2.1 PRODRUG OF DICLOFENAMIC ACID

Succinimide esters and glycine amides of diclofenac, d-naproxen, ibuprofen, ketoprofen, aspirin and indomethacin were studied by Singh et al., 1990 for in vitro enzymatic hydrolysis and their anti-inflammatory and ulcerogenic properties were compared with diclofenac.

The synthesis and study of morpholinoalkyl esters of diclofenac by Tammara et al. 1993 for oral delivery indicated that prodrugs followed biphasic kinetics of solid state decomposition, possess greater extent of absorption and found to be less irritating to gastric mucosa than diclofenac.

Tabrizi et al., 1996 synthesizes polymeric prodrugs of the diclofenac by attaching Diclofenac to poly(chloromethylstyrene), polyvinyl chloroacetate and polyethylene glycol through the hydrolyzable ester bonds, and assessed in vitro for usefulness as diclofenac prodrugs. These polymers were observed potentially useful as polymeric prodrugs but polyvinyl chloroacetate was found an appropriate carrier for release of the drug in human conditions.

Akgun et al., 1996 synthesized amide prodrugs of diclofenac, ibuprofen, naproxen and ketorolac by reacting with R-(−)-2-amino-1-butanol and did enantiomeric separation by preparative chromatography or crystallization. Prodrugs showed significant analgesic activity.

Jilani et al., 1997 prepared hydroxyethyl esters of diclofenac and mefenamic acid with the aim of obtaining enzymatically labile prodrugs, and their stability was evaluated in aqueous buffer solutions of pH 7.4, 1 N HCl, and also in human plasma. They found slow hydrolytic degradation of diclofenac ester in aqueous buffer solutions as shown by t_{1/2} values greater than 22 hr, while rapid enzymatic hydrolysis in the plasma (t_{1/2} = 1.12 hr).

Bandarage et al., 2000 synthesized a series of novel diclofenac esters containing a nitrosothiol (−S-NO) moiety as a NO donor functionality and evaluated in vivo for bioavailability, pharmacological activity, and gastric irritation. All S-NO-diclofenac derivatives were found orally bioavailable prodrugs, producing significant levels of diclofenac in plasma within 15 min after oral administration to mice and were gastric-sparing
in that they elicited markedly fewer stomach lesions as compared to the stomach lesions caused by a high equimolar dose of diclofenac in the rat.

The alkyl ester prodrugs of diclofenac were synthesized, and their physicochemical properties such as solubilities, partition coefficients, pKa's and stabilities in buffered solution and in human serum were investigated by Seung et al., (2000). They studied the permeation of prodrugs across hairless mouse skin employing flow-through diffusion cell. The result obtained by them was that the methyl and ethyl ester prodrugs showed higher lipid solubilities in terms of octanol-buffer partition coefficients (log P_{apparent}) of 5.5 and 5.1 at pH 7.0, respectively, when compared with diclofenac. They also investigated that prodrugs possessed moderate chemical stability in aqueous solutions of various pH except strong acidic and basic conditions and were readily converted to diclofenac in human serum. The prodrugs showed a higher flux across the hairless mouse skin than diclofenac, with a maximum enhancement of 2.6-fold compared to diclofenac. They, however, showed shorter lag time than diclofenac did, and poor aqueous solubilities. They were 1000 times more soluble in propylene glycol than in aqueous solution. Methyl and ethyl ester prodrugs had the pKa of 6.9 and 7.2, respectively.

The glycolamide ester prodrugs of diclofenac, ibuprofen, naproxen, mafenamic acid and indomethacin were evaluated for their GI toxicity, anti-inflammatory and analgesic activities. Prodrugs showed reduced GI toxicity and comparable results of biological activities (Khan et al., 2002).

Hirabayashi et al., 2002 synthesized novel bisphosphonic prodrug of diclofenac (DIC-BP), with the aim of osteotropic delivery of diclofenac and determined rat
pharmacokinetics as well as \textit{in vivo} disposition at whole body, organ and cellular levels in a dose range 0.32-10mg/kg.

Dalpiaz \textit{et al.}, 2004 investigated the transporter-mediated effects of diclofenamic acid and its ascorbyl prodrug in the \textit{in vivo} neurotropic activity of ascorbyl nipecotic acid conjugate. They investigated in detail the uptake mechanisms of SVCT-2 mediated anticonvulsant effect of ascorbic acid- Nipec into human retinal pigment epithelial cells (HRPE) and the \textit{in vivo} delivery of drugs such as diclofenac and nipecotic acid potentially effective in the CNS pathologies.

Khan \textit{et al.}, 2004 synthesized glyceride derivatives of diclofenac and evaluated their ulcerogenicity, anti-inflammatory and analgesic activity. They had also studied hydrolysis of prodrug at different pH and found that prodrugs showed better anti-inflammatory and analgesic activity the parent drug with low ulcerogenic index.

To improve the entry of certain drugs like Diclofenamic, Nipecotic and Kynurenic into brain, their ascorbic acid (AA) conjugates as prodrugs were synthesized and their capacity to interact with SVCT2 ascorbate transporters was explored by Manfredini \textit{et al.}, 2004. Kinetic studies clearly indicated that all of the conjugates were able to competitively inhibit ascorbate transport in human retinal pigment epithelial cells (HRPE) and \textit{in vivo} studies, in a mouse model system, demonstrated that conjugates showed better absorption as compared to the nonconjugated parent drugs.

Manon \textit{et al.}, 2009 synthesized the diclofenac-antioxidant mutual prodrugs by conjugating diclofenac with different antioxidants having antiulcerogenic activity. Screening of synthesized derivatives showed the retention of anti-inflammatory activity with reduced ulcerogenic side effects.

Nemmani \textit{et al.}, 2009 designed, synthesized and evaluated novel NO-releasing NSAID prodrugs such as NO-Aspirin and NO-Diclofenac. Although the amide-containing derivative 1d did not show any bioavailability, the remaining compounds showed fair to excellent pharmacokinetic, anti-inflammatory and gastric-sparing properties. Among them, however, the NO-Diclofenac showed the most promising pharmacokinetic, anti-inflammatory and NO-releasing properties and protected rats from NSAID-induced gastric damage which could be attributable to the beneficial effects of NO released from these prodrugs.
2.2 PRODRUGS OF IBUPROFEN

Klaus et al., 1989 studied 5-aminosalicylic acid conjugates of ibuprofen and naproxen for anti-inflammatory activity and gastrointestinal toxicity. They proved to be potent inhibitor of prostaglandin release in vitro.

Singh et al., 1990 synthesized Succinimide esters and glycine amides of diclofenac, d-naproxen, ibuprofen, ketoprofen, aspirin and indomethacin and studied for in vitro enzymatic hydrolysis and their anti-inflammatory and ulcerogenic properties have been compared with diclofenac.

Shanbhag et al., 1992 synthesized ester and amide prodrugs of ibuprofen and naproxen and evaluated their anti-inflammatory activity and GI toxicity. They found that maximum prodrugs were having better activity than parent drug.

Murtha et al., 1994 synthesized Cholesteryl ibuprofen and cholesteryl flufenamate and demonstrated for the feasibility of formulating prodrug into phospholipid microemulsions.
Samara et al., 1995 studied the pharmacokinetics of diethylcarbonate prodrugs of ibuprofen and naproxen and has been investigated in dogs. The rationale for development of prodrugs has been to suppress GI toxicity without adversely affecting their anti-inflammatory activity and to achieve rate and time controlled drug delivery of active entities. It has been concluded that the rapid conversion led to the lack of sustained release performance following oral administration of prodrug.

![Chemical structure](image1)

Akgun et al., 1996 synthesized amide prodrugs of diclofenac, ibuprofen, naproxen and ketorolac by reacting with R-(−)-2-amino-1-butanol and did enantiomeric separation by preparative chromatography or crystallization. Prodrugs showed significant analgesic activity.

![Chemical structure](image2)

Mahfouz et al., 1999 synthesized N-hydroxymethylsuccinimide −l isatin esters of ibuprofen and observed for release pattern of prodrug in a non enzymatic simulated gastric fluid model. These esters possess good potential as prodrugs with an improved therapeutic index.

Ingram et al., 2000 synthesized Glycerol-1,2-di-ibuprofenate-3-nitrate and has been studied for release pattern of prodrug in a simulated gastric fluid model with direct analysis by reverse phase HPLC. Nitroxylated derivatives of NSAIDs appeared to offer protection against GI toxicity normally associated with NSAIDs, ostensibly via local production of nitric oxide.

![Chemical structure](image3)
Bansal et al., 2001 synthesized a series of alkyl ester prodrugs of ibuprofen and studied their physicochemical properties and activity in the carrageenan induced rat paw oedema by topical route. They observed that favourable shift in lipophilicity and self penetration were factor in enhancing the response of prodrugs in improved topical activity over the parent drug ibuprofen.

Marco et al., 2001 obtained a new series of NSAIDs by linking ibuprofen to selected furoxan moieties and to release furazans and tested for their anti-inflammatory, antiaggregatory and ulcerogenic properties. The furoxan derivatives trigger potent antiaggregatory effects, principally as a consequence of their NO-donor ability.

Khar et al., 2001 made a series of Glycolamide ester prodrugs of ibuprofen and studied their physicochemical properties and activity in the carrageenan induced rat paw oedema. They showed better anti-inflammatory and analgesic activity but did not exhibit reduction in the ulcerogenicity on oral administration.

Doshi et al., 2002 studied the kinetics of decomposition of N-Mannich base derivatives of ibuprofenamide to assess their utility as a prodrug for ibuprofen, in an aqueous buffer at different pH in simulated gastric and intestinal fluids and in human plasma. The pH rate profile for these compounds had a sigmoidal shape.

Khan et al., 2002 synthesized Ibuprofen β-D-glucopyranoside. The prodrug has been tested for its biological activities and determined in vivo hydrolysis, partition coefficient and LD₅₀. Their results indicated a remarkable improvement in anti-inflammatory activity and analgesic activity with almost negligible number of GI ulcers as compared to ibuprofen.
Cocco et al., 2003 synthesized series of amides of ibuprofen with heteroaromatic amines and assayed *in vivo* activity for their analgesic properties. They concluded that some of the new amides exhibited a comparable or improved analgesic activity and a lower ulcerogenic effect as compared to ibuprofen.

Shaaya et al., 2003 synthesized mixed anhydrides of ibuprofen with fatty acids of different chain lengths and studied *in vitro* degradation of mixed anhydrides, drug release and analgesic effects.

Davaran et al., 2003 prepared 2-Mercaptoethyl ibuprofenate polyethylene glycol and the prodrug has been studied for hydrolytic behaviour and release pattern. It has been concluded that these prodrug could be used in topical formulations of NSAIDs because of enhanced transdermal penetration and stability to oxidation.

Khan et al., 2004 synthesized Glyceride prodrugs of ibuprofen. He has been studied for hydrolytic behaviour. Prodrugs did not break in stomach but released ibuprofen at pH 7.4 in adequate amounts. They suggested that both prodrugs were having better anti-inflammatory (upto 8 hours), better analgesic activity as compared to the parent-drug and were advantageous in having less GI side effects.

Chatterjee et al., 2007 masked carboxylic acid group by synthesizing its amide conjugates with ethylenediamine and benzathine by carbodiimide assisted coupling method.
Hydrolysis studies were carried out. Conjugates showed better analgesic, anti-inflammatory activity and less gastrointestinal side effects.

**Knaus E. et al., 2007** synthesized group of O$_2$-acetoxymethyl-protected diazeniumdioxide-based non-steroidal anti-inflammatory prodrugs (NONO-NSAIDs) by esterifying the carboxylate group of aspirin, ibuprofen, or indomethacin with O$_2$-acetoxymethyl 1-[N-(2-hydroxyethyl)-N-methylamino] diazeniumdioxide. Prodrugs significantly decreased carrageenan-induced rat paw edema showing enhanced in vivo anti-inflammatory activities relative to those of the parent NSAIDs. Prodrugs were significantly less ulcerogenic compared to the parent drugs.

**Babazadeh et al., 2008** synthesized vinyl ether type polymeric prodrugs of ibuprofen, ketoprofen and naproxen. He showed that drug could be released by hydrolysis of the amide bond. The polymer-drug conjugates were hydrolyzed in cellophane membrane dialysis bags containing aqueous buffered solutions (pH 1, 7.4 and 10) at 37°C and the hydrolysis solutions were detected by UV spectrophotometer at selected intervals. The polymer could be useful carriers for release of profens in controlled release system.

**Yu-Shiang et al., 2006** synthesized chondroitin sulfate based anti-inflammatory macromolecular based prodrugs and evaluated the release of drug in the absence and presence of either esterase or chondroitinase. Their results indicated a remarkable improvement in anti-inflammatory activity and analgesic activity with almost negligible number of GI ulcers as compared to ibuprofen.

### 2.3.1 PRODRUGS OF MEFENAMIC ACID

**Jilani et al., 1997** synthesized various acyloxyethyl mefanamates as potential prodrugs and examined their kinetics of hydrolysis in aqueous solutions of pH 1.0 and 7.4 and in human plasma at 37°C. Among the synthesized compounds, the beta-carboxypropionylethyl mefenamate and the pivaloyloxyethyl mefenamate showed high stability against enzymatic and non-enzymatic hydrolysis.

**Tantishayakul et al., 2002** synthesized mefenamic-guaiacol ester and investigated its physicochemical properties, stability, and transport across Caco-2 monolayers.
Series of N-Arylhydrazone derivatives of mefenamic acid (a known non-steroidal anti-inflammatory drug) were synthesized by Almasirad et al., 2005 in order to obtain new compounds with potential analgesic and anti-inflammatory activity. All compounds were evaluated for their analgesic and anti-inflammatory activities by abdominal constriction test (writhing test) and carrageenan-induced rat paw edema test respectively. Most of the synthesized compounds induced significant reduction in the writhing response when compared to control.

Khan et al., 2005 synthesised glyceride derivatives of mefenamic acid in order to reduce the gastrointestinal side effect. Its carboxylic group was condensed with the hydroxyl group of 1, 2, 3-trihydroxy propane 1, 3- dipalmitate/stearate to give ester prodrugs. These compounds were evaluated for their gastric toxicity, anti-inflammatory activity by the carageenan induced paw oedema test and analgesic activity by the acetic acid induced writhing method. The release of mefenamic acid from the esters was studied at pH 3, 4, 5 and 7.4 with direct analysis by reverse phase HPLC using acetonitrile : acetate buffer (0.1 M, pH 3.5) : methanol (40 : 25 : 35) at 1 mL/min. The prodrugs showed less hydrolysis at pH 5 compared to pH 7.4 indicating that the prodrugs do not dissociate at stomach pH but release mefenamic acid at pH 7.4 in adequate amounts. The hydrolysis studies were also performed in rat plasma.

In 2006, mutual prodrugs of mefenamic acid with D- glucosamine were evaluated for its analgesic, anti-inflammatory, ulcerogenic activity and performed Fruend’s adjuvant induced arthritis assay. The prodrug showed better anti-inflammatory, analgesic activity and found to possess excellent antiarthritis activity without any ulcerogenic tendency as compared to mefenamic acid (Hunja et al., 2006).

Dev et al., 2007 synthesized mefenamic acid prodrug of β-cyclodextrins. The primary hydroxy group of β-cyclodextrins was used to block the acid group. The synthesis involved a series of protection and deprotection reaction. The ester was evaluated for stability in simulated gastric and intestinal fluid. The hydrolysis of cyclodextrin conjugate in colon is confirmed by the hydrolysis kinetics studies in rat faecal material. The ester was also evaluated for ulcerogenicity. Results of these studies established the primary aim of masking
the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of mefenamic acid and equivalent doses of the ester.

**Rasheed et al., 2010** did synthesis, pharmacological activity, and kinetic studies of mefenamic acid (MA) prodrugs of tyrosine and glycine. The glycine prodrug showed maximum analgesic activity of 86%, and both tyrosine and glycine prodrugs showed better anti-inflammatory activity of 74% and 81%, respectively, when compared to the 40% of MA. Further, the prodrugs showed fewer gastric ulcers compared to MA.

### 2.4 PRODRUGS OF INDOMETHACIN

**Kahns et al., 1989** studied the hydrolytic kinetics of indomethacin and a glycolamide ester of the the drug to assess the possibility of designing a water soluble and solution stable prodrug of indomethacin suitable for parenteral or ocular administration. The esters showed a very pronounced water catalyzed hydrolysis which accounted for the limited stability. It was concluded that the design of an indomethacin ester prodrug with a stability allowing formulation of a ready to use aqueous solution might be difficult.

1-alkylazacycloalkan-2-one esters of indomethacin were investigated for their stability in aqueous media, in vitro enzymatic hydrolysis and their flux through excised human skin. 1-ethylazacycloalkan-2-one esters were readily hydrolyzed in vitro by porcine esterase and penetrated through excised human skin better than the parent drug (**Bomina et al., 1991**).

**Ueda et al., 1991** designed, synthesized and antiinflammatory activity of a new indomethacin ester 2-[N-[3-(3-(piperidinomethyl)phenoxy)propyl]carbamoylmethylthio]ethyl 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetate.

Morpholinoalkyl esters (HCl salts) of indomethacin and naproxen were evaluated by **Tammara et al., 1993** for in vitro and in vivo for their potential use as prodrugs for oral delivery. Prodrugs were 30-36% more bioavailable orally and significantly less irritating to gastric mucosa than parent drug.

**Caprariis et al., 1994** synthesized five indomethacin oligoethyl esters by using oligoethylene glycols (mol. Wt. range 106 to 282). Esters showed similar anti-inflammatory
activity, better or similar analgesic activity and found to be less or nonirritating to the gastric mucosa than indomethacin.

A prodrug of indomethacin, indomethacin octyl ester (IM-OE), was synthesized and its pharmacokinetics was investigated in rat. To describe the time course of the plasma indomethacin and IM-OE after intravenous (IV) and oral administrations, a pharmacokinetic model with four compartments was developed. A good fit was obtained between the observed and calculated curves based on the model (Ogiso et al., 1994).

Six indomethacin N-aclactam esters were studied for in vitro enzymatic hydrolysis and human skin permeation activity by using IPM (Isopropylmyristate) as a vehicle. Only three derivatives showed increased lipophilicity and water solubility compared to the parent drug and provided a moderate enhancement of in vitro indomethacin skin permeation (Bonina et al., 1995).

The time course of the pharmacodynamic response and the pharmacokinetic profile of triethylene glycol indomethacin ester after oral administration in rats had shown the good pharmacological activity without eliciting ulcerogenic effect (Bonina et al., 1997).

Palagiano et al., 1997 synthesized indomethacin terpenoid esters by using (-)-Limonen-10-ol, (s)(-)-perillyl alcohol,(1S-endo)(-) borneol and (1R, 2S,5R)- (-) menthol as terpenoidal promoieties and assessed both in vitro and in vivo as indomethacin dermal prodrugs.

1-Ethylazacycloalkan-2-one indomethacin esters were evaluated by Bo and concluded that prodrugs were stable in pH 7.4 phosphate buffer and in simulated gastric fluid, Prodrugs showed anti-inflammatory, analgesic activity and notably inhibit the GI irritation induced by indomethacin (Bonina et al., 1997).

Mutual prodrugs of indomethacin with salicylicamiide and its mannich bases were synthesized by Bahekar et al., 1998. The results of hydrolytic studies indicated that hydrolysis followed first order kinetics. Prodrug displayed moderate analgesic activity, comparable anti-inflammatory activity and no ulcerogenic activity in comparision to indomethacin due to blockage of free acidic group of indomethacin by its glyceride formation.
2.5 PRODRUGS OF KETOPROFEN

Larsen and Jensen assessed the bioavailability of ketoprofen after oral administration of aqueous solutions of various ketoprofen-dextran ester prodrugs in pigs. The average absorption fractions for the different prodrugs ranged from 100 to 67%. Thus, they concluded that dextran ester prodrug could be applied to provide selective colon delivery of drugs possessing a carboxylic acid functional group (Larsen et al., 1991).

**Larsen et. al., 1992** applied deconvolution to estimate the in vivo dissolution/release process of ketoprofen from a ketoprofen-dextran ester prodrug in pigs. They concluded that following administration of the dextran prodrug, the plasma concentration curves and the dissolution/release profiles were uniform with small inter individual variations.

**Rautio et al., 1998** synthesized a series of acyloxyalkyl esters of ketoprofen as well as naproxen and investigated as topical dermal prodrugs. Generally the prodrugs showed similar dermal delivery as the parent drug through cadaver skin.

Six new 1-alkylaza-cycloalkan-2-one esters of ketoprofen were prepared and evaluated as potential dermal prodrugs of ketoprofen. Prodrugs were evaluated for their lipophility, chemical and enzymatic stability, permeation through excised human skin and investigated the in vivo topical anti-inflammatory activities of esters (Bonina et al., 2003).

Mutual prodrug of ketoprofen with D-glucosamine was synthesized and found to be resistant to acidic hydrolysis and followed first order kinetics. The compounds showed comparable anti-inflammatory activity by carrageenan induced rat paw edema method, slightly less analgesic activity compared to ketoprofen when screened carrageenan induced hyperalgesia method. The prodrug was found to possess excellent antiarthritic activity without any ulcerogenic activity as compared to ketoprofen when screened for ulcerogenic activity by cold stress method of Rainsford (Pophalikar et al., 2004).

2.6 PRODRUGS OF ACELOFENAC

**Rasheed et al., 2009** did synthesis, hydrolysis studies and pharmacodynamic profile of novel colon-specific mutual prodrug of aceclofenac with amino acids through the formation of amide linkage. The amino acids like histidine, alanine, tyrosine and glycine were chosen as promoiety because they had broad spectrum of anti-inflammatory,
cytoprotective and immunomodulatory properties and therefore would synergize the effect of prodrug. In vitro reconversion of prodrugs carried out in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF) showed that the prodrugs remained intact in SGF and SIF, except SCF. In SCF, the rat fecal content containing colonic enzyme (amidase) hydrolyzed the amide linkage of synthesized prodrugs and free aceclofenac was released marked reduction of ulcer index and an increase in anti-inflammatory activities were observed for the prodrugs and proved to be better in action in the colon as compared to the parent drug.

Dhaneshwar et al., 2011 did synthesis, studied release kinetics and pharmacological profile of chimeric Aceclofenac prodrug. They reported design and development of prodrug of aceclofenac with L-tryptophan aiming at reducing its ulcerogenic propensity and enhancing its anti-inflammatory potential using chimeric approach. The amide prodrug was synthesized by routine DCC coupling and its structure was established and confirmed by spectral analysis. The release kinetics was studied by HPTLC in hydrochloric acid buffer (pH 1.2) and phosphate buffer (pH 7.4) simulating the pH environment of stomach and small intestine respectively. The prodrug was extensively screened for analgesic, anti-inflammatory and ulcerogenic activities in acute and chronic animal models to evaluate the correctness of chimeric prodrug design. Prodrug showed longer duration of action with better inhibition of inflammation, anti-arthritis activity and rise in the pain threshold than aceclofenac and diclofenac owing to contribution of L-tryptophan towards anti-inflammatory and analgesic activities.

Novel amino acid conjugates of aceclofenac were developed and characterized by Bendale et al., 2011. Amino acid conjugate of Aceclofenac was synthesized by conventional coupling method using N,N-dicyclohexylcarbodiimide and it was characterized by melting point, TLC, UV, FT-IR, NMR and mass spectroscopy. Alanin-aceclofenac conjugate has maximum water solubility, while in methanol and chloroform solubility of remaining synthesized compounds showed greater result than parent compound.

2.7 PRODRUGS OF ASPIRIN

Ankersen et al., 1989 synthesized eleven new aspirin prodrugs and these superaspirin were subjected to non- enzymatic hydrolysis for a first rapid screening in vitro. Only 2-(2,6-
dimethoxybenzyloxy)-2-methyl-4H-1,3-benzodioxin-4-one was observed to act as an exclusive aspirin prodrug, while 2(2-methoxybenzyloxy)-2-methyl-4H-1,3 benzodioxin-4-one and 2-(2-ethoxybenzoyloxy)-2- methyl-4H-1,3-benzodioxin-4-one were shown to release both aspirin and salicylic acid. These three candidates were further characterized by investigation of the pH profile of their hydrolysis rates.

The synthesis and study of a novel series of potential prodrugs of indomethacin, ketoprofen, ibuprofen and aspirin were reported by Abordo et al., 1998. 2-Formylphenyl esters of the NSAIDs, together with two 6-substituted 2-formyl and two 2-acylphenyl aspirins and 4-formylphenyl indomethacin, have been prepared. A study of their alkaline and neutral hydrolysis showed that these compounds, with the exception of 2-acetylphenyl aspirin, act as true prodrugs of the NSAIDs, giving the NSAID and acylphenol. The rates of hydrolysis and activation parameters indicated that the 2-acylphenyl esters employ an intramolecular catalytic route. The 2-formylphenyl esters were found to be more potent as anti-inflammatory agents than the parent compounds in the carragheenan-induced paw oedema test.

Ester prodrugs of Aspirin, Ibuprofen, Naproxen and indomethacin were synthesized by Mahfauz et al., 1999 using N-Hydroxymethylsuccinimide and N-Hydroxymethylisatin as promoieties to reduce their gastrointestinal toxicity and improve bioavailability. The kinetics of hydrolysis of synthesized prodrugs was studied at 37 °C in nonenzymatic simulated gastric fluid (pH 1.2) and 0.02M Phosphate buffer (pH 7.4), 80% human plasma and 10% rat liver homogenate.

Erdmann et al., 2000 synthesized a biodegradable poly (anhydride-ester) by melt condensation polymerization of the acetylated monomer to yield a novel polymeric prodrug. The synthesized polymer was composed of alkyl chains linked by ester bonds to aromatic moieties, specifically salicylic acid, the active component of aspirin. With the medicinal properties attributed to salicylic acid and the ease of metabolism, the incorporation of this compound into a polymer backbone yielded a polymeric prodrug with hopeful potential in a variety of applications (i.e., inflammatory bowel disease). The in vitro hydrolytic degradation of these polymers indicated that the polymer degradation rate was pH-dependent.

### 2.8 PRODRUGS OF PROPYPHENAZONE
Naproxen-propyphenazone (NAP-PP) esters were synthesized by Sheha et al., 2002 as prodrugs with the aim of improving the therapeutic index through prevention of gastrointestinal irritation and bleeding. The kinetics of ester hydrolysis was studied in two different non-enzymatic buffer solutions, at pH 1.2, and 7.4 as well as in liver homogenates. Study of analgesic and anti-inflammatory properties in comparison with the reference compounds has shown that both analgesic and anti-inflammatory activities were present at the same doses of the investigated compounds. The ester prodrug was found to be less irritating to gastric mucosal membrane than the parent drugs.

2.9 PRODRUGS OF ALLOPURINOL

Seven novel N1-acyl derivatives of allopurinol were synthesized and evaluated as potential prodrugs by Bundgaard et al., 2002, with the purpose of developing preparations suitable for rectal and parenteral administration. The kinetics of hydrolysis of the derivatives was studied in aqueous solutions at various pH-values and in human plasma solutions at 37°C. All the compounds hydrolyzed to yield allopurinol in quantitative amounts and rate expressions were derived to account for the pH-rate profiles observed. The rates of hydrolysis were accelerated by plasma enzymes, the half-lives of hydrolysis in 80% human plasma solutions at 37°C being 6, 4, 2.5 and 4 min for the N1-acetyl, N1-propionyl, N1-butyryl and N1-benzoyl derivatives, respectively. These N-acyl derivatives were more lipophilic than allopurinol as determined by partition experiments in octanol-water but the solubility in water was even greater (the N1-acetyl derivative) or only slightly reduced (the other derivatives) as compared with allopurinol. This behaviour was attributed to decreased intermolecular hydrogen bonding in the crystal lattice achieved by blocking the 1-NH group by acylation. It was suggested that N1-acylation may be a promising means of obtaining prodrug forms of allopurinol with the aim of enhancing the rectal delivery characteristics of the drug.