effects on arachidonic cyclooxygenase system. It was also reported to produce less GI bleeding than other NSAIDs such as indomethacin, ibuprofen or naproxen. After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3 h following ingestion. 4-hydroxy aceclofenac is the main metabolite detected in plasma. The structure of aceclofenac is shown in Fig 3.1.

Solubility: Practically insoluble in water, soluble in ether and methyl alcohol, sparingly soluble in acetone and chloroform.

Standard: It contains not less than 99 % and not more than 101 % of aceclofenac, calculated with reference to dried substance.

Dose: The general dose of aceclofenac used is 50 mg per kg.

Side Effects: The most frequently reported adverse experiences occurring in patients administered with aceclofenac are

- Gastro intestinal toxicity including abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding (perforation, heart burn, nausea, GI ulcers, vomiting).
• Other events including – abnormal renal function, anemia, dizziness, oedema, elevated liver enzymes, headaches, increased bleeding time, pruritis and rashes.

**Storage:** Aceclofenac must be kept in tightly closed container and out of reach of children. It should be stored at room temperature and away from excess heat and moisture.

**3.3.2 Methods of Analysis**

A simple, rapid and precise reversed phase liquid chromatographic method has been developed for determination of aceclofenac combinations in a commercial pharmaceutical preparation \(^{164}\). Zorbax SB C18, 250 x 4.6 mm, 5 μm analytical column was used for the study with acetonitrile as the mobile phase and orthophosphoric acid as buffer. The pH of the buffer was adjusted to 6 with 10 % w/v sodium hydroxide solution and the detector wavelength was 270 nm. The method was validated and showed to be linear with a correlation coefficient of 0.999.

In another model, it has been reported that aceclofenac was analyzed spectrophotometrically at 275 nm in phosphate buffer medium at a pH 6.8 \(^{165}\).

In the study involving formulation and evaluation of fast dispersible aceclofenac tablets, twenty tablets were weighed and powdered. An amount of the powder equivalent to 20 mg of aceclofenac was dissolved in 100 ml of pH 7.4 phosphate buffer \(^{166}\). It was filtered, suitably diluted and analyzed for drug content at 273 nm using UV visible spectrophotometer (UV 160 Shimadzu, Japan).
A high performance thin layer chromatographic method has been developed and validated for the simultaneous estimation of drotaverine and aceclofenac in combined dosage forms. The stationary phase and mobile phase used were pre coated silica gel 60F$_{254}$ and a mixture of methanol-ethyl acetate-glacial acetic acid (1:9:0.01 v/v/v). The detection of spots was carried out at 300 nm. The calibration was found to be linear between 100 to 700 ng/spot for aceclofenac. The statistical analysis proved that the method was precise, accurate and reproducible for routine analysis $^{167}$.

### 3.4 PROFILE OF MEFENAMIC ACID $^{168-172}$

**Fig 3.2 Structure of mefenamic acid**

- **IUPAC name**: 2-(2, 3-dimethylphenyl)amino benzoic acid
- **Molecular formula**: C$_{15}$H$_{15}$NO$_2$
- **Molecular weight**: 241.3 g/mol
- **Colour**: White crystalline powder
- **Odour**: Odourless
- **Melting point**: 230-231°C
- **pK$_a$ value**: 4.65
- **Log P**: 1.82 at pH 1.2 (n-octanol vs. acidic buffer)
- **Protein binding**: 90 %
- **Half life**: 2-4 h
- **Excretion**: Renal and fecal
3.4.1 General Characteristics

Mefenamic acid is a NSAID used to treat pain, including menstrual pain. Mefenamic acid decreases inflammation (swelling) and uterine contractions and is mainly due to the inhibition of prostaglandin synthesis. This medication may interact with other blood pressure medications or other anti inflammatory drugs. It may also affect lithium, methotrexate, rifampin and anticoagulants. The structure of mefenamic acid is shown in Fig 3.2.

**Solubility:** Practically insoluble in water, soluble in alcohol, acetone, dimethyl formamide, ether and sparingly soluble in chloroform.

**Standard:** Mefenamic acid, when dried, contains not less than 99 % of C₁₅H₁₅NO₂.

**Dose:** The general dose of mefenamic acid used is 50 mg per kg.

**Side Effects:** Mefenamic acid is known to cause an upset stomach, therefore it is recommended to take prescribed doses together with food or milk. Instances of drowsiness may also occur. As such, it is recommended to avoid driving or consuming alcohol while taking this medication. Other known mild side effects of mefenamic acid include, nervousness, head ache and vomiting. Serious side effects may include bloody vomit, diarrhoea, blurred vision, skin rash, itching and swelling, sore throat and fever.

**Storage:** Mefenamic acid should be kept in tightly closed container, and out of reach of children. It should be stored at room temperature and away from excess heat and moisture.
3.4.2 Methods of Analysis

An effective and low cost spectrophotometric method for the determination of mefenamic acid in its pure form and pharmaceutical preparations was reported. It is based on the charge transfer complexation between mefenamic acid as an $n$-electron donor and chloranil as a $\pi$-acceptor to form a violet chromogen measured at 540 nm. A linear relationship with a good correlation coefficient (0.9996) was found between the absorbance and concentration of mefenamic acid in the range of 10–60 μg/ml.

Preparation of standard curves of MA in cupric chloride method was attempted. To 1 ml of each dilution, 5 ml (1 %) of cupric chloride solution was added and shaken vigorously for 15 minutes. All volumes were made up to 10 ml with distilled water. These were transferred to separating funnels and extracted with dichloromethane. The extracts were evaporated, digested with 10 ml (0.1 M) nitric acid, aspirated directly in the atomic absorption spectrometer and measured the absorbance at 324.8 nm. Standard curves were generated by regression analysis.

Preparation of standard curves of MA in cobaltous chloride was attempted. To 1 ml of each dilution, 5 ml (1 %) of cobaltous chloride reagent was added and heated at 60°C for 15 minutes. 1 ml (0.5 %) of triethanolamine reagent was added further and made up to 10 ml with distilled water. These were transferred to separating funnels and extracted with dichloromethane. The extracts were evaporated and digested with 10 ml (0.1 M) nitric acid. Aspirated the acid extracts
directly in the atomic absorption spectrometer and measured their absorbance at 240.7 nm for cobalt. Standard curves were generated by regression analysis.

In p-chloroanilic acid (p-CA) method, aliquots equivalent to 10-300 μg/ml of mefenamic acid were transferred to a series of 10 ml volumetric flasks. 3 ml of p-CA reagent were added to each flask and the volumes were made up to the mark with acetone. The absorbance was measured at 520 nm against a reagent blank. The calibration curve was obtained by plotting the absorbances vs. the final concentrations \(^{175}\).

In N-Bromosuccinamide (NBS) method, different aliquots of mefenamic acid stock solution equivalent to 5-70 μg/ml were transferred into a series of 10 ml volumetric flasks \(^{175}\). 2 ml of NBS reagent were added to each flask and volumes were completed with methanol. The absorbance was measured at 362 nm against a reagent blank and the calibration curve was obtained.

In 3-methylbenzo-thiazolin-2-one-hydrazone (MBTH) method, different aliquots of mefenamic acid stock solution equivalent to 1-6 μg/ml were transferred to a series of 10 ml volumetric flasks \(^{175}\). 4 ml of FeCl\(_3\) aqueous solution were added followed by 2 ml of MBTH reagent. The volumes were made up to the mark with methanol and the absorbance was measured at 602 nm against a reagent blank. The calibration curve was plotted.
3.5 PROFILE OF DEXIBuprofen

![Structure of dexibuprofen](image)

**Fig 3.3 Structure of dexibuprofen**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name</td>
<td>(2S)-2-[(4-(2-methylpropyl)phenyl]propanoic acid</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C\textsubscript{13}H\textsubscript{18}O\textsubscript{2}</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>206.3 g/mol</td>
</tr>
<tr>
<td>Colour</td>
<td>White crystalline powder</td>
</tr>
<tr>
<td>Odour</td>
<td>Odourless</td>
</tr>
<tr>
<td>Melting point</td>
<td>49-53°C</td>
</tr>
<tr>
<td>(p^{\text{Ka}}) value</td>
<td>4.65</td>
</tr>
<tr>
<td>Log P</td>
<td>1.60 at pH 1.2 (n-octanol vs. acidic buffer)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>97%</td>
</tr>
<tr>
<td>Half life</td>
<td>1.8-2 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal</td>
</tr>
</tbody>
</table>

### 3.5.1 General Characteristics

Dexibuprofen is the S (+) (dextrorotatory) enantiomer of ibuprofen and accounts for analgesic, anti-inflammatory, antipyretic activities of racemic compound. It is employed to treat rheumatoid arthritis, osteoarthritis and dysmenorrhea. The anti-inflammatory effects are believed to be due to inhibition of both (COX-1) and (COX-2) which leads to the inhibition of prostaglandin synthesis. Antipyretic effects may be due to the action on hypothalamus, resulting in an increased peripheral blood flow, vasodilation and subsequent heat dissipation. The advantages of dexibuprofen include greater clinical efficacy, ease in dose optimization, less variability in therapeutic effects, all of these at
half the dose of ibuprofen. Greater peak analgesia was also seen with dexibuprofen.

It is indicated for the relief of sign and symptoms of osteoarthritis, rheumatoidal disorders such as osseous rheumatism, ankylosing sodalities, juvenile arthritis, muscular rheumatism and degenerative joint disease. It is used for the acute symptomatic treatment of painful menstruation, symptomatic treatment muscle pain, head ache and dental pain. The structure of dexibuprofen is shown in Fig 3.3.

**Solubility:** Practically insoluble in water, soluble in ethyl alcohol methanol, acetone, ether and dimethyl formamide.

**Standard:** It contains not less than 99 % of dexibuprofen when calculated with reference to dried substance.

**Dose:** The recommended dose is 600 to 900 mg dexibuprofen daily, divided in three single doses for the treatment of mild to moderate pain. The maximum single dose is 400 mg dexibuprofen.

**Side Effects:** The adverse effects of dexibuprofen are similar to those of racemic ibuprofen. The common side effects are diarrhoea, fatigue, head ache, nausea, vomiting and abdominal pain. The gastro intestinal side effects include dyspepsia, flatulence and gross bleeding.

**Storage:** Dexibuprofen should be kept in a tightly closed container, and out of reach of children. It should be stored in a cool, dry area and must be properly labeled.

**3.5.2 Methods of Analysis**

A simple, sensitive, precise and rapid HPTLC method has been developed and validated for the analysis of dexibuprofen in
pharmaceutical formulation. The method uses aluminum foil HPTLC plates coated with silica gel 60F254 as stationary phase and hexane-ethyl acetate-glacial acetic acid as mobile phase. Densitometric analysis of dexibuprofen and the internal standard (aceclofenac) was performed in reflectance mode at 217 nm. Linear regression analysis of the calibration data revealed a good linear relationship between response and concentration with $r^2 = 0.9902$ and found to be successful in the analysis of an oral solid dosage formulation. Three simple spectrophotometric methods have been developed for simultaneous estimation of dexibuprofen and paracetamol from tablet dosage form using ethanol as solvent. Method-I involves absorbance of dexibuprofen at 235.5 nm, while in method-II and III, the measurement of absorbance was at 223 nm. The accuracy and precision of the methods were determined and validated statistically. The methods were found to be rapid, specific, precise and accurate and can be successfully applied for the routine analysis of dexibuprofen and paracetamol in bulk and combined dosage form.

In the study involving the formulation of an extended release tablet containing dexibuprofen, the concentrations were quantified using an HPLC/PDA system. The compounds were separated on a Capcell pak C18 UG120 (5 μm, 4.6×150 mm) with an isocratic mobile phase consisting of 0.1 M sodium acetate buffer and acetonitrile (6:4) at 272 nm.