LITERATURE REVIEW OF NSAIDs AND DRUGS SELECTED
CHAPTER IV

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Inflammation\textsuperscript{1} is defined as a directed tissue response to noxious and injurious, external and internal stimuli. Cell damage associated with inflammation acts on cell membranes to cause leukocytes to release lysosomal enzymes; arachidonic acid is then liberated from precursor compounds and various eicosanoids are synthesized. Cyclooxygenase (COX)\textsuperscript{2} pathway of arachidonate metabolism produces prostaglandins, which have a variety of effects on blood vessels, on nerve endings and on cells involved in inflammation. Among the COX isoforms, COX-1 is constitutively present in nearly all cell types at a constant level and tends to be homeostatic in function\textsuperscript{3}. It produces the prostaglandins necessary for the autocrine / paracrine responses and for the maintenance of normal renal functions, integrity of gastric mucosa and homeostasis. High concentrations of COX-1 are found in platelets, vascular endothelial cells, stomach and collecting tubules in kidneys. COX-2 activity is normally absent from cells (except those of kidneys and brain), but is induced\textsuperscript{3} during inflammation and tends to facilitate the inflammatory response.

Anti-inflammatory activity of NSAIDs is mediated chiefly through inhibition of biosynthesis of prostaglandins by inhibiting COX enzymes either non-selectively (inhibition of both COX-1 and COX-2) or selectively (inhibition of COX-2). Inhibition of COX-2 is thought to mediate the anti-pyretic, analgesic and anti-inflammatory actions of NSAIDs, but the simultaneous inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcers, most common side effect associated with non-selective COX inhibitors. NSAIDs are characterized by their ability to relieve pain without interacting with opioid receptors. They possess anti-platelet activity to varying
degree and are non-addicting. These drugs are chemically diverse, but most are organic acids with ionization constants ranging from 3.0 to 11.0. They have varying degrees of lipid solubility and are absorbed almost completely orally. They are highly protein bound and have small volumes of distribution. They are classified as

I. Non-Selective COX Inhibitors:

1. Salicylates and their congeners
   Aspirin, Sodium Salicylate, Diflunisal, Salsalate, Sulfasalazine

2. Para-aminophenol derivatives
   Acetaminophen

3. Pyrazolone derivatives
   Phenylbutazone, Oxyphenbutazone

4. Indoles and related drugs
   Indomethacin, Sulindac

5. Heterocyclic arylacetic acid derivatives
   Diclofenac, Tolmetin, Ketorolac, Aceclofenac

6. Propionic acid derivatives
   Ibuprofen, Fenprofen, Naproxen, Ketoprofen, Flurbiprofen.

7. Anthranilicacid derivatives (fenamates)
   Flufenamic acid, Mefenamic acid

8. Oxicams
   Piroxicam, Tenoxicam
II. Preferential COX-2 Inhibitors:

Nimesulide, Meloxicam, Nabumetone.

III. Selective COX-2 Inhibitors:

Celecoxib, Valdecoxib, Parecoxib, Etoricoxib
DICLOFENAC – A PROFILE

Diclofenac sodium is a synthetic non-steroidal, anti-inflammatory and analgesic compound.

Structure:

![Structure diagram]

It is chemically designated as 2-[(2,6-dichlorophenyl) amino] phenyl acetate mono sodium salt.

**Molecular formula:** C$_{14}$H$_{10}$Cl$_{2}$NO$_{2}$Na

**Molecular weight:** 318.3

**Physical characteristics:**

Diclofenac sodium is an odourless, white to half white, crystalline, slightly hygroscopic powder.

**Solubility:**

Freely soluble in methanol, soluble in ethanol (95%), sparingly soluble in water and glacial acetic acid, practically insoluble in ether, chloroform and toluene.

**Melting point:** 282.0° – 286.0° C
Dissociation constant and partition coefficient:

\[ p^{\text{Ka}} \text{ of diclofenac sodium in water is 4 and partition coefficient in octanol/aqueous buffer of } p^H 6.8 \text{ is 13.4.} \]

Pharmacological properties:

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

\[ \text{ED}_{50} \text{ is many times lower than anti-inflammatory NSAIDs and at least half that of indomethacin and naproxen. It markedly inhibits platelet aggregation in rats.} \]

Pharmacokinetics and metabolism:

Diclofenac is rapidly and completely absorbed after oral administration. Peak concentration in plasma is reached within 2-3 hours. Administration with food slows the rate but not alter the extent of absorption. There is a substantial first pass effect, such that only 50% of diclofenac is available systemically. The drug extensively bound to plasma proteins (99%) and its half-life in plasma is 1-2 hours. Diclofenac accumulates in synovial fluid after oral administration, which may explain duration of therapeutic effect that is considerably longer than plasma half-life. Diclofenac is metabolized in the liver by cytochrome P 450 isozyme of the CYP2C subfamily to 4-hydroxy diclofenac, the principle metabolite, and other hydroxylated forms, after glucuronidation and sulfonation, the metabolites are excreted in urine and bile (35%).
Therapeutic uses:

Diclofenac is used in long-term symptomatic treatment of rheumatoid arthritis, ankylosis and spondylitis. It is used for short-term treatment of musculoskeletal injury, acute painful shoulder, post operative pain and dysmenorrhea.

Toxic effects:

Gastrointestinal effects are more common. Other untoward effects include CNS effects, skin rashes, allergic reactions, fluid retention and edema and rarely impairment of renal function. Not recommended for children, nursing mothers of pregnant women.

Pharmacokinetic parameters:

Oral bioavailability (%) - 54±2

Urinary excretion (%) - 4

Bound in plasma (%) - >99.5

Half-life (hours) - 2 – 4

Dose:

Osteoarthritis: 50mg t.i.d or 75mg b.i.d

Rheumatoid arthritis: 50mg 3 or 4 times a day

Ankylosis spondylitis: 25mg q.i.d with an extra dose of 25mg at bed.
NEED FOR CONTROLLED RELEASE OF DICLOFENAC

Controlled release formulation is needed for diclofenac because of its short biological half-life of 2.0 – 4.0 h and also to minimize the g.i. disturbances such as peptic ulceration with bleeding, if present in larger concentration 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 gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.
PAST WORK ON CONTROLLED RELEASE OF DICLOFENAC

Design and evaluation of diclofenac CR tablets employing a new starch based polymer was carried out by Chowdary, K.P.R.\textsuperscript{10} et al. The objective of the investigation is to synthesize starch-urea-borate, a new starch based polymer and to evaluate its application in controlled release (CR) and in the design of diclofenac controlled release tablets. Starch-urea-borate polymer was synthesized by gelatinization of starch in the presence of urea and borax. Matrix tablets each containing 100mg of diclofenac sodium were formulated employing starch-urea-borate polymer in different proportions of drug and polymer and the tablets were evaluated. Diclofenac release from the formulated tablets was slow and spread over 24h and depended on percent polymer in the tablet. Release was diffusion controlled and followed zero order kinetics. Non-Fickian diffusion was the drug release mechanism from the formulated tablets. Diclofenac release from matrix tablets formulated employing 33% starch-urea-borate was similar to that from Reactin SR tablets, a commercial sustained release formulation of diclofenac. Starch-urea-borate polymer was found suitable for the design of oral controlled release tablets of diclofenac.

Design and Evaluation of Matrix-Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate was carried out by Amelia Avachat\textsuperscript{11} et al. The purpose of the study was to develop and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulphate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using tablet granulation technique to contain 100mg of DS and 400mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9hours in p\textsuperscript{H} 6.8 phosphate buffer using United States Pharmacopoeia (USP) type II dissolution apparatus. Along
with usual physical properties, the dynamics of water uptake and erosion degree of tablet were also investigated. The \textit{invitro} drug release study revealed that HPMC K 100CR at a concentration of 40\% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The releases of DS match with the marketed CR tablet of DS with similarity factor \((f_2)\) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release. The \textit{in vitro} release data of CS and DS can be effectively controlled from a single tablet using HPMC matrix system.

Design and evaluation of diclofenac sodium controlled drug delivery systems was carried out by Manjunatha. K.M.\textsuperscript{12} \textit{et al.} Sustained release dosage form of diclofenac sodium containing immediate and controlled release components was designed. Solid dispersion of immediate release component was prepared using polyvinyl pyrrolidone and mannitol carriers by common solvent method. Controlled release component was prepared in form of spherical beads by iontropic gelation technique. The beads were prepared based on dispersing drug in solutions of ionic polysaccharides such as chitosan and sodium alginate. These dispersions were dropped into solutions of counter ions such as tetrasyodium pyrophosphate and calcium chloride, respectively. The beads were also prepared using agar–drug hot solution into a mixture of chilled liquid paraffin and water. Then, diclofenac sodium controlled release drug delivery systems were prepared by combining the immediate release and controlled release components in different ratios. The formulations were found to be effective in providing controlled release of drug for a longer period of time. The beads were characterized by scanning electron microscopy and X-ray diffraction studies.

The role of polymer/drug interactions on the sustained release from poly (d,l-lactic acid) tablets was studied by Proikakis, C.S.\textsuperscript{13} \textit{et al.} The release profiles of model
drugs (propranolol HCl, diclofenac sodium, salicylic acid and sulfasalazine) from low molecular weight poly (d,l-lactic acid) [d,l-PLA] tablets immersed in buffer solutions were investigated in an attempt to explore the mechanism of the related phenomena. It was confirmed that drug release is controlled by diffusion through the polymer matrix and by the solubility as well as swelling and degradation rate of the polymer and therefore the overall drug release process. Physicochemical interaction between d, l-PLA and drug is an additional factor which influences the degree of matrix swelling and therefore is porosity and diffusion release process. Propranolol HCl shows extended delivery time at both examined pH values (5.4 and 7.4) and especially at pH 7.4 where release was accomplished in 190 days, most probably due to its decreased solubility at higher pH values. The acidic drugs gave shorter delivery times especially at pH 7.4. A slower drug release rate and more extended delivery time at pH 7.4 in comparison with that at pH 5.4 was recorded for tablets loaded with diclofenac sodium and salicylic acid. The opposite effect was observed with samples loaded with propranolol HCl.

Design and evaluation of Xanthan gum-based sustained release Matrix tablets of diclofenac sodium was carried out by Yeole, P.G. et al. In the present investigation, an attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios such as F1 (1:0.12), F2(1:0.16), F3(1:0.20), F4(1:0.24) and F5(1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution using basket method, and swelling index. All the formulations showed
compliance with Pharmacopoeial standards. Among different formulations, F1 showed sustained release of drug for 12 hours with 89.67% release. The effect of other parameters like addition of release modifier (PEG 6000), gum concentration, pH of dissolution medium, rotation speed and dissolution by paddle method, were also studied. Selected formulation (F1) was subjected to stability studies for three months at 0°-4°, room temperature (28°), and 45° with RH 75±5%, and showed stability with respect to release pattern. The kinetic treatment showed that the release of drug follows zero order kinetics ($R^2=0.9758$). Korsmeyer and Peppas equation gave value of $n=0.9409$ which was close to one, indicating that the drug was released by zero order kinetics. Thus, Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium.

Nanostructure-coated diclofenac-loaded microparticles: preparation, morphological characterization, in vitro release and in vivo gastrointestinal tolerance was done by Beck15 et al. This work reports the preparation and characterization of polymeric nanostructure-coated diclofenac-loaded microparticles. After spray-drying, powders presented 80% of yield and encapsulation efficiency of 83%. SEM analysis showed nanostructures adsorbed onto the surface of microparticles presenting surface area (BET) and pore volumes (BJH) (83 m² g⁻¹, 0.10 cm³ g⁻¹) smaller than the uncoated-core (163 m² g⁻¹, 0.25 cm³ g⁻¹). In vitro drug release experiments at pH 5.0 and 7.4 showed dissolution efficiencies of 34% and 78% (uncoated-core), 74% and 83% (physical mixture of raw materials), and 58% and 85% (nanostructure-coated microparticles), respectively. Mathematical modeling of the dissolution profiles fitted a biexponential model at pH 5.0 and a monoexponential model at pH 7.4. Regarding the digestive tolerance experiments, the total lesional indexes were 156.1 ± 48.5 for sodium diclofenac aqueous solution, 132.4 ± 45.7 for uncoated-core, 109.1 ± 35.8 for physical mixture and 29.9 ± 12.1 for microparticles showing a protective effect of these microparticles against the mucosal
diclofenac damage. This strategy of coating presents a potential use for oral administration of drugs.

Transdermal Delivery of an Analgesic Agent Using Elastic Liposomes: preparation, characterization and performance evaluation was made by Jain, N.\textsuperscript{16} et al. The aim of the present study was to prepare and characterize novel vesicular carrier elastic liposomes, of most commonly used non-steroidal anti-inflammatory agent diclofenac for its sustained and targeted delivery. Elastic liposomes of diclofenac were prepared and characterized \textit{in vitro} and \textit{in vivo}. The effect of different formulation variables like type of surfactant, concentration of surfactant and dose of drug on transdermal flux, amount of drug deposited into the skin, muscle and plasma concentration was investigated. The biological activity of optimized formulation was evaluated using carrageenan induced rat paw edema model and results were compared with commercial hydrogel formulation. The elastic liposomal formulations achieved muscle drug concentration between $2.2 \pm 0.14$ to $5.3 \pm 0.22\mu g/g$ at 12hr. The same dose of commercial hydrogel formulation produced drug levels between $0.41 \pm 0.07$ to $1.1 \pm 0.09\mu g/g$ in the muscle. Plasma concentration study showed regio specificity of elastic liposomal formulation. The results of \textit{in vivo} study revealed that incorporation of diclofenac in elastic liposomes increased its biological activity two fold as compared to commercial hydrogel formulation. The results of the present study demonstrated greater effectiveness of dermally applied diclofenac elastic liposomal formulation in comparison to conventional delivery system. The optimized elastic liposomal formulation offers a promising means for the non-invasive treatment of local pain and inflammation by topical application.

Biswajit Mukherjee\textsuperscript{17} and Kanupriya, prepared transdermal matrix patches containing diclofenac diethylamine with various polymeric combinations of polyvinyl
pyrrolidone and ethylcellulose and to study the mechanism of release of the drug from the patches and its skin permeation. Sorbitan monolaurate 20 (Span 20) of 0.1% w/v was added to this as a skin permeation enhancer. Cumulative amounts of drug released, per cm² of patch after 48 hours, were found to be 2.6111 mg, 3.53.

Oya Sanli and Gulsen Asman developed a controlled-release preparation of diclofenac sodium for transdermal administration. Poly (vinyl alcohol) (PVA) and PVA/poly (acrylic acid) (PAA) alloy membranes were prepared from a solvent-casting technique using different PVA/PAA (v/v) ratios. The release of the drug from the membrane was evaluated under in vitro conditions at pH 7.4. The delivery system provided linear release without time lag, burst effect, and boundary layer resistance. Effects of variables such as film thickness and PVA/PAA ratio on the permeation behavior of the polymeric membranes were discussed. The optimal PVA/PAA was determined as 50/50.

Synthesis of Chitosan Succinate and Chitosan Phthalate and their Evaluation as Suggested Matrices in Orally Administered, Colon-Specific Drug Delivery Systems was investigated by Khaled Aiedeh and Mutasem O. Taha. The naturally occurring polymer chitosan was reacted separately with succinic and phthalic anhydrides. The resulting semisynthetic polymers were assessed as potential matrices for colon-specific, orally administered drug delivery. Sodium diclofenac was used as the dispersed model drug. The prepared matrices were incorporated into tablets, which were evaluated in vitro. The evaluation included dissolution studies conducted under simulated gastrointestinal conditions of pH and transit times. The percentage fluid uptake was used to indicate the ability of the matrix to protect an embedded drug from gastric juices. The prepared matrices resisted dissolution under acidic conditions. On the other hand, improved drug release profiles were observed under basic conditions. Therefore, the results suggest the
suitability of the prepared matrices in colon specific, orally administered drug delivery system. However, future *in vivo* testing is planned to fully establish the suitability of the prepared polymers for colon-specific drug delivery.

Comparison of Diclofenac Spray and Gel on Knee Joints of Patients with Osteoarthritic Pain, was studied by Kilminster, S.G.\(^{20}\) and Mould G.P. Pain ratings by diary card and the SPI showed significantly improved analgesia and pain-induced mood changes equally with both preparations compared with a washout period with no drug treatment. The spray showed significantly faster onset of action than the gel on the SPI. 39 of 40 patients on both active treatments reported no gastrointestinal irritation. Subscales of the SPI also showed highly significantly improved pain-induced mood disturbance. Diclofenac gel and spray significantly improved osteoarthritis knee pain. Patient well-being was also significantly improved on the SPI. The spray showed significantly faster onset of action than the gel on the SPI.

Rosin derivatives: novel film forming materials for controlled drug delivery was investigated by Mandaogade, P.M.\(^{21}\) *et al.* Two new rosin derivatives (RD-1 and RD-2) were synthesized in the laboratory and evaluated for physicochemical properties, molecular weight (\(M_w\)), polydispersity (\(M_w/M_n\)) and glass transition temperature (\(T_g\)). Plasticizer free films of the derivatives were produced by casting/solvent evaporation method. The surface morphology (SEM), water vapour transmission and mechanical properties (tensile strength, percent elongation and modulus of elasticity) of the films were investigated. The derivatives were further evaluated for pharmaceutical film coating by characterizing the release of a model drug (diclofenac sodium) from non-pariel beads (pellets) coated with the derivatives. Pellet film coating could be achieved without agglomeration of the pellets within a reasonable operation time. Drug release from the
coated pellets was sustained up to 10h with the two rosin derivatives. These findings suggest the possible application of rosin derivatives (RD-1 and RD-2) for film coating.

*In vitro* studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices was carried out by Silvina, A.  et al. The objective of this study was to develop uncoated HPMC matrix tablets, evaluating the relationship and influence of different content levels of microcrystalline cellulose (MCC), starch and lactose, in order to achieve a zero-order release of diclofenac sodium. HPMC matrix tablets of diclofenac sodium using microcrystalline cellulose (MCC), starch and lactose were prepared by wet granulation process. The USP paddle method was selected to perform the dissolution profiles carried out in 900ml 0.1N HCl, and phosphate buffer. There was no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was modified in low percentage. Release kinetics of diclofenac sodium from these swollen matrices was principally regulated by starch (17 percent) or lactose (17 percent), even on the presence of MCC. When starch (8.5 percent) and lactose (8.5 percent) were mixed at lower concentration in a ratio 1:1, MCC (5 percent or 7.5 percent) appeared to control the drug release. The release profile remained unchanged after three months storage of tablets. The best-fit release kinetics was achieved with the zero-order plot, followed by the Higuchi and first-order equations. The data obtained proved that the formulations are useful for a sustained release of diclofenac, due to the percentage released after 8 hours is nearly to 70 percent. The release of diclofenac sodium was influenced by the presence of MCC, and by the different concentrations of starch and lactose. Drug release kinetics from these formulations corresponded best to the zero-order kinetics. Compared to conventional tablets, release of the model drug from these HPMC matrix tablets was prolonged; as a result, an oral release dosage form to avoid the gastrointestinal adverse effects was achieved.
Silvina A. Bravo and Maria, C. evaluated the effects of hydroxypropyl methylcellulose (HPMC) and carboxypolymer (Carbopol 934) on the release behaviour of diclofenac sodium (DS) from a swellable matrix tablet system. Nine different DS controlled-released tablets were compressed by using the wet-granulation technology. The influence of the polymer content, the polymer ratio, the polymeric swelling behaviour, and the pH changes and the release rate of DS was investigated. There was no significant difference in drug release when total polymer concentration was 10%. When the tablets were formulated having 20% or 30% of HPMC/carbomer, it was observed that a more rapid release of DS occurred as the carboxy polymer ratio within the matrices increased. The DS release from all matrix tablets was pH dependant, being markedly reduced at lower pH, and could be attributed to the poor solubility of DS at this pH value. In 0.1N HCl solution, HPMC controlled drug release because the carbomer has a low solubility at this pH. As the pH increased, the carbomer became ionized, being able to interact with HPMC to control the drug release.
ACECLOFENAC – A PROFILE

Chemically aceclofenac is [2, [(2,6-dichlorophenyl) amino] phenyl acetooxy acetic acid].

\[
\begin{align*}
\text{Molecular formula: } & \text{C}_{16}\text{H}_{13}\text{Cl}_{2}\text{NO}_{4} \\
\text{Molecular weight: } & 354.19 \\
\text{Melting point: } & 149-150^\circ\text{C} \\
\text{UV max: } & 275\text{ nm}
\end{align*}
\]

Properties

Aceclofenac is a white or almost white crystalline powder. Practically insoluble in water, freely soluble in acetone, soluble in alcohol. Aceclofenac is an orally administered non-steroidal analgesic and anti-inflammatory agent with a good gastrointestinal tolerability profile. It is official in B.P. Aceclofenac is used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and scapulohumeral periarthritis. It is also indicated for pains of various etiologies, such as musculoskeletal pain, dental pain or post surgical pain.

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase...
(selectivity cox-2 being evident)\textsuperscript{37,38} which is involved in the production of prostaglandins, believed that they mediate many of symptoms of inflammation such as oedema and pain.

**Pharmacokinetics**

**Absorption**

Aceclofenac is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached 1.0 to 3.0 hours following ingestion. The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced.

**Distribution**

Aceclofenac is highly protein bound (> 99.7%). The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. The volume of distribution is approximately 30 L.

**Elimination**

Renal excretion is the main route of elimination of aceclofenac with 70-80% of an administered dose found in the urine, 20% is excreted in the faeces mainly as conjugated hydroxyl metabolites. The mean plasma elimination half-life is 4.0 – 4.3 hours. Clearance is estimated to be 5 liters per hour. Aceclofenac is metabolized to a major metabolite, 4-hydroxy aceclofenac, and to a number of other metabolites including 5-hydroxy aceclofenac, 4-hydroxy diclofenac, diclofenac and 5-hydroxy diclofenac.

**Drug Interactions**

Aceclofenac may increase plasma concentrations lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics,
enhance cyclosporine nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. The co-administration of aceclofenac with other NSAIDs of corticosteroids may result in increased frequency of adverse event. The concomitant administration of aceclofenac and anti diabetic drugs may result hypo or hyperglycemia.

**Adverse Drug Reactions**

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%).

Although the incidence of gastrointestinal adverse events with aceclofenac was similar to those of other NSAIDs in individual clinical trails, withdrawal rates due to these events were significantly lower than with ketoprofen and tenoxicam. Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), and in rare cases paraesthesia and tremor.

**Dosage and Administration**

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening can be taken before or after food. There is no evidence that the dose of aceclofenac needs to be modified in patient with mild renal impairment but as with other NSAIDs caution should be exercised.

Elderly: Generally no dose reduction necessary.

Children: Safety and efficacy not established.

Hepatic insufficiency: Mild to moderate, 100 mg daily, severe – not recommended.
Renal insufficiency: Mild – treat with caution.

**Aceclofenac – A Balanced COX Inhibitor**

Human whole blood assays data shows inhibition of COX-2 by both the parent compound and 4-hydroxy aceclofenac, IC 50 values of COX-1 and COX-2 respectively were > 100 and 0.8 for aceclofenac and > 100 and 36 for 4-hydroxy aceclofenac.

Further evidence of COX-2 selectivity of aceclofenac has been shown by an IC 50 ratio (COX-2 : COX-1) of 0.26, which fell between IC 50 ratios of 0.7 and 0.12 for the COX-2 inhibitors celecoxib and Rofecoxib respectively.

Most recent data have shown aceclofenac to have the highest COX-1: COX-2, IC 50 ratio of a range of agents, including rofecoxib, celecoxib, nimesulide, diclofenac and tenoxicam.

Aceclofenac may prevent the degradation of particular connective tissue in patients with rheumatoid arthritis and osteoarthritis and this should be classified as unique NSAID.
NEED FOR CONTROLLED RELEASE OF ACECLOFENAC

Aceclofenac is a relatively new and widely prescribed NSAID drug. Aceclofenac is a potent inhibitor of cyclo-oxygenase enzyme (COX –2 Inhibitor). The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Controlled release formulation is needed for aceclofenac because of its short biological half life of 4.0 h, low and variable oral bioavailability due to its poor aqueous solubility and also to minimize the g.i. disturbances such as peptic ulceration with bleeding, if present in larger concentration in g.i. tract\textsuperscript{39}
Dashora, K. et al.\textsuperscript{40} investigated the effect of processing variables on microparticulate system of aceclofenac. The systems were prepared by modified solvent evaporation method using different variables such as polymer (cellulose acetate) : drug ratios ($1 : 9$, $1 : 6$, $1 : 3$ and $1 : 1$), agitation speed ($500 - 1500$ rpm) and stirring time ($5 - 15$ min). The effects of processing variables were evaluated by microparticle size and entrapment efficiency. The \textit{in vitro} drug release study was carried out with prepared microcapsules of various polymer concentrations and optimized processing variables and compared with conventional and SR- tablets. The conventional tablet and SR tablets releases maximum drug within 3 and 6 h respectively while microparticulate system releases more than 12 h. All formulations followed first order release kinetic and diffusion controlled drug release.

Vishal, Y. Joshi \textit{et al.}\textsuperscript{41} studied on dissolution rate enhancement of poorly water soluble drug, contributions of solubility enhancement and relatively low micelle diffusivity. Aceclofenac is the drug, alkyl polyglucosides and SLS are the surfactants used. Solid dispersion of drug with single and mixed surfactants was prepared using solution method with ethanol as the solvent. Physico-chemical evaluation was conducted by using Du Noux tensiometer method. The results showed that the mixed surfactant system enhances drug solubilization by many folds in comparison of single surfactant.

Dahiya, S. \textit{et al.}\textsuperscript{42} developed physico-chemical characterization and dissolution enhancement of aceclofenac by preparing solid binary systems of aceclofenac with HP\textbeta CD in equimolar ratio, using co-grinding, kneading and co-evaporating methods and compared with a physical mixture. The binary systems were characterized by differential scanning Calorimetry, thermo gravimetric analysis, mass spectroscopy, $^1\text{H}$ NMR
spectroscopy, scanning electron microscopy and in vitro dissolution studies. All the binary systems showed superior dissolution and lower dose: solubility ratio (D: S ratio) as compared to pure aceclofenac. The kneaded product exhibited the best dissolution. Hence, it was suggested that complexation of aceclofenac with HPβCD may be used as an approach to change the drug from BCS class II to BCS class I without changing its intrinsic permeability.

Shaikh, I.M. et al. studied the preformulation part and topical delivery of aceclofenac from lecithin organogels. Lecithins and excipients purity was determined. Partition coefficient of the drug was estimated. Effect of water added on the properties of lecithin organogels such as X-ray diffraction pattern, conductivity and viscosity were determined. The permeation study of aceclofenac from different concentrations of lecithin organogels has been determined. Aceclofenac solubility was found to be more in lecithin/oil reverse miscellar system as compared to its solubility in oil. These results showed that organogel exhibits useful pharmaceutical properties.

Yong, C.S. et al. carried out trails of clear aceclofenac loaded soft capsules with accelerated oral absorption in human subjects. They prepared five preparations containing various ratios of different solubilizers and their dissolution tests were studied. Among five preparations, a preparation with ethanolamine was selected because of its clear in appearance and showed the fastest dissolution rate. To evaluate and compare the pharmacokinetics of aceclofenac – loaded soft capsules with the conventional tablets, 2 x 2 crossover study was performed. Blood samples were collected and analysed for aceclofenac by HPLC method using UV detector. The results indicated that the soft capsule with ethanolamine was a more effective oral dosage form with fast absorption for poorly water – soluble aceclofenac than did conventional tablet.
Lee J. et al.\textsuperscript{45} formulated microemulsion systems for transdermal delivery of aceclofenac. They developed an o/w microemulsion system to enhance the skin permeability of aceclofenac. Eight different formulations with various values of oil, water and the mixture of surfactant and co-surfactant. The \textit{in vitro} transdermal permeability of aceclofenac from the microemulsions was evaluated using rat skin. The level of aceclofenac permeated was analyzed by HPLC and the droplet size of the microemulsions was characterized using a zetasizer nano-ZS. The results indicated that the microemulsion system studied was a promising tool for the percutaneous delivery of aceclofenac.

Yang, J.H. et al.\textsuperscript{46} prepared and evaluated of aceclofenac microemulsion for transdermal delivery system. Microemulsion was spontaneously prepared by mixing ingredients and the physicochemical properties were studied. The microemulsion system was physically stable at room temperature at least for 3 months. \textit{In vitro} and \textit{in vivo} performance of microemulsion formulation was evaluated. Skin permeation of aceclofenac from microemulsion formulation was higher than that of cream.

Zema, et al.\textsuperscript{47} studied the application of ultrasonics in assessing a dissolution test with improved discriminating ability towards micronised powders. They prepared two batches of a poorly soluble drug aceclofenac, the known and measurable differences in the dimensions characteristics of the powdered samples, particle size and specific surface area, were not reflected in the \textit{in vitro} dissolution rates assessed according to pharmacopoeial procedures. The test performed by using assembled apparatus enabling ultrasound application, allowed a clear distinction between the dissolution profiles of the two batches. The ultrasonics seems to promote drug particle dispersion, which overcomes their tendency to agglomerate due to the increase in the specific surface area associated with particle size reduction.
Alonso, M.J. et al.\textsuperscript{48} studied aceclofenac – loaded polyepsilon – caprolactone nanocapsules and the effect of coadjuvants on morphometrical, physico-chemical properties and drug entrapment. A central composite design was used to investigate the influence of polymerization adjuvants on these properties and the effect of polymer, oil and drug concentrations in organic phase on the size and encapsulation efficiency has been analysed.

Cordero, J.A. et al.\textsuperscript{49} made a comparative study on the transdermal penetration of a series of NSAIDs namely indomethacin, ketoprofen, diclofenac, Piroxicam, tenoxicam, ketorolac, and aceclofenac for the determination of the intrinsic transdermal permeabilities and to predict their potential for formulation in a transdermal therapeutic system. \textit{In vitro} studies demonstrated that the used drugs have low intrinsic permeation capacities and therefore, formulation with enhancers would have to be considered in an attempt to increase the fluxes of the NSAIDs.

Perez-Ruiz, F. et al.\textsuperscript{50} carried out the comparative study of the efficacy and safety of aceclofenac and tenoxicam in rheumatoid arthritis. Bioequivalence study data demonstrated that aceclofenac shows similar efficacy to tenoxicam in the treatment of rheumatoid arthritis and better safety profile than tenoxicam, mainly regarding gastrointestinal tolerability.

Arano, A. et al.\textsuperscript{51} studied the comparison of the anti-inflammatory effect and gastrointestinal tolerability of aceclofenac and diclofenac. Single and repeated demonstration for 5 days they reported that both drugs exerted an anti-inflammatory activity and exhibited a similar gastrointestinal tolerability in the rat.

Gowda, K.V. et al.\textsuperscript{52} carried out the evaluation of bioequivalence of two formulations containing 100 mg of aceclofenac. The study was designed as a single dose,
fasting, two-period two-sequence crossover study with a washout period of 1 week. The 
content of aceclofenac in plasma was determined by a validated HPLC method with UV 
detection. Pharmacokinetic parameters for both the formulations were found to be in 
better agreement with reported values. The 90% confidence interval of both the 
formulations ratios for the parameters were found to be within the acceptable range. They 
concluded both formulations were equal in terms of rate and extent of absorption.

Naji Najib, et al. studied the bioequivalence evaluation of two brands of 
aceclofenac 100 mg tablets in healthy human volunteers. The drug was administered with 
240 ml of water after a 10 hour overnight fast on two treatment days separated by one 
week washout period. Plasma samples were analyzed for aceclofenac by a validated 
HPLC method with UV-visible detector. Various pharmacokinetic parameters were 
determined from plasma concentrations for both formulations and found to be in good 
agreement with reported values. No significant difference was found based on ANOVA. 
90% confidence interval of test / reference ratio for these parameters were found to be 
within the bioequivalence acceptance range of 80-125%. Based on these statistical 
inferences they were concluded that test aceclofenac is bioequivalent to the reference 
tablet.

A bioequivalence study of aceclofenac tablets of two brands (Hifenac and 
Preservex) was conducted by INTAS in 12 healthy adult male Indian volunteers who 
received each medicine at a dose of 100 mg in a 2 x 2 cross over study. There was a two 
week wash out period between the doses. Plasma concentrations of aceclofenac were 
monitored by HPLC over a period of 24 hours after the administration. AUC_{inf} was 
calculated by the linear-log trapezoidal method. C_{max} and t_{max} were compiled from the 
plasma concentration – time data. ANOVA was carried out using logarithmically 
transformed AUC_{inf} and C_{max}, and non-transformed t_{max} : there were no significant
differences between the medications in $AUC_{inf}$ and $C_{max}$. The point estimates and 90% confidence intervals for $AUC_{inf}$ (parametric) and $C_{max}$ (parametric) were 91.17% - 105.88% and 85.10% - 109.09% respectively, satisfying the bioequivalence criteria of the European committee for proprietary medicinal products and the US Food and Drug Administration Guidelines. Moreover, the modified Pitman-Morgan's adjusted F-test indicated that the bioavailability of aceclofenac in the 2 medications were comparable regarding intra- and inter individual variability. Therefore, these results indicate that the 2 medications of aceclofenac are bioequivalent and, thus, may be prescribed interchangeably.

Kim, Y.G. et al.\textsuperscript{55} studied the bioequivalence of two aceclofenac tablet formulations after a single oral dose to healthy male Korean volunteers, who received each medicine at a dose of 100 mg in a 2 x 2 crossover study. Plasma concentrations of aceclofenac were monitored by HPLC. Pharmacokinetic parameters were determined and found to be in good agreement with reported values. The modified Pitman-Morgan's adjusted F-test indicated that the bioavailability of aceclofenac in the two medications were comparable regarding intra- and inter individual variability. On the base of the reports they concluded that the two medications of aceclofenac are bioequivalent and, thus, may be prescribed interchangeably.
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