CHAPTER – III

DRUG PROFILES AND LITERATURE ON CONTROLLED RELEASE OF SELECTED DRUGS
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DILTIAZEM - A PROFILE

Diltiazem hydrochloride chemically is d-3-acetoxy-2,3-dihydro-5-(2-dimethyl amino) - ethyl) -2-(p-methoxyphenyl) -1,5-benzothiazepin-4 (5H)-one hydrochloride. Diltiazem is the d-cis form of a benzothiazepine hydrochloride salt derivative. Its structural formula is given below.

![Structural formula of Diltiazem hydrochloride](image)

\[ C_{22}H_{26}N_2O_4S.HCl \]  \hspace{1cm}  \text{Molecular weight: 450.99}

**Description:**

The compound can be either a white crystalline substance or a powder and has a bitter taste and no odour.

**Solubility:**

Diltiazem hydrochloride is freely soluble in water, methanol or chloroform, is slightly soluble in absolute ethanol and is rarely soluble in benzene.

**Melting point:** 187-188°C.
Specific rotation:

Between +110° and -116° calculated on the dried basis determined in a 1 in 100 solution in water.

Loss on drying:

It losses not more than 0.5% of its weight when dried at 105°C for 3 hours.

Heavy metal:

Not more than 20 ppm.

Storage:

Diltiazem should be stored in tight containers at room temperature.

Pharmacokinetics:

Diltiazem hydrochloride is rapidly absorbed after oral administration and detectable plasma concentration are reached in 30 to 60 minutes and peak levels are reached within three hours. The plasma half-life following a single oral dose is approximately 3.5 h\(^1\). Therapeutic blood levels are probably in the range of 50 to 200 ng/ml. Toxic levels are unknown but appear to be in excess of atleast 1200 ng/ml. After single oral and intravenous doses in varying population of humans. A comparison of areas under the plasma concentration Vs time curve, corrected for dose suggested an absolute bioavailability of 0.4-0.6\(^1\)\(^2\). Diltiazem is subjected to significant presystemic elimination (first-pass effect). The time necessary to reach peak concentrations after single oral dose
of diltiazem tablets 60, 90 and 120 mg ranges from 3.0 to 4.5 hours, with corresponding peak concentration values of 72 ± 17, 117 ± 20 and 151 ± 46 ng/ml, respectively\(^1\). The time to reach peak concentrations is significantly shorter after the administration of diltiazem capsules (0.5-1.0 h).

Diltiazem is extensively metabolized in man with only 0.1-4.0 percent of the drug excreted unchanged in the urine in 24 h\(^3\). Studies revealed that > 90% of the administered diltiazem can be removed from urine and faeces in 72 hours. The main metabolic pathways appear to be deacetylation, N-demethylation, and O-demethylation\(^4\). Desacetyl diltiazem, a major metabolite is found to be having 40-50% of the activity of the parent compound.

Oral studies employing 24 h blood sampling schedules have, documented a mean terminal half-life of four to six hours in healthy volunteers. After single and multiple oral dosing over the range 60-120 mg, the half-life remains relatively unchanged, and the area under the plasma concentrations Vs time curve is linearly related to dose, suggesting linear absorption and, disposition pharmacokinetics of diltiazem. There is no evidence for unusual accumulation of the drug during oral therapy\(^1,4\).

**Actions and Uses:**

Early studies on the mechanism of action of diltiazem confirmed that it is not a \(\beta\)-blocker. Studies revealed that diltiazem is an excitation contraction uncoupler in the cardiac cell and this is because of its ability to reduce intracellular concentrations of free calcium ions\(^5\). Subsequent experiments
confirmed that diltiazem blocked the flow inward calcium channel. Diltiazem like other calcium antagonists has the property of coronary artery and arteriolar dilatation, inhibition of coronary constriction and reduction of myocardial oxygen demand by systemic arteriolar dilatation.

Diltiazem is found to be effective in the prophylaxis of effort induced and variant angina. It is also used in the management of hypertension.

Adverse effects:

Central nervous system side effects have been the most commonly reported adverse reactions, which include headache, vertigo and fatigue, cardiovascular effects including bradycardia, AV block, oedema and congestive cardiac failure have been reported. Gastrointestinal disorders such as gastric irritation, nausea and constipation have been reported.

Dosage and administration:

Effective oral doses of diltiazem range from 90-240 mg/dl. The usual maintenance dose is 240 mg/dl administered as 60 mg every six hours. Dosage must be adjusted to each patient's needs. Starting with 30 mg dosage can be gradually increased to 240 mg/day.

Preparations:

Diltiazem is available as conventional tablets at 30 mg, 60 mg strength and as SR (90 mg) tablets. Diltiazem extended release capsules are official in USP XXIV⁶. USP XXIV specified a drug release test for extended release capsules of diltiazem hydrochloride. The following test is prescribed.
For products labeled for dosing every 12 h.

Test 1: If the product complies with this test the labeling indicates that it meets USP Drug Release Test I.

Medium: Water (900 ml)

Apparatus: 100 rpm

Timers: 3, 9 and 12 h

**Tolerances:** The percentages of the labeled amount of diltiazem hydrochloride dissolved at the times specified confirm to the acceptance as given below.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Between 10% and 25%</td>
</tr>
<tr>
<td>9</td>
<td>Between 15% and 85%</td>
</tr>
<tr>
<td>12</td>
<td>Not less than 70%</td>
</tr>
</tbody>
</table>
NEED FOR THE CONTROLLED RELEASE OF DITIAZEM

Diltiazem is a calcium channel blocker, which has been useful in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has a short biological half life of 3.5 h and is rapidly eliminated. The oral bioavailability of diltiazem is 40% in humans. Because of its low bioavailability and short biological half-life, attempts have been made to develop sustained release products with extended clinical effects and reduced dosing frequency. Diltiazem hydrochloride extended release capsules are official in USP XXIV.

PAST WORK ON CONTROLLED RELEASE OF DILTIAZEM

As diltiazem is a highly water-soluble drug, its formulation into SR products is rather difficult. There are few reports on the formulation of oral controlled release products of diltiazem employing coated beads, pan coating, microencapsulation and complexation techniques.
GLIPIZIDE - A PROFILE

Chemically glipizide is 1-cyclohexyl-3-[[p-(2-(5-methyl) pyrazine carboxamido)ethyl] phenyl] sulfonylurea.

Mol. Formula: \( \text{C}_{27}\text{H}_{24}\text{N}_{4}\text{O}_{5} \)

Mol. Wt.: 445.55

Properties:

It is a white or almost white, odourless or almost odourless crystalline powder. Practically insoluble in water and alcohol, sparingly soluble in acetone, soluble in chloroform. It dissolves in dilute solutions of alkali hydroxides.

Absorption and Fate:

Glipizide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins and half-life\(^{13}\) of approximately 3.4 ± 0.7 h. It is metabolized in the liver and excreted in the urine largely as inactive metabolites.

Pharmacokinetics:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral availability</td>
<td>-</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Bound in plasma</td>
<td>98.4%</td>
</tr>
<tr>
<td>Clearance</td>
<td>0.52 ± 0.18 ml/minute/ Kg</td>
</tr>
</tbody>
</table>
Volume of distribution - 0.17± 0.02 L/Kg
Half-life - 3.4± 0.7 h

Adverse Effects, Treatment and Precautions:

Adverse Effects:

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea and metallic taste may occur with sulfonylureas and are usually mild and dose dependent. Increased appetite and weight gain may occur.

Hypoglycemia occurs with all hypoglycemic agents and may be severe, prolonged and sometimes fatal. Other severe effects may be manifestations of a hypersensitivity reaction. They include cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema, multiforme or the Stevens Johnson Syndrome, exfoliative dermatitis and erythema nodosum.

Treatment of Adverse Effects:

In acute poisoning the stomach should be emptied by emesis or lavage. Hypoglycemia should be treated with urgency.
Precautions:

Glipizide use in non-insulin dependent diabetes mellitus is contraindicated in patients with ketoacidosis and in those with severe infection, stress and trauma.

Glipizide should not be given in severe impairment of renal or hepatic function because of increased risk of hypoglycemia.

Packing and Storage:

Preserved in tight containers and protected from light, Glipizide (glucotrol) is marketed as 5 mg and 10 mg tablets. SR tablets containing 10 mg of glipizide are available commercially.

Therapeutic Uses:

Glipizide is used to control hyperglycemia in type-II diabetes. Usual initial dose in treatment of diabetes mellitus is 2.5 to 5 mg daily 3 or 4 times.

Immediate Release Tablets:

Mechanism of Action:

Glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning of beta cells in the pancreatic islets. The mechanism by which glipizide lowers blood glucose during long term administration has not been clearly established. Fasting insulin levels are not elevated even on long-term glipizide
administration, but the post-prandial insulin response continues to be enhanced after at least 6 months of treatment.

Pharmacokinetics:

Gastrointestinal absorption of glipizide in man is uniform, rapid and essentially complete. Peak plasma concentrations occur 1-3 h after a single oral dose. The half-life of elimination ranges from 2-4 h in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that the first pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. It has been reported that total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with a test meal in diabetic patients. Protein binding was studied in serum and found to be 98-99%, One hour after either oral or intravenous administration of glipizide.

The apparent volume of distribution of glipizide after intravenous administration was 11 L, indication of localization with in the extra cellular fluid compartment.

Metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and excreted mainly in the urine. Less than 10% unchanged glipizide found in the urine.
NEED FOR CONTROLLED RELEASE OF GLIPIZIDE

Oral hypoglycemic agents represent the most commonly practiced pharmacological approach to the treatment of NIDDM. Most of the physicians initially use sulphonylurea medications in the management of NIDDM, because they have a long history of proven efficacy and safety\textsuperscript{14-18}. Differences in the pharmacokinetic and Pharmacodynamic characters of the various sulphonylurea compounds produce different therapeutic side effect profiles\textsuperscript{19}. Longer – acting agents like glyburide or chlorpropamide are efficacious but tend to produce more sustained hyperinsulinemia and have higher rates of hypoglycemia during routine clinical use\textsuperscript{20-22}.

Short acting sulphonylureas such as glipizide is thought to be more efficacious in enhancing post-prandial insulin secretion and generally have a lower risk of hypoglycemia\textsuperscript{23-28}. But glipizide is having short biological half-life\textsuperscript{29} 3.4 ± 0.7 h, need to be administered more than once a day, which increases the possibility of non compliance and produce greater fluctuations in plasma drug levels both above and below therapeutic range\textsuperscript{30-31}. The drug profile makes glipizide a suitable candidate for formulating controlled release dosage form. This will reduce frequent dosage administration necessary to control hyperglycemia. It also maintains the optimum therapeutic drug concentrations with reduced adverse effects and finally will improve the patient compliance.
The physiology of NIDDM is associated with abnormalities in pancreatic insulin secretion and insulin resistance. Since, insulin resistance and hyper insulinemia have been observed as independent risk for clinical cardiovascular complications i.e., cardiomyopathy. Excellent glucose control with lower circulating insulin levels is considered to be a goal of therapy of NIDDM. The control of plasma glucose in patients with NIDDM is likely to have benefits in reducing or preventing the long term complications such as Diabetic nephropathy, Diabetic cardiomyopathy, Diabetic retinopathy, Diabetic neuropathy and gangrene.

The clinical reports on extended release glipizide indicated that it was significantly more effective than immediate release glipizide in reducing fasting plasma glucose levels. Both formulations reduced post-prandial plasma glucose levels equally; however, extended release glipizide extended its control in maintaining optimum therapeutic insulin and C - peptide levels. This suggests that controlled release of glipizide improves insulin sensitivity.

Controlled release of glipizide produces maximum therapeutic effect based on pharmacokinetic and pharmacodynamic relationships and it is much effective even in poorly controlled patients (those with fasting plasma glucose levels greater than 250 mg/dl). It was safe and well tolerated in a wide variety of patients with NIDDM and did not produce weight gain or adversely affect lipids. Cefalu et al, also reported that glipizide extended - release preparation is effective in lowering glucose tolerance and improving insulin
sensitivity without an increase in fasting insulin, weight gain, or change in abnormal fat composition.

Some of the adverse effects such as leucopenia, agranulocytosis, thrombocytopenia, hemolytic anaemia, aplastic anaemia, pancytopenia, hepatic porphyria, hyponatremia, syndrome of inappropriate antidiuretic hormone which are reported with usage of conventional dosage forms and other sulphonylureas, have not been observed with controlled release glipizide dosage forms\textsuperscript{40}. Controlled release formulations of glipizide will lower monthly drug acquisition costs and improves the patient compliance.

Controlled release formulations of glipizide will provide more stable therapeutic plasma drug concentrations over longer periods of time. This not only assists better glycemic control but also produce less fasting insulinemia. The incidence of hypoglycemia with controlled release formulations of glipizide is low (less than 3 %)\textsuperscript{41}.

**PAST WORK ON CONTROLLED RELEASE OF GLIPIZIDE**

Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients was studied by D.C. Gibbes et al\textsuperscript{42}. An evaluation of bioadhesive glipizide spheres and compacts from spheres prepared by Extruder / marumerizer technique was done by E.S. Ghaly et al\textsuperscript{43}. Development and evaluation of osmotically controlled oral drug delivery system of glipizide was done by Verma R.K. and Garg. S\textsuperscript{44}. Cyclodextrin complex osmotic tablet for glipizide delivery was developed by Gan, Y., et al\textsuperscript{45}. A preliminary evaluation
of glipizide spheres and compacts from spheres prepared by crosslinking technique was done by Garcia, J.G. and Ghlay, E.S\textsuperscript{46}. Characterization, \textit{in vitro} and \textit{in vivo} evaluation of mucoadhesive microcapsules of glipizide was made by Chowdary K.P.R. and Rao Y.S.\textsuperscript{47}. Bioavailability assessment of immediate and extended release formulations of glipizide in healthy volunteers was made by Dhawan, S. et al\textsuperscript{48}. Development of a controlled release low dose class II drug glipizide was made by Jamjad S. and Fassihi R\textsuperscript{49}. Pharmacological evaluation of membrane moderated transdermal systems of glipizide was done by Mutalik S. and Udupa N\textsuperscript{50}. Formulation and evaluation of mucoadhesive glipizide microspheres was carried out by Patel et al\textsuperscript{51}. 
Diclofenac sodium is a widely used non-steroidal anti-inflammatory analgesic and antipyretic drug.

**IUPAC Name:** Benzene acetic acid, 2-[(2,6-dichlorophenyl) amino], monosodium salt

**Formula:** C_{14}H_{10}Cl_{2}NO_{2}Na

**Molecular weight:** 318.13

**Description:** White to slightly yellowish crystalline powder, slightly hygroscopic.

**General Properties:**

**Melting Point:** Melts at about 280°C with decomposition.

**Solubility:** Freely soluble in methanol, soluble in ethanol (95%), sparingly soluble in water and in glacial acetic acid, practically insoluble in ether, in chloroform and in toluene.
Light Absorption: Absorbance of a 5% w/v solution in methanol at about 440 nm, not more 0.050 against methanol as blank.

Category: Analgesic and anti-inflammatory.

Dose: Orally or by Intramuscular injection, 25 to 75 mg.

Pharmacological Properties:

Diclofenac has analgesic, antipyretic, and anti-inflammatory activity. It is an inhibitor of cyclooxygenase, and its potency is substantially greater than that of indomethacin, naproxen, or several other agents. In addition diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of fatty acid.

Biopharmaceutics and Pharmacokinetics:

Absorption, Blood Plasma Concentration and Excretion: Diclofenac sodium is completely absorbed from the gastrointestinal tract after oral administration. The half life of diclofenac sodium is approximately two hours, with mean peak plasma levels of approximately 0.5 µg/ml and 1.0 µg/ml occurring 2-3 hrs after single doses of 25 mg and 50 mg of enteric coated tablets, respectively. Mean peak plasma levels of 1.9 µg/ml are reached two hours after a single dose of 75 mg. Four hours after dosing the levels still detectable in the plasma are equivalent to about 10% of the maximum concentrations. Rectal administration of diclofenac sodium suppositories produces rapid peak plasma concentration at a rate and level of the same order as oral administration of the drug in solution. In rats and dogs, majority of the
drug is found in the faeces, indicative of biliary excretion, whereas in rhesus monkeys 76% is excreted via the kidneys. In man renal excretion is greater than biliary excretion\textsuperscript{54}.

**Synovial Fluid Concentration:** Diclofenac sodium penetrates the Synovial membrane and diffuses into the Synovial fluid. From 4 to 24 h after dosing, Synovial levels for diclofenac sodium are higher than the corresponding plasma levels.

**Tissue Distribution:** Following rapid absorption, the drug is widely distributed with highest concentrations in the elimination organs (liver and kidneys) and in the blood.

**Pharmacokinetic Data:** The pharmacokinetic data of diclofenac sodium is summarized below\textsuperscript{55}.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability (oral)</td>
<td>54 ± 2%</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bound in plasma</td>
<td>&gt; 99.5%</td>
</tr>
<tr>
<td>Clearance</td>
<td>4.2 ± 0.9 ml min(^{-1}) kg(^{-1}), assuming 70 kg.</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.17 ± 0.11 L/kg, assuming 70 kg weight</td>
</tr>
<tr>
<td>Half-life</td>
<td>1.1 ± 0.2 h</td>
</tr>
<tr>
<td>Effective concentration</td>
<td>1.5-2 (\mu)g/ml</td>
</tr>
<tr>
<td>Toxic concentration</td>
<td>&gt; 4.5 (\mu)g/ml</td>
</tr>
</tbody>
</table>
Therapeutic Uses: Diclofenac sodium is approved for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The usual daily dosage for those indications is 100 to 200 mg given in several divided doses. It also may be useful for short-term treatment of acute musculo-skeletal injury, acute painful shoulder, postoperative pain and dysmenorrhea.

Toxic Effects: Gastrointestinal effects are the most common. Bleeding and ulceration or perforations of the intestinal wall have been observed. Elevation of hepatic amino transferase activities in plasma occurs in about 15% of patients. Other untoward responses to diclofenac include CNS effects. Skin rashes, allergic reactions, fluid retention, edema and rarely impairment of renal function.

Official Formulations: Diclofenac sodium injection I.P., Diclofenac sodium tablets I.P. with 25 mg and 50 mg strength56.
NEED FOR SUSTAINED RELEASE OF DICLOFENAC

Sustained release formulation is needed for diclofenac because of its short biological half-life\(^{57}\) of 2.0 h. The drug also causes\(^{58}\) g.i disturbances, peptic ulceration with bleeding if present in large concentrations in g.i. tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in g.i. tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac. A few sustained release products of diclofenac are available commercially.

PAST WORK ON CONTROLLED RELEASE OF DICLOFENAC

Various investigations described the sustained and controlled release of diclofenac by various techniques. Controlled release of diclofenac could be achieved by microencapsulation with ethyl cellulose\(^{59,60}\), cellulose acetate\(^{61,62}\), Eudragits\(^{63,64}\), Chitosan\(^{65}\) and hydroxypropyl methylcellulose phthalate\(^{66}\). Controlled release of diclofenac was also reported from matrices employing hydroxypropyl methylcellulose\(^{67}\), ethyl cellulose\(^{68}\), chitosan\(^{69}\), and pectin\(^{70}\) coating\(^{71}\) was also used to obtain controlled release of diclofenac sodium.
INDOMETHACIN - A PROFILE

Indomethacin is a widely used non-steroidal anti-inflammatory, analgesic and antipyretic drug.

IUPAC Name: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl indole-3-acetic acid.

Molecular formula: C_{19}H_{18}ClNO_4

Molecular weight: 357.79

Description: A pale yellow to brownish yellow, crystalline, odourless, almost tasteless powder.

GENERAL PROPERTIES:

Melting point: Crystals exhibiting polymorphism, one form melting at about 155°, the other at 162°C.

Solubility: Very slightly soluble in water. Soluble at 20°C in 51 parts of alcohol, 45 parts of ether, 30 parts of chloroform.
UV absorption: In a mixture containing 1 volume of 1N hydrochloric acid and 9 volumes of methanol, indomethacin exhibits maxima at 230 nm ($E_{1\%, 1\, \text{cm}} = 1006$) and 284 nm ($E_{1\%, 1\, \text{cm}} = 225$).

IR absorption: Major peaks in the infrared absorption spectrum of indomethacin are observed at 1226, 1236, 1478, 1690 and 1714 cm$^{-1}$.

Biopharmaceutics and Pharmacokinetics$^{72}$:

Absorption:

Absorption is delayed but not decreased after oral administration. After an oral dose of 25 mg of indomethacin, peak serum concentration of 0.88 μg/ml in case of fasting and 0.68 μg/ml in case of non-fasting humans are attained in 4 and 6 hrs respectively$^{73}$.

Half-life:

The decline in blood concentration is biphasic; the initial phase having a half-life of about 20 minutes and the second a half-life of about 70 minutes. Values ranging from 90 minutes to 16 h have been reported for biological half-life of indomethacin in the literature$^{74}$.

Distribution:

Indomethacin is 90% bound to plasma proteins and also extensively bound to tissues. It is not taken up by red blood cells and it enters the Synovial fluids.
Metabolism:

O-demethylation and N-deacylation followed by glucuronic acid conjugation, deacylation may occur directly or after demethylation, the products thus formed are desmethyl indomethacin (DMI), deschlorobenzoyl indomethacin (DBI), desmethyl deschloro benzoyl indomethacin (DMBI).

Excretion:

About 66% of a dose is excreted in the urine and 33% in the faeces, of the dose excreted in urine, 11% is unchanged. Probenecid reduces the renal excretion of indomethacin and dosing may increase the peak blood concentration by 50%.

Pharmacokinetic Data:

The pharmacokinetic data of indomethacin is summarized below:

- Availability (oral) 98%
- Urinary excretion 15 ± 8%
- Bound in plasma 90%
- Clearance 2.0 ± 0.4 ml min⁻¹ kg⁻¹, assuming 70 kg wt.
- Volume of distribution 0.26 ± 0.07 L/kg, assuming 70 kg wt.
- Half-life 2.4 ± 0.4 h
- Effective concentration 0.3 – 3 µg/ml
- Toxic concentration > 5 µg/ml
Action and Uses:

Indomethacin is an anti-inflammatory, antipyretic substance with analgesic properties. It is effective in relieving pain and swelling in cases of gout and rheumatoid and allied forms of arthritis and painful symptoms in other disorders of bone and joint, such as osteoarthritis and ankylosing spondylitis. It reduces swelling and tenderness of the joints, increases grip strength and decreases severity and duration of morning stiffness. A large single dose at bedtime enables the patient to obtain better quality sleep and provides good analgesia until mid morning. It may also reduce fever and relieve symptoms of febrile inflammatory condition such as glandular fever.

The usual dosage by mouth is 25 mg 2, 3 or 4 times a day with meals, but the dose may be increased if necessary to 200 mg daily if the drug is well tolerated. A suppository of 100 mg may be administered rectally once or twice daily when 100 mg is given by rectum on retiring; symptomatic relief is obtained through the night and ease from pain and stiffness the following morning. 75 to 100 mg given by mouth with food at bedtime may prove equally effective.

Undesirable Effects:

The most common undesirable effects are headache and various unpleasant cerebral sensations such as fullness, severe frontal headache, vertigo, light-headedness, mental confusion and dizziness. It also causes peptic ulceration with bleeding.
Formulations:

Indomethacin capsules (25 mg), Indomethacin Sustained Release and Timed-Release Capsules (75 mg) are available commercially.

Indomethacin Capsules and Indomethacin Extended-Release Capsules are official in USP XXIV\textsuperscript{75}. The following dissolution and drug release tests are prescribed in USP XXIV for indomethacin products.

Dissolution Test for Indomethacin Capsules:

Medium : One volume of pH 7.2 phosphate buffer mixed with 4 Volumes of water, 750 ml
Apparatus : Basket type
Speed : 100 rpm
Time : 20 minutes
Tolerances : Not less than 80\% (Q) of the labeled amount of indomethacin is dissolved in 20 minutes.

Drug Release Test for Indomethacin Extended Release Capsules

Test-I:

Medium : pH 6.2 Phosphate buffer, 750 ml
Apparatus : Basket type
Speed : 75 rpm
Time : 1, 2, 4, 6, 12 and 24 h
Tolerances: The percentage of the labeled amount of indomethacin dissolved at the times specified is as follows.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>between 10% and 25%</td>
</tr>
<tr>
<td>2</td>
<td>between 20% and 40%</td>
</tr>
<tr>
<td>4</td>
<td>between 35% and 55%</td>
</tr>
<tr>
<td>6</td>
<td>between 45% and 65%</td>
</tr>
<tr>
<td>12</td>
<td>between 60% and 80%</td>
</tr>
<tr>
<td>24</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>

Test.2:

Medium: pH 6.2 Phosphate buffer, 900 ml

Apparatus: Basket type

Speed: 75 rpm

Time: 1, 2, 4 and 12 h

Tolerances: The percentage of the labeled amount of indomethacin dissolved at the times specified is as follows.
<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>between 12% and 32%</td>
</tr>
<tr>
<td>2</td>
<td>between 27% and 52%</td>
</tr>
<tr>
<td>4</td>
<td>between 50% and 80%</td>
</tr>
<tr>
<td>12</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>

**Test - 3:**

- **Medium**: pH 6.8 Phosphate buffer, 750 ml
- **Apparatus**: Basket type
- **Speed**: 75 rpm
- **Time**: 1, 2, 4, 6, 12 and 24 h.
- **Tolerance**: The percentage of the labeled amount of indomethacin dissolved at the times specified is as follows.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>between 15% and 40%</td>
</tr>
<tr>
<td>2</td>
<td>between 35% and 55%</td>
</tr>
<tr>
<td>4</td>
<td>between 55% and 75%</td>
</tr>
<tr>
<td>6</td>
<td>between 65% and 85%</td>
</tr>
<tr>
<td>12</td>
<td>not less than 75%</td>
</tr>
<tr>
<td>24</td>
<td>not less than 85%</td>
</tr>
</tbody>
</table>
NEED FOR SUSTAINED RELEASE OF INDOMETHACIN

Sustained Release formulation is needed for indomethacin because of its short biological half-life\(^7\) of 2.4 ± 0.4 h and also due to its gastro-intestinal side effects such as peptic ulceration with bleeding if present in larger concentration in g.i. tract. Hence indomethacin is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in g.i. tract not only to prolong its therapeutic action, but also to minimize possible side effects of indomethacin. A few sustained release products of indomethacin are available commercially.

PAST WORK ON CONTROLLED RELEASE OF INDOMETHACIN

Several reports described the sustained and controlled release of indomethacin by various techniques\(^7\)\(^7\),\(^7\)\(^8\). Controlled release of indomethacin could be achieved by microencapsulation with ethyl cellulose\(^7\)\(^9\)\(^-\)\(^1\)\(^1\), calcium pectinate\(^8\), lactan-acetate\(^8\), and chitosan\(^8\). Controlled release of indomethacin was also reported from matrices employing polycarbophil\(^8\), chitosan\(^8\), hydrophilic cellulose\(^8\), and Eudragits\(^8\),\(^8\). Coating\(^9\),\(^9\),\(^9\), has also been used to obtain controlled release of indomethacin. Prolonged release of indomethacin was also achieved from w/o/w multiple emulsion systems\(^9\).

Sub-cutaneous implants made of appetite cements were reported to control release of indomethacin\(^9\). Lactate copolymeric hydrogels achieved longer periods of indomethacin release when given as injectables\(^9\) and were used for sustaining its release. Spheronization and coating techniques enabled
to formulate indomethacin for extended release. Application of a controlled –
porosity osmotic pump tablet (OPT) utilizing (SBE) 7m-β-CD was studied for
controlled release of indomethacin.
REFERENCES


89. Azarmi, S., Farid, J., Nakhodchi, A., Bahari, S.S. and Valizadeh, H.,


91. El-Mahrouk, G.M., Al-Meshal, M.A., Al-Angary, A.A. and Mahrous,


