Chapter 4 Drugs and Excipients
A single daily dose of non-steroidal anti-inflammatory drug is widely recognized as the best dose regimen in chronic diseases such as degenerative osteoarthropathy, inflammatory afflictions of skeletal muscles etc. For several years biomedical research has been involved in the development of anti-inflammatory and antirheumatic compound to be used in these chronic conditions. These drugs should possess the following requirements.

(a) A rapid and long-lasting analgesic effect.

(b) A sustained anti-inflammatory and antirheumatic activity.

(c) Good tolerability even after prolonged treatment in the elderly patients and

(d) Easy dose schedule and possibly one single daily administration

As far as point (d) is concerned, research has attempted to develop drugs both with a longer half-life or a slow release formulation. The long half-life drugs have quick absorption and slow excretion and once daily administration allows the maintenance of drug plasma levels for 24 hours.

In this background Diclofenac and Ketorolac were selected as the drug candidates for the development of transdermal systems for the NSAIDs. Diclofenac has low molecular weight, considerable first pass metabolism in the liver and short plasma half-life. Ketorolac has low molecular weight, low dosage, and tendency to cause gastrointestinal disturbances and hepatotoxicity.

4.1 DICLOFENAC SODIUM/ DIETHYL AMMONIUM

Diclofenac is a synthetic, non-steroidal, anti-inflammatory and analgesic compound.
Chemical name:

Monosodium /diethyl ammonium salt of 2-[(2,6-dichlorophenyl) amino] benzene acetic acid

Molecular weight:

Diclofenac sodium: 318.13

Diclofenac diethyl ammonium: 369.30

Chemical structure:

Diclofenac sodium: R: Na

Diclofenac Diethyl ammonium: R: \((\text{C}_2\text{H}_5)_2\text{NH}_2\)

![Chemical structure diagram]

It occurs as white to off white crystalline, practically odorless, slightly hygroscopic powder.

Melting point:

Diclofenac sodium: 283-285° C

Diclofenac diethyl ammonium: 149-153° C
Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>&gt;9</td>
</tr>
<tr>
<td>Methanol</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Acetone</td>
<td>6</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>&lt;1</td>
</tr>
<tr>
<td>pH 7.2 phosphate buffer</td>
<td>6</td>
</tr>
<tr>
<td>pH 1.1 HCl</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Dissociation constant (pKa) and Partition coefficient:

The pKa in water is 4 and partition coefficient in n-octanol/aqueous buffer pH is 13.4. Partition coefficient of Diclofenac diethyl ammonium in n-octanol/aqueous buffer pH is 10.

Pharmacology:

It is potent anti-inflammatory agent. The potency is about 2.5, 10, 24, 80, 430 times that of Indomethacin, Naproxen, Phenylbutazone and Aspirin respectively, as determined by inhibition of carrageenan – induced rat paw edema.

Anti-inflammatory activity:

The analgesic potency was similar to that of Indomethacin and about 5, 10, 22 and 38 times that of Naproxen, Phenylbutazone and Aspirin respectively.

Antipyretic effect:
In rats the antipyretic activity of Diclofenac 0.5 mg/Kg is similar to that of 1.2, 24, 35, 55, 185 mg/Kg of Indomethacin, Penybutazone, Naproxen and Aspirin respectively.

Pharmacodynamic properties:

It suppresses acute and chronic inflammation in various animal models. Studies in healthy subjects show that usual therapeutic doses cause less gastrointestinal damage than Aspirin, Naproxen, Indomethacin and Naproxen. Its pharmacological effects appear to be positively correlated with, their ability to inhibit prostaglandin synthesis. It is potent inhibitor of cyclo-oxygenase (prostaglandin synthetase and this leads to a marked reduction in the synthesis of prostaglandin’s, prostacyclin and thromboxane products.

Pharmacokinetic properties:

Absorption, Distribution and Elimination:

The drug is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive first pass metabolism in the liver, with only about 50 - 60 % of a dose reaching the systemic circulation as unchanged drug. Peak Plasma concentrations following oral administration of the drug generally occur with in 2-3 hrs with enteric coated tablets compared to within 10 - 30 minutes with an oral solution of the drug. Following oral administration of a single 25, 50, 75 or 150 mg dose of an enteric coated Diclofenac sodium tablets in healthy adults, average peak plasma Diclofenac concentrations of 0.5 - 1, 1 - 1.5, 2 and 2.5 mg/l, respectively, are achieved within about 1.5 to 3 hours. Food decreases the rate of absorption of enteric-coated tablets. Following intravenous administration of Diclofenac, the drug is widely distributed into the synovial fluid. The terminal half-life appears to be about 1 to 2 hours. The drug is rapidly and extensively metabolized in the liver.
Therapeutic uses:

It is indicated for the following conditions:

- Rheumatoid Arthritis, Osteo Arthritis, Ankylosing Spondylitis, Acute Gout, Non-articular Rheumatic conditions and other acute painful states,

- Good analgesic in painful, post traumatic and postoperative inflammation and swelling.

- In painful and/or inflammatory conditions in gynecology such as primary dysmenorrhoea.

- Also in curing headache, biliary colic pain, severe painful inflammatory infections of the ear, nose or throat.

Dosage and administration:

Diclofenac can be administered by oral, rectal or intramuscular route. The initial dose of Conventional tablet is 150mg daily in two or three divided doses. Intra-muscular Diclofenac 75mg can be given in acute and severe pain due to inflammatory and degenerative forms of rheumatism, rheumatoid arthritis etc. It is available as tablets, capsules, injections and gels.

Analytical methods available for the estimation of Diclofenac

A Non-aqueous titration:

The dried sample is titrated with 0.1 N perchloric acid, using Crystal violet as the indicator.

B Spectrophotometer methods

a. The drug in acidic medium reacts with sodium cobalt nitrate to form a light yellow colored complex, which has absorption maxima at 368 nm.
b. Diclofenac reacts with Potassium ferricyanide in basic medium to give Yellow color, which shows maximum absorbance at 450nm.

c. It gives yellow color when reacted with Sodium nitrite in the presence of hydrochloric acid, which exhibits maximum absorbance at 390 nm.

d. It gives color complex on reaction with 3- Methyl, 2-benzothiazolinone hydrazone hydrochloride in the presence of Ce⁴⁺ under acidic conditions, which has a maxima at 600 nm.

C Gas Liquid Chromatography

The column conditions are present in the following table and electron captured detector is the detector of choice.

<table>
<thead>
<tr>
<th>SL.No.</th>
<th>Column Conditions</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>2.5 x 0.3 mm id; coated with barium carbonate and statistically coated with Carbowax 40 M</td>
<td>240</td>
</tr>
<tr>
<td>b.</td>
<td>2m x 3 mm id; 3% OV-17 Gas chrom Q on 80-120 mesh glass beads</td>
<td>300</td>
</tr>
<tr>
<td>c.</td>
<td>4 ft x 3 mm id; 3% JXR (Methyl silicone) on glass chrom Q</td>
<td>205</td>
</tr>
<tr>
<td>d.</td>
<td>2x3 mm id; 1.5% Silicone OV-17 on Shimalite W AW DMCS, 8-100 mesh</td>
<td>260</td>
</tr>
</tbody>
</table>
**D  High performance liquid chromatography**

Numbers of methods for the determination of Diclofenac in biological fluids by HPLC are described. These fluids include blood, plasma, and synovial fluid. The detection limits are 5-25 ng/mL of the fluid. Reverse phase C18 columns are most suitable. Prominent amongst them are:

<table>
<thead>
<tr>
<th>St. No.</th>
<th>Column</th>
<th>Fluid</th>
<th>Mobile phase</th>
<th>(\lambda_{max})</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Spherisorb</td>
<td>Plasma</td>
<td>Methanol-Acetonitrile (50:50 v/v) adjusted to pH 3.3 with glacial acetic acid.</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>RP-18 Column (5(\mu)m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>Spherical C-18 (5(\mu)m)</td>
<td>Plasma</td>
<td>Isopropanolol-acetonitrile</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.02 M acetate buffer pH-7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5:18:77)</td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td>Supelcosil</td>
<td>Plasma</td>
<td>Methanol-Acetonitrile</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>LC-18 (5(\mu)m)</td>
<td></td>
<td>Synovial fluid 0.02 M Sodium acetate buffer (25: 20: 55)</td>
<td></td>
</tr>
<tr>
<td>d.</td>
<td>Nucleosil</td>
<td>Synovial fluid</td>
<td>Methanol-Acetonitrile</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>C-18 (10(\mu)m)</td>
<td>urine</td>
<td>PH 7 phosphate buffer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(30: 17: 53v/v)</td>
<td></td>
</tr>
<tr>
<td>e.</td>
<td>Microbondapack C-18</td>
<td>Plasma</td>
<td>Methanol 55% in 50 mM</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(30 cm x 3.9 cm)</td>
<td>orthophosphoric acid</td>
<td></td>
</tr>
<tr>
<td>SL No.</td>
<td>Column</td>
<td>Fluid</td>
<td>Mobile phase</td>
<td>λ_{max}</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>----------</td>
<td>--------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>f.</td>
<td>Microbodnapack CN</td>
<td>Plasma</td>
<td>Methanol-Acetate buffer (65: 35 v/v) pH 3.7</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>(30 cm X 3.9 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g.</td>
<td>Shinpak CLS-ODS</td>
<td>Plasma</td>
<td>Acetonitrile-Water (50:50) With 0.1% glacial acetic acid</td>
<td>274</td>
</tr>
<tr>
<td></td>
<td>250 x 4.0 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h.</td>
<td>Hypersil 5-ODS</td>
<td>Plasma</td>
<td>Methanol: Acetonitrile: Tetrahydrofuran: Water</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>(250mm x 4.6mm)</td>
<td>Urine</td>
<td>(10: 15: 3:72)</td>
<td></td>
</tr>
</tbody>
</table>

E Thin layer chromatography

a. Aliquots of the solution of Diclofenac in aqueous 50% methanol were applied on Plate coated with silica gel R, impregnated with a mixture of Magnesiumfluorogermanate, Zinc silicate, and Zinc sulphide (7:8:2). The mobile phase was glass chloroform-methanol and aqueous ammonia (18:15:5). After running the solvent, the plates were dried at 100°C for 15 minutes. The spots were detected at 254 nm.

b. A drop of ethanolic solution containing 0.005 - 0.1 % Diclofenac was spotted on a TLC plate prepared with silica gel. The TLC plate was developed with benzene propanol (9: 1) or benzene-methanol-acetone (7:2:3) and sprayed with 1% solution of potassium dichromate in 40 % sulphuric acid. Pink colored spots were obtained.

c. In another method chloroform - methanol and 25% ammonia (6:3:1) were used as the mobile phase after developing for thirty minutes, the silica gel plates were dried in the air and heated at 120°C for fifteen minutes. A solution of 9
isothiocyanate acridine derivative (0- 1%) in dichloromethane or benzene was used as spraying agent and the drug detected at 254 nm

4.2 KETOROLAC TROMETHAMINE:

Ketorolac tromethamine is a non-steroidal analgesic, anti-inflammatory drug. It is indicated for the short-term management of moderate to severe painful conditions.

Chemical name:

5-benzoyl, 2,3-,dihydro- 1 H-pyrrrolizine 1 - carboxylic acid,2-amino - (hydroxy methyl) - 1,3 - propanediol.

Molecular weight: 376.41

Structural formula:

\[
\text{\includegraphics[width=0.5\textwidth]{structure.png}}
\]

\[P_{Ka}: 3.34\]

Partition Co-efficient: 0.26 (n-Octanol/Water)

Solubility: Freely soluble in water and methanol

Clinical Pharmacology:

It exhibits analgesic, anti-inflammatory and antipyretic activity. It inhibits synthesis of Prostaglandin's and it may be considered a peripherally acting analgesic. Pain relief is
evident clinically when plasma levels exceed 0.3µg/ml, while side effects are frequent above concentrations of 5 µg/ml. It has up to 800 times the potency of Aspirin. It shows more potent analgesic activity than Indomethacin, Naproxen and Phenylbutazone. A single dose of 10 - 20 mg orally appeared superior to that of Aspirin 650 mg, Paracetamol 500 - 1000 mg, and Naproxen 550 mg after major surgery. In dental surgery it was superior to Aspirin, Paracetamol or Ibuprofen 400 mg in alleviating pain after surgery. In acute musculoskeletal pain, Ketorolac 10mg four times a day demonstrated better pain relief than provided by the combination of Paracetamol 600 mg plus Codeine 60 mg or Ibuprofen 400 mg given 4 times a day. Repeated doses of Ketorolac are equivalent to repeated doses of Pentazocine 100 mg.

Pharmacokinetics:

It is completely and rapidly absorbed after oral and intramuscular administration. Peak plasma concentrations are achieved in 30 - 60 minutes after administration. It does not appear to undergo a significant degree of presystemic metabolism. Food reduces the rate but not the extent of absorption. Plasma levels are approximately proportional to dosage. Steady state plasma levels are achieved after dosing every 6 hours for one day. Mean plasma concentrations of 0.86 to 0.87 mg/L after 10 mg oral dose have been reported in healthy volunteers and a concentration of 2.2 to 3 pg/ml after a single 30 mg Intramuscular dose. The tromethamine salt enhances the solubility and rate of absorption. It dissociates into the anionic form of Ketorolac at physiological pH. It exhibits more than 99% binding to the plasma proteins. It achieves high concentration in the aqueous humour. The terminal plasma half-life is 3.8 - 6.3 hours in young adults. The kinetics of Ketorolac tromethamine is altered in the elderly and in patients with renal dysfunction. The major metabolic pathway is glucuronic acid conjugation. The primary route of excretion of Ketorolac tromethamine and its metabolites is in the urine (91.4%) and the remainder (6.1%) is excreted in the faeces. Decreases in serum albumin, e.g. in liver cirrhosis generally change Ketorolac tromethamine clearance. It poorly penetrates the blood brain barrier.
Indications and usage

It is indicated for the short-term management of moderate to severe painful states such as:

- Postoperative pain after major surgery, abdominal surgery, gynecological surgery, orthopedic surgery etc.
- Acute musculoskeletal painful conditions such as dislocation, fracture and soft tissue injury.
- Dental pain including pain after oral surgery.
- Post partum pain (not indicated in labor pain).
- Other painful states like cancer pain, sciatica, chronic pain states, and as an adjuvant in renal and biliary colic.

Contra indications:

Hypersensitivity to Ketorolac tromethamine, complete or partial syndrome of nasal polyps, angioedema, and bronchospasm related to Aspirin or other NSAIDs.

Side effects:

Adverse reactions rates from short-term use of Ketorolac are generally from 1/2 to 1/10 the rates associated with chronic usage. Incidence of nausea, dyspepsia, gastrointestinal pain, and drowsiness was around 3% to 9%. Incidence of diarrhea, flatulence, liver function abnormalities, rectal bleeding, stomatitis, nervousness, insomnia, Pruritis, abnormal taste and vision was less than 1%.
Precautions:

As with other NSAIDs it should be used with caution in patients with impaired renal or hepatic functions. Caution should also be exercised in patients with cardiac disorder, hypertension and coagulation disorders. It should be used in pregnancy only if benefit outweighs the risks. Not recommended for use during labor and delivery and should be used with caution in nursing mothers. Safety and efficacy in children is not established.

Drug interactions:

Therapeutic concentrations of salicylate reduces its binding and hence should be used with caution in patients being treated with salicylates. Concomitant administration of methotrexate has been reported to reduce the clearance of methotrexate, enhancing its toxicity.

Dosage and Administration:

Ketorolac is administered by oral or intramuscular route. Usual dose of tablets is 10 mg tablet 1 to 4 times a day. In severe painful states the dosage may be increased to 20 to 30 mg, 4 times a day. For intramuscular injection, the recommended initial dose is 30 or 60 mg as a loading dose, followed by half of the loading dose i.e. 15mg or 30 mg every 6 hours as long as needed to control pain. The lower end of the recommended dosage range is for patients under 50 Kg and for patients over 65 years of age.

Analytical methods available for estimation of Ketorolac tromethamine:

The various analytical methods available for the estimation of Ketorolac tromethamine in raw materials, biological fluids and pharmaceuticals are as follows:

A Non-aqueous titration:

Standard Ketorolac tromethamine is dissolved in 50 ml Glacial Acetic Acid and titrated against 0.1 N perchloric acid using crystal violet as indicator. The end point is found to be blue to emerald green. A calibration curve was plotted with the
weights of standard drug against the volume of the 0.1 N perchloric acid consumed. The results are found to be linear in the range of 250 mg to 500 mg of the drug. For UV Spectroscopy it has absorption maxima at 243 nm and 313 nm. 313 nm was selected because it was better. A standard stock solution of concentration 1 mg/ml of the drug was pre-prepared using methanol and further dilutions were made with 0.1 N Hydrochloric acid. The absorbance was measured at 313 nm. It exhibited a linear response in the concentration range of 4 \mu g/mL to 16 \mu g/mL.

B UV spectroscopy:

It has absorption maxima at 243 nm and 313 nm. 313 nm was selected because the absorption was better at 313 nm. A standard stock solution of 1 mg/mL was prepared using methanol. Further dilutions were made using 0.1 N hydrochloric acid. Absorbance was measured in the linear portion and it gives linear response in the range of 4 \mu g/mL-16 \mu g/mL.

C Colorimetric Method:

This method was developed based on the reaction of Ketorolac tromethamine with p-dimethyl amino benzaldehyde in acid medium i.e., concentrated Hydrochloric acid to yield an orange red colored chromogen that exhibits absorption maxima at 501 nm. The chromogen is stable for more than 24 hours and Beer's law is obeyed in the concentration range of 20 \mu g to 100 \mu g.

D Liquid chromatographic Methods:

HPLC after automated on line solid phase extraction Centrifuged heparin zed plasma was applied to solid phase C - 18 disposable cartridges conditioned with methanol, water, sodium acetate of pH 3.4. Elution was performed by on line connection of the cartridge with the HPLC system on a Nova pak C 18 with acetonitrile and 0.1% acetic acid at 258 nm. The calibration graph was linear from 25-2500 ng/mL of Ketorolac tromethamine.
<table>
<thead>
<tr>
<th>SL No.</th>
<th>Column</th>
<th>Fluid</th>
<th>Mobile phase</th>
<th>$\lambda_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Bondapack C-18</td>
<td>Plasma</td>
<td>40% Acetonitrile pH 2.8</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>(30 cm x 3.9 cm)</td>
<td></td>
<td>Adjusted with phosphoric acid.</td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>Spherisorb ODS (25 x 4.6 mm) Guard column Pellosil C-18 (7 cm x 2.1 mm)</td>
<td>Plasma</td>
<td>Methanol-Acetonitrile, 10mM tetrabutyl ammonium phosphate of pH 6 (4:3:13)</td>
<td>280</td>
</tr>
<tr>
<td>c.</td>
<td>Chiral RP-8 (25cm x 4.6mm)</td>
<td>Plasma</td>
<td>20mM Potassium dihydrogen phosphate of pH 7 and Propan-2-ol. (199:1)</td>
<td>320</td>
</tr>
<tr>
<td>d.</td>
<td>Lichrospher RP-8</td>
<td>Post Mortem blood.</td>
<td>36% Acetonitrile in 0.5 molar Potassium dihydrogen phosphate-Metaphosphoric acid buffer, pH 3 &amp; phosphate buffer, pH 7</td>
<td>Photo Diode array</td>
</tr>
<tr>
<td></td>
<td>(2.5 cm x 4.6mm)</td>
<td></td>
<td>(30:17:53v:w)</td>
<td></td>
</tr>
</tbody>
</table>
**Thin layer Chromatography (TLC):**

Aliquots of Ketorolac in aqueous methanol were applied on a glass plate (20x20 cm) coated with silica gel with a layer thickness of 0.20 mm. After developing with n-Hexane, Ethyl acetate, glacial acetic acid in volume ratio 15:5:1 respectively, the plates were dried and spots were detected under UV light.

### 4.3 EXCIPIENTS

#### 4.3.1 SELECTION OF POLYMERS AS MATRIX MATERIAL

The selection of polymer is an important step in the overall development of Transdermal systems. Especially the polymer matrix is an open cell molecular sponge saturated with a solvent, which contains a drug in either, a dispersed and/or dissolved state. The polymer selected for development of Transdermal system should satisfy following conditions. *(Baker and Heller, 1989)*

- Molecular weight and chemical functionality of the polymer must allow the proper diffusion and release of the specified drug.
- It should be able to hold the drug in a stable condition and in a stable matrix Reservoir
- It should have little or no affinity for the drug allowing for zero order release kinetics from the matrix.
- The polymer and its degradation products must be non-toxic, non-allergic and non-irritant to the host.
- The polymer must not decompose on storage or during the shelf life of the device.
- The functionality of the polymer should be such that it should not chemically react with the drug.
- The polymer properties must be easily modifiable to allow the drug to be delivered at appropriate rate.
Finally, cost of the polymer should not be excessive which may render the controlled release device to be non-competitive in the market.

The polymer should be easy to handle using standard fabrication techniques. Materials that are known to be difficult to work with should be avoided. If the polymer is to be used as drug containing matrix, then it is important that the drug should be incorporated simply and in such a way that the properties of the polymer and drug remain unchanged. Chemical stability is also important. Stability must be considered especially with drugs that contain reactive functional groups such as carboxyl, amine or hydroxyl.

Ease of Modification: The final and most important factor that enters into the selection of membrane or matrix materials is the ability to tailor the physical and chemical properties to allow the drug to be delivered at an appropriate rate. The permeability of the films can be controlled by appropriate adjustment of the molecular weight of the polymer, humidity pretreatment and polysorbate 20 content. (Fites et al., 1970).

Because it is rare to find a commercial polymer that has exactly the properties required for a particular system, some form of modification will be necessary. It is essential to choose polymers that can be modified as the circumstances dictate. Number of techniques can be used to tailor polymer properties.

• Cross linking

• Chemical structure modification

• Blending polymers

• Addition of plasticizers

a. Cross-linking: By cross-linking the polymer, it is possible to modify the diffusion characteristics. The higher the degree of cross-linking, the harder the material and slower the diffusion of drug from the matrix.
b. Chemical Structure: Varying the chemical structure of polymer varies its properties. The changes in permeability are related to changes in the glass transition temperature and crystallinity of the polymers.

c. Polymer Blends: A blend of ingredient is chosen and tailored to vary the release Properties of the matrix or membrane and get the desired diffusion characteristics for the drug in question.

d. A final important method of varying membrane properties is to incorporate plasticizers to decrease the stiffness of the polymer backbone and thereby increase diffusion rate from the device.

4.3.2 POLYMERS AS CHEMICAL AND BIOLOGICAL ADHESIVES

Adhesive - Linear or branched amorphous polymer above its Glass Transition Temperature ($T_g$) needs to be able to flow to grip on a molecular scale. An example is the postage stamp adhesive made of a linear poly (vinyl alcohol), which is plasticized by water from below its $T_g$ to above its $T_g$. On drying the adhesive "sticks." Adhesion is if the two materials are different cohesion is if the same. All cemented surfaces with a cementing agent are bonded by adhesion; hence, the cementing agent is an adhesive. Usually for maximum interfacial strength, the thickness of the adhesive has some optimal value (not too thick, not too thin.) Lower polyacrylate polymers have $T_g$ below room temperature; they are typically soft and rubbery and are used as pressure-sensitive adhesives.

Pressure Sensitive Adhesives (PSAs)

Lower polyacrylate polymers have $T_g$ below room temperature they are typically soft and rubbery and are used as pressure-sensitive adhesives.

PSA (pressure-sensitive adhesive) matrix device fastening of Transdermal devices to skin is done with PSA The adhesive polymers used in the formulation of Transdermal system are classified as pressure- sensitive adhesive and are defined as adhesive capable of
bonding to surfaces with the application of light pressure. In Transdermal delivery system, the PSA accomplishes the adhesion to skin function and serves as the formulation foundation, containing the drug and all excipients. (Goulding, 1994)

Desirable features of PSA are:

- No irritation or skin sensitivity
- Sufficiently adhesive
- Easily removable

Commonly three types of PSA are used in Transdermal delivery systems. Polyisobutylene (PIB), Silicones and Acrylates. The permeation rate of a drug, the compatibility with enhancers, and the skin adhesion must be considered before the Selection of a PSA. In the present study the pressure sensitive adhesives were used to get the adhesive matrix type of TDDS. The adhesives used are:

- Acrylate copolymer (Gelva-737) in organic solvents (ethyl acetate and toluene)
- Silicone pressure sensitive adhesives (Silicone-2920) in a Freon solution.
- Polyisobutylene (PIB, molecular weight 1,450,000 in a solid state.)

4.3.3 SELECTION OF THE PLASTICIZER

A plasticizer is defined as substantially Non-Volatile, high-boiling, non-separating substance that when added to a polymer changes the physicochemical properties of the polymer such as mobility, imparts flexibility, reduces brittleness and increases the resistance of the film to break by mechanical stress. Plasticizers normally have a molecular weight ranging from 100-20,000 and contain one or more hydrophilic groups in the molecule, for example, hydroxy, ester, or amino groups. Examples of suitable plasticizers include alkyl citrate, glycerol ester, alkyl phthalate, alkyl sebacate, sucrose
ester, sorbitan ester, dibutyl sebacate, and polyethylene glycols 4,000-20,000. Preferred plasticizers are triethyl citrate and acetyltrietiiyl citrate. The addition of the plasticizer permits the adaptation of physical characteristics to the requirements of the individual medications, so that sufficient adhesion forces are attained at room or body temperature. Furthermore, in the indicated ratios, the plasticizers can advantageously decrease the melt viscosity of the polymers employed, in the liquid state. At room temperature, softening effects can be recognized. Moreover, influences on the release behavior of embedded active substances are possible. Variations of the composition make it possible, if necessary, to compensate for undesired effects of medication-affected additives. The adhesive binders of the invention can optionally contain other additives in small amounts, if the special formulation requires, like, neutral polymers, tackifiers, stabilizers, dyes, antioxidants, wetting agents, pore-forming agents, moisturizers, complexing agents, and so forth. They are usually low molecular weight compounds. They are considered to be associated with polymer chains by secondary valence forces, separating the molecules and finally reducing the intermolecular forces. The most effective plastizer closely resemble in structure to the polymer they plasticize. Thus the water-soluble polymers polyvinyl alcohol, polyvinylpyrrolidine etc. are best plasticized by propylene glycol and other polyols, glycerol and polyethylene glycols. The lipophilic polymer ethyl cellulose is best plasticised by dibutylphthalate, diethylphthalate, dimethylphthalate etc.

The plasticizers used in the present study are Propelyene Glycol and Polyethylene Glycol 4000 (PEG 4000).

4.3.4 SELECTION OF PENETRATION ENHANCER

The most common and necessary excipients of almost any formulation used for Transdermal delivery is the penetration enhancers, which are used to increase the permeation of drug molecules through the skin. The selection of a transdermal product should be based on its efficacy lack of toxicity, and compatibility with other components of the TDDS. Penetration enhancers are the chemicals, which enhance the permeation of
solute across a membrane. In the case of skin, Penetration enhancers are required to modify the diffusional barrier so that the drug can reach the blood in adequate concentration. An ideal penetration enhancer should have following attributes. The material should be pharmacologically inert and should possess no action of itself at receptor sites in the skin or in the body generally. The material should not be toxic, irritating or allergenic. On application, the onset of penetration enhancing action should be immediate; the duration of effect should be predictable and suitable (Walters, 1988).

When the material is removed from the skin, the tissue should immediately

- Recover normal barrier property.
- The substance should be an excellent solvent for drugs.
- The barrier function of the skin should reduce in one direction only so as to promote the penetration into the skin.
- The enhancer should be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuvant
- The material should spread well on the skin and should be cosmetically acceptable.
- The material should be easily formulated into lotions, suspensions, ointments, creams, gels, aerosols and skin adhesives

The terpenes were studied as penetration enhancer in the present study. Chamomile oil was found to be most effective of the enhancers used.

**Chamomile oil**

**Herbal / Folk Tradition:** This herb has had a medical reputation in Europe and especially in the Mediterranean region for over 2,000 years, and is still in widespread use. The ancient Egyptians and the Moors employed it, and it was on of the Saxons' nine sacred
herbs. It is in the current British Herbal pharmacopoeia for the treatment of dyspepsia, nausea, vomiting in pregnancy and specifically flatulent dyspepsia associated with mental stress.

- **Functional Category:** Essential oil of chamomile is an ingredient for pharmaceutical and medicinal preparations. The optically active terpene (-) \( \alpha \)-Bisabolol was identified as pharmacologically active compound (BASF and Dragoco Active substances catalogues).

- **Synonym:** Matricaria recutita L.; syn. Chamomilla recutita (L.) Rauschert

- **Common method of extraction:** Steam distillation

- **Chemical name:** The chemical name for the main component which may be upto 50% in the essential oil of Chamomile oil is 1-methyl-4- (1,5-dimethyl-1-hydroxyhex-4 (5)-enyl) cyclohexen-1.

- **Description:** Pinkish coloured liquid with pleasant sweet herbal odor.

- **Use:** It is used as an anti-inflammatory agent in high quality skin and mouth care products.

- **Safety:** It has an oral LD \(_{50}\) greater than 5g/kg with zero primary skin irritation.

- **Possible uses:**

  **Physical uses:** Gum Disease, Allergies, Colitis, Eczema, Teething and Toothache, Bug Bites, Dermatitis and Sensitive Skin, Chilblains, Cuts and Wounds, Arthritis and rheumatism, Sprain, Indigestion, Nausea, Painful Menstruation, Menopause
Problems, Excessive Menstruation, Headache, Migraine, Abscess, Intestinal Infection, Fever, Colic (Lawless, 1995)

Effects: Anti-inflammatory, Analgesic (relieves pain), Antispasmodic, Bactericidal, Febrifuge (reduces fever), Carminative (reduces flatulence), Digestive, Wound Healing, Emmenagogue (brings delayed menses), Hypnotic, Nerve Sedative, Sudorific, Tonic, Vermifuge.

Constituents: High ester content, bisabolol, pinacarveol, pinene, farnesol, cineole, azulene, Beta-caryophyllene, camphene, myrcene, cinocarvone,

4.3.5 SELECTION OF BACKING LAYER

The different parts of the drug delivery system are critical to its eventual success. The transdermal system is fabricated in such a way that the patch will adhere to the skin, deliver the prescribed dosage, and then be removed easily without irritation. The backing layer that is chosen determines the performance and the physical appearance of the system. A backing layer should

- Gives good protection to the system.
- A good backing layer should stay strong, comfortable and have an aesthetic appeal.
- They should also maintain their appearance in a variety of environments.
- A backing layer may need to be waterproof, heat sealable, printable and may range from occlusive to permeable.
- It should be compatible with drug and other adhesives in the system.

The various backing layers that were considered in the study are
Tan polyester film laminate: This is a laminate consisting of three different layers viz. an outer pigmented (tan color) layer, and an inner polyester layer bonded together with additives or additional chemicals. The resulting laminate is tan in color hence blends well with the color of the skin. It conforms to the contours of the portion of the body applied to. It is occlusive and has a thickness of 0.034 mm. The moisture vapor transmission and oxygen transmission are 0.3 g/m²/24 hr and 4.6 cc/m²/24 hours respectively.

Translucent tan polyester film laminate: The laminate is tan colored, conformable, occlusive and translucent. It has a thickness of 0.042 mm. A moisture vapor transmission and oxygen transmission rates of 12/ m² / 24 hr and 100 cc/m²/ 24 hr respectively. The laminate consists of three different layers. An outer tan colored pigmented layer, middle clear polythene layer and an inner polyester layer. These three layers are bond together to produce a laminate.

Heatsealable tan polyester film laminate: This laminate is tan colored, conformable, occlusive and heat seal able. It has a thickness of 0.072 mm. A moisture vapor transmission and oxygen transmission rates of 0.3/ m² / 24 hr and 4.6 cc/m²/ 24 hr respectively. The laminate consists of four different layers. An outer tan colored pigmented layer, a second aluminum vapor coated layer, a third polyester layer and an innermost a heatseal able layer. These layers are bond together to produce a laminate.

White foam tape: The tape is white. Thick polyolefin foam is coated on one side with a pressure sensitive acrylate adhesive. The adhesive is hypoallergenic in nature with minimum adhesive residue. The tape thickness is 1.0mm together with the foam. It is conformable and occlusive.

Pearlescised polyester: Polyester film consists of mixtures of dimethyl terephthalate and monoethylene glycol. The polyester is pigmented with titanium oxide to give a pearl like look. It has good tensile strength, stiffness and good chemical resistance and barrier properties. It has very low moisture and gas permeability. It has a thickness of 100 microns.
Metalised polyester: Metallisation is a process by which a thin layer of metal vapor is made to condense and adhere to the substrate. Aluminum metal is vaporized and deposited on continuously moving substrate. The process improves the barrier properties of the film.

Alu Poly: It is an aluminum film with plastic. It offers good protection from varying temperatures and humidity conditions. The foil gauge and the coating weight of heat seal thermoplastic synthetic resinous compound come in a range of varieties. Generally 0.4mm aluminum foil with heat seal resin coating of 9 gm/m² in weight is used. The protection given by aluminum foil laminated to polythene is best for products that are particularly hygroscopic.

Adhesive Alu Poly: This is Alu poly, which is coated on one side with a pressure sensitive adhesive to impart to it the property of adhesion. It has all the properties of Alu poly.

Cellophane: This is transparent wrapping material made from viscose. Viscose is a form of cellulose in a highly viscous state suitable for drawing into yarn.

4.3.6 SELECTION OF COVERING LINER

The fabrication of a Transdermal system cannot be considered complete without the selection of a suitable covering liner for the system. The covering liner

- Should protect the drug and other components of the system during storage and shelf life
- Should be firm and not destroy during handling.
- Should easily peel off from the system at the time of usage
- It should not affect the adhesive nature of the system. It should adhere to the skin effectively.
The Covering liner is responsible along with the backing layer for the
effectiveness and appearance of the system

The materials selected as a covering liner for selected formulations are

1. Low adhesion polyester film
2. Pearlesced polyester film
3. Silicone coated paper-I
4. Silicone coated paper-II
## MATERIALS

<table>
<thead>
<tr>
<th>Drugs Source</th>
<th>Source</th>
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<tbody>
<tr>
<td>Ketorolac tromethamine</td>
<td>Cadila Health Care, Ahmedabad.</td>
</tr>
<tr>
<td>Diclofenac diethylammonium</td>
<td>Cadila Health Care, Ahmedabad.</td>
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<tr>
<td>Piroxicam</td>
<td>Torrent Research Centre, Ahmedabad.</td>
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<table>
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<tr>
<th>Polymers Source</th>
<th>Source</th>
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<tbody>
<tr>
<td>Acrylate copolymer (Gelva- 737)</td>
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<td>A solution of vinyl acetate acrylate multipolymer in toluene 11, ethyl acetate 53 and ethanol 36 Total solids 30-32.0% was a gift (Supplied by Monsanto, St. Louis, MO)</td>
<td>Torrent Research Centre, Ahmedabad.</td>
</tr>
<tr>
<td>Silicone- 2920 in a Freon solution.</td>
<td>Torrent Research Centre, Ahmedabad.</td>
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<tr>
<td>Solid content varied from 35% 50% (Supplied by Dow Corning, Midland, MI)</td>
<td>Torrent Research Centre, Ahmedabad.</td>
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<tr>
<td>Polyisobutylene (Supplied by Exxon Chemical Co., St. Paul MN)</td>
<td>Torrent Research Centre, Ahmedabad.</td>
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<table>
<thead>
<tr>
<th>Penetration enhancers Source</th>
<th>Source</th>
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<tr>
<td>Chamomile oil</td>
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<tr>
<td>Mentha oil</td>
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<td>Eucalyptus</td>
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<td>Thymol</td>
<td>Cadila Health Care, Ahmedabad.</td>
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<tr>
<td>Geraniol</td>
<td>Bioved Remedies, Pune.</td>
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<tr>
<td>Lemon oil</td>
<td>Bioved Remedies, Pune.</td>
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<td>Chemicals</td>
<td>Source</td>
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<td>Sodium dihydrogen orthophosphate (AR) dihydrate</td>
<td>S.D Fine Chemicals Pvt. Ltd., Boisar.</td>
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<td>Disodium hydrogen orthophosphate (AR) dihydrate</td>
<td>BDH, India.</td>
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<tr>
<td>Sodium acetate (AR)</td>
<td>S.D Fine Chemicals Pvt. Ltd., Boisar.</td>
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<tr>
<td>Sodium Hydroxide (AR)</td>
<td>S.D Fine Chemicals Pvt. Ltd., Boisar.</td>
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<td>Hydrochloric acid (AR)</td>
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<td>Acetonitrile (HPLC)</td>
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<tr>
<td>Methanol (HPLC)</td>
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<tr>
<td>Ethyl acetate (HPLC)</td>
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**INSTRUMENTS**

<table>
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<th>Instrument</th>
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<tr>
<td>Double beam UV Spectrophotometer</td>
<td>Hitachi – 120 Japan.</td>
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<td>Single beam UV Spectrophotometer</td>
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<td>Oven</td>
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<td>Magnetic Stirrer</td>
<td>Adair Dutt. And Co., Delhi.</td>
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<td>High Pressure Liquid Chromatograph</td>
<td>Schimadzu LC-10AD</td>
</tr>
<tr>
<td>High Pressure Thin Layer Chromatograph</td>
<td>CAMAG, Perkin Elmer.</td>
</tr>
</tbody>
</table>
PHTURE: TRANSDERMAL PATCH