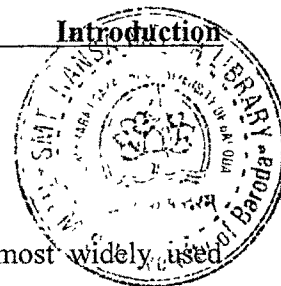


Chapter – 1

INTRODUCTION



1. INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely used therapeutics, used primarily for the treatment of pain and inflammation in general, and especially arthritis¹. From a historical viewpoint, the first NSAID with therapeutic benefits was aspirin, which has now been used for more than a 100 years as an NSAID. The overall worldwide production of about 50,000 tons of aspirin a year reflects the importance of this substance even today². In 1970s, a scientific breakthrough occurred with the elucidation of the molecular mechanism of aspirin and other NSAIDs. Since then, many different NSAIDs have been introduced in market, which are a heterogeneous group of compounds¹, often unrelated chemically (although most of them are organic acids). These anti-inflammatory substances block the biosynthesis of prostaglandins (PGs), which contribute to a variety of physiological and pathophysiological functions. The therapeutic effects and side effects of these acidic anti-inflammatory agents are closely related to their biochemical mechanism of action.

1.1 CHEMICAL CLASSIFICATION¹

The acidic non-selective COX inhibitor NSAIDs are classified into the following subclasses:

1. Salicylic acid derivatives: Aspirin, sodium salicylate, choline magnesium trisalicylate, diflunisal, salicylsalicylic acid, sulfasalazine, osalazine.
2. *p*-Aminophenol derivatives: Acetaminophen
3. Indole and indene acetic acids: Indomethacin, sulindac
4. Heteroaryl acetic acids: Tolmetin, diclofenac, ketorolac
5. Arylpropionic acids: Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin, fenbufen
6. Anthranilic acids (fenamates): Mefenamic acid, meclofenamic acid
7. Enolic acids: Oxicams (piroxicam, tenoxicam), pyrazolidinediones (phenylbutazone, oxyphenbutazone)
8. Alkanones: Nabumetone

Selective COX-2 inhibitors

1. Indole acetic acids: Etodolac
2. Sulfonamides: Nimesulide
3. Diaryl-substituted furanones: Rofecoxib
4. Diaryl-substituted pyrazoles: Celecoxib

1.2. PHARMACOLOGICAL ACTIONS AND THERAPEUTIC ACTIVITIES OF NSAIDS

The major mechanism by which NSAIDs elicit their therapeutic effect is inhibition of prostaglandin (PG) synthesis. All NSAIDs, including selective COX-2 inhibitors are anti-inflammatory, antipyretic and analgesic¹. One important exception is acetaminophen, which is antipyretic and analgesic but is largely devoid of anti-inflammatory effect.

1.2.1 Anti-inflammatory effect

The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury, although in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reason. Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms:

- 1) an acute transient phase, characterized by local vasodilation and increased capillary permeability;
- 2) a delayed, subacute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells; and
- 3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur

Several classes of leukocytes play an essential role in inflammation. Although earlier studies emphasized the promotion of migration of cells out of microvasculature, recent studies have examined the role of endothelial cells and of cell adhesion molecules, including E-, P-, and L- selectins, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and leukocyte integrins in the adhesion of leukocytes, platelets, and endothelial cells at sites of inflammation³⁻⁵.

NSAIDs may inhibit expression or activity of certain of these cell adhesion molecules. Such effects have been described for some NSAIDs, but not others, suggesting that interference with action of cell adhesion molecules is not a common mechanism of action of all NSAIDs. Nonetheless, effects of adhesion molecules may contribute in part to the anti-inflammatory action of some NSAIDs⁶.

The NSAIDs inhibit the biosynthesis of PGs in most of the cells, however, they generally do not inhibit the formation of eicosanoids such as leukotrienes, which also contribute to inflammation, nor do they affect the synthesis of numerous other inflammatory mediators for eg. histamine.

NSAIDs find their chief clinical applications as anti-inflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, oosteoarthritis, and ankylosing spondylitis. In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease and do not arrest progression of pathological injury to tissue.

1.2.2 Anti-pyretic effect

Hypothalamus regulates the set point at which body temperature is maintained⁷. Fever may be the result of infection or one of the sequel of tissue damage, inflammation, graft rejection, malignancy, or other disease states. A common feature of these conditions is the enhanced formation of cytokines such as IL-1 β , IL-6, interferons alpha and beta, and tumor necrosis factor (TNF α). The cytokines increase the synthesis of PGE₂ in circumventricular organs in and near preoptic hypothalamus, which then leads to increase in body temperature. NSAIDs inhibit the PG production in hypothalamus and act as antipyretic agents.

1.2.3 Analgesic effect

Bradykinin, released from plasma kininogen, and cytokines, such as TNF α , IL-1 and IL-8 appear to be particularly important in eliciting the pain in inflammatory condition. These agents liberate prostaglandins and probably other mediators that promote hyperalgesia. In general, NSAIDs do not affect the hyperalgesia or the pain caused by direct action of prostaglandins, consistent with the notion that the analgesic effect of

these agents is due to inhibition of prostaglandin synthesis. However, some data have suggested that relief of pain by these compounds may occur via mechanisms other than inhibition of prostaglandin synthesis, including antinociceptive effects at peripheral or central neurons^{8,9}.

When employed as analgesics, these drugs usually are effective only against pain of low-to-moderate intensity, such as dental pain. Although their maximal effects are much lower, they lack the unwanted effects of opioids on the central nervous system, including respiratory depression and the development of physical dependence. NSAIDs do not change the perception of sensory modalities other than pain. Chronic postoperative pain or pain arising from inflammation is particularly well controlled by NSAIDs whereas, pain arising from the hollow viscera usually is not relieved.

Some other uses of NSAIDs also depend upon their capacity to block prostaglandin biosynthesis. The release of prostaglandins by the endometrium during menstruation may be a cause of severe cramps and other symptoms of primary dysmenorrhea; treatment of this condition with NSAIDs has met with considerable success¹⁰.

1.2.4 Other uses

Prostaglandin E₂ has been implicated in the humoral hypercalcemia associated with some neoplasms, and treatment with NSAIDs can effectively suppress serum calcium levels in some cancer patients^{11,12}.

Excessive production of renal prostaglandins has been implicated in the pathogenesis of some of the metabolic abnormalities in the Bartter's syndrome, and NSAIDs have been found to be useful in the treatment of this disorder¹³.

An important area where the use of NSAIDs is emerging is in the prevention of colon cancer. Frequent use of aspirin has been reported¹⁴ to be associated with striking reduction (approximately 50%) in the incidence of colon cancer.

1.3. SIDE EFFECTS OF NSAIDs THERAPY

In addition to sharing many therapeutic effects, NSAIDs share several unwanted side effects as listed below:

1.3.1 Blockade of platelet aggregation

Platelet function is impaired because NSAIDs prevent the formation by the platelets of thromboxane A₂ (TXA₂), a potent aggregating agent. This accounts for the ability of these drugs to increase the bleeding time. This side effect has been exploited in the prophylactic treatment of thromboembolic disorders

1.3.2 Inhibition of uterine motility

Prolongation of gestation by NSAIDs has been demonstrated in both experimental animals and women. Accordingly, some NSAIDs have been used as tocolytic agents to inhibit preterm labor, including selective COX-2 inhibitors¹⁵.

1.3.3 Inhibition of PG-mediated renal function

Clinically relevant, adverse effects on renal function have been well recognized with the use of nonselective NSAIDs; recent evidence suggests that selective COX-2 inhibitors also have the propensity to cause such effects¹⁶. NSAIDs have little effect on renal function in normal human subjects presumably because the production of vasodilatory prostaglandins has only minor role in sodium-replete individuals. However, these drugs decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure, hepatic cirrhosis with ascitis, chronic renal disease, or in those who are hypovolemic. Acute renal failure may be precipitated¹⁷ under these circumstances

In addition to their hemodynamic effects in the kidney, NSAIDs promote the retention of salt and water by reducing the prostaglandin-induced inhibition of both the reabsorption of chloride and the action of antidiuretic hormone. This may cause edema in some patients who are treated with NSAIDs; it also may reduce the effectiveness of antihypertensive regimens¹⁸. These drugs also promote hyperkalemia by several mechanisms.

1.3.4 Hypersensitivity reaction (Bronchoconstriction)

Certain individuals display intolerance to aspirin and most NSAIDs; this is manifested by symptoms that range from vasomotor rhinitis with profuse watery secretions, angioneurotic edema and bronchoconstriction with resultant asthma, flushing, hypotension and shock. The underlying mechanism for this reaction is not known, but a common factor appears to be ability of the drugs to inhibit cyclooxygenase activity. This has promoted the hypothesis that the reaction reflects the diversion of arachidonic acid metabolism towards the formation of increased amounts of leukotrienes (which act as bronchoconstrictors)¹⁹ and other products of lipoxygenase pathways.

1.3.5 NSAID- induced gastroduodenal mucosal injury

The mammalian gastrointestinal (GI) system may be conceptualized as a segmentally differentiated tube ("alimentary canal") to optimize nutrient absorption and waste excretion from ingested foodstuffs^{20, 21}. Along the GI tract, a mucosal lining functions as the dynamic interface between the deeper layers of the tissue wall and the lumen content. In the stomach, the mucosa and the surface layer of cells lining the gastric epithelium are interposed between the deeper blood vessel-rich layers of the muscular stomach wall and the gastric content being digested within the strongly acidic stomach lumen. The mucosal lining of the GI tract, particularly in the stomach, is exposed continuously to potentially damaging agents such as acids, microbial toxins, bile, and digestive enzymes²¹. Several endogenous mechanisms help to maintain the integrity and restitution of the gastric mucosa and defend it from potential injury^{22, 23}. The mucus gel layer secreted by mucosal cells act at the gastric epithelium as a barrier to acidic (pH 2.0) gastric juice and noxious substances such as alcohol, bile acids, and digestive enzymes. The mucus gel layer thereby helps to maintain the tissue pH (7.2) of the cells in the stomach wall and reduce mechanical tissue trauma during food digestion²⁴. A second major contributor to gastric protection is locally secreted bicarbonate, which serves to neutralize the acidic gastric juice and maintain organ acid/base balance²⁵. A third critical element in gastric homeostasis is perfusion of the stomach wall with nutritive, oxygenated blood at a level sufficient to support normal cellular physiology and remove unnecessary, if not potentially damaging substances from the tissue²⁶. Finally, mucosal PGs support several gastric defence mechanisms by inhibiting stomach acid secretion, promoting mucus and bicarbonate secretion, and enhancing the gastric mucosal blood flow^{27, 28}. PGs E₂ and I₂

additionally exert a cytoprotective effect upon the gastric mucosa independent of their influence upon gastric acid secretion^{29, 30}.

The chronic use of NSAIDs compromises the mucosal defense system and elicits the most common unwanted side effect of inducing gastric or intestinal ulceration that sometimes can be accompanied by anemia from the resultant blood loss. Patients who use non-selective NSAIDs on a chronic basis have about three times greater relative risk for serious adverse gastrointestinal events compared to nonusers³¹. Non-selective NSAIDs vary considerably in their tendency to cause such erosions and ulcers. Schoen and Vender²² proposed that NSAID-induced gastric damage occurs as a result of a dual insult when NSAID-mediated direct (and indirect) acid damage is followed almost simultaneously by the deleterious effect of PG inhibition. This dual mechanism has also been described by other investigators^{32, 33}. Hence, gastric damage caused by these agents can be brought about by at least two different mechanisms involving a local ("Topical") effect and the systemic effects.

a) Local effect on GI tract

The first mechanism involves a local action comprising of a direct contact mechanism and an indirect effect on the GI mucosa. The direct effect can be attributed to a combination of a local inhibition of PG synthesis in the GI tract. The indirect effect can be attributed to a combination of an ion-trapping mechanism of NSAIDs in mucosal cells and back diffusion of H^+ ions from the lumen into the mucosa. Most NSAIDs are weak organic acids ($pK_a \sim 3-5$) bearing a free carboxylic acid group under moderately acidic or neutral conditions. The lipophilicity of most NSAIDs allows them to diffuse readily through the gastric mucus and into gastric epithelial cells. The cytoplasmic pH (7.2) favors intracellular NSAID dissociation to water soluble ionized forms, resulting in trapping of hydrogen ions. In this way, a significant NSAID concentration gradient is established across the epithelial-cell membrane and causes back-diffusion of damaging acidic gastric juice in an attempt to reduce the tissue load of free NSAID ions. This results in increased membrane permeability of gastric epithelial cells²². Topical irritation is considered an important factor in establishing superficial stomach erosion, particularly in the corpus region of the stomach.

b) Systemic effects

The second mechanism is based on the generalized systemic action occurring after absorption and can be manifested after i.v. dosing. Systemic effects^{22, 29} of NSAIDs also play a role in the tissue pathologic response, mainly reflecting a reduction in the constitutive biosynthesis of PGs that serve as cytoprotective mediators in the GI system. The principal therapeutic effects of NSAIDs reflect their inhibition of cyclooxygenase enzymes catalyzing PG production. Most of the currently used NSAIDs non-selectively inhibit the two known COX isoforms, the constitutive COX-1 enzyme and the enzyme induced in settings of inflammation, COX-2. Inhibition of gastric PG (particularly PGI₂ and PGE₂) synthesis promotes gastric acid secretion, reduces bicarbonate and mucus production, and restricts mucosal blood flow-responses that counter gastric defense and could predispose stomach tissue to damage. Enhanced adherence of activated neutrophils to the gastric vascular endothelium in regions of low mucosal blood flow may exacerbate and amplify tissue damage in a pro-inflammatory manner through the release of oxygen-derived free radicals and proteases³⁰.

Hence, the pathogenesis of GI injury in any given case of NSAID-induced gastropathy likely reflects a multifactorial tissue insult from NSAID ion-trapping, NSAID-mediated topical irritation, and the deleterious consequences of reduced tissue PGs due to the NSAID inhibition of cyclooxygenase.

1.4. APPROACHES USED TO REDUCE GI TOXICITY OF NSAIDs

To prevent the topical injury due to the carboxyl group of acidic NSAIDs, various approaches have been explored in past. The strategies that have been used to reduce the GI injury caused by these drugs include design of prodrugs requiring hepatic drug metabolism for cyclooxygenase activity, enteric coating to prevent absorption in stomach, parenteral administration, co-administration of acid secretion inhibitors or exogenous prostaglandins. The development of selective COX-2 inhibitors was thought to be a reasonable target for safer NSAIDs. However, serious doubts for a substantial benefit³⁴ have been recently expressed for such an approach.

1.4.1 The prodrug approach

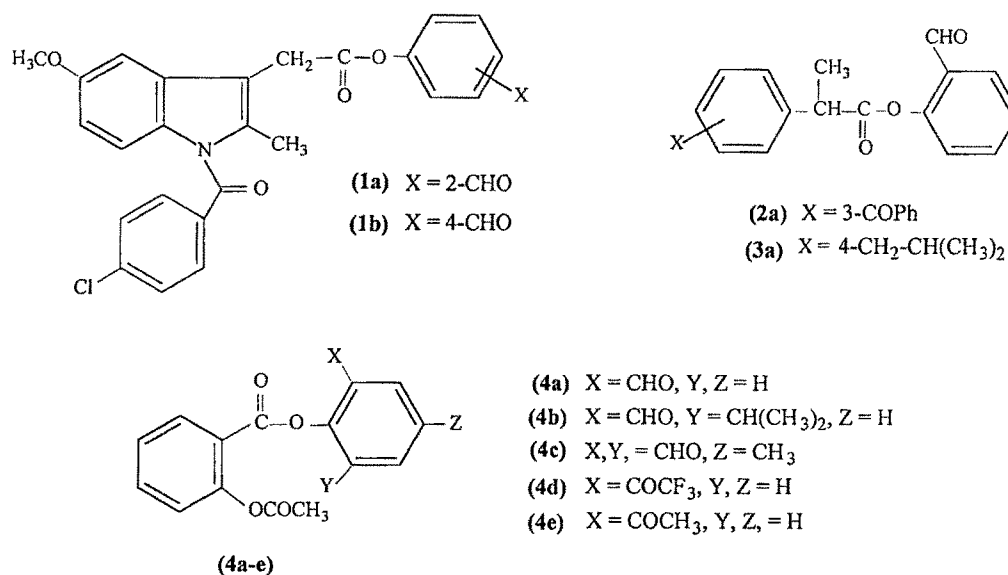
The development of prodrugs to mask the acidic group of NSAIDs temporarily has been regarded as a promising approach to reduce their GI toxicity. As proposed by Albert³⁵ (1958), a prodrug is defined as an inactive pharmacological derivative of an active parent compound, which undergoes a spontaneous or enzymatic transformation resulting in the release of free drug. Prodrugs have been designed for several purposes, e.g., to overcome pharmaceutical and/or pharmacological problems such as incomplete absorption, poor systemic bioavailability, too rapid absorption or too rapid excretion, toxicity, poor site-specificity, as well as formulating problems³⁶⁻³⁸. A compound can be regarded as a potential NSAID prodrug when it maintains the desired activity of the parent drug while unwanted side effects are eliminated or notably reduced. To achieve such a pharmacological profile, an NSAID prodrug should exhibit some important requirements³⁹ as given below:

- 1) The prodrug should show a good stability in aqueous solutions and in the gastrointestinal fluid so as to temporarily mask the acidic group of the NSAIDs prior to absorption in the GI tract.
- (2) The prodrug should have suitable water solubility and lipophilicity to ensure absorption by the oral route, and
- (3) The prodrug should be readily hydrolyzed following gastric absorption to release the parent drug.

Besides decreasing the GI toxicity, different promoeities have been taken into consideration to design new efficacious prodrugs of NSAIDs to improve bioavailability, or for target organ delivery or for increasing the topical absorption in comparison with parent drug. The chemical coupling of a nitric oxide (NO)-releasing moiety to the parent NSAID (based on the fact that NO is an important mediator in gastric mucosal defence⁴⁰) is another recent strategy for devising a GI-sparing NSAID. However, the present chapter describes the various attempts made with different moieties for decreasing the GI toxicity of NSAIDs by derivatizing the acidic carboxyl group to ester or amide moieties.

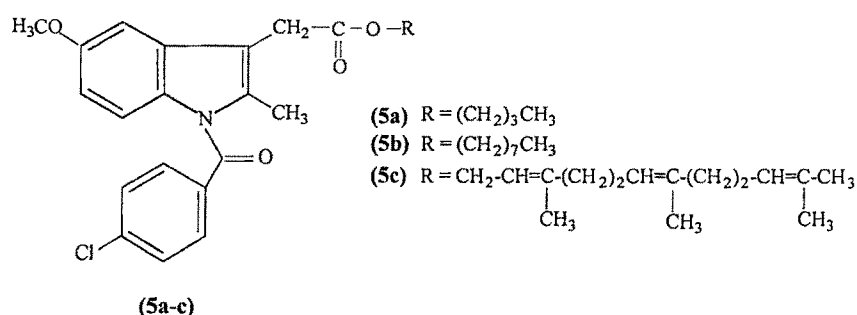
1.4.2 The ester and amide prodrugs of clinically used NSAIDs

The synthesis and studies of a novel series of potential prodrugs of indomethacin, ketoprofen, ibuprofen and aspirin were carried out by Abordo *et al*⁴¹. The 2-Formylphenyl esters of indomethacin (**1a**), ketoprofen (**2a**), ibuprofen (**3a**) and aspirin (**4a**), together with two 6-substituted-2-formyl (**4b**, **4c**) and two 2-acylphenyl aspirins (**4d**, **4e**)



and 4-formylphenyl indomethacin (**1b**) were prepared. The 2-formylphenyl esters (**1a**, **2a**, **3a**, **4a**) were found to be more potent as anti-inflammatory agents than the parent compounds in the carrageenan-induced paw edema test.

In order to develop a potential prodrug of indomethacin which causes less gastric irritation, the ester prodrugs, n-butyl ester (**5a**) and n-octyl ester (**5b**) of indomethacin

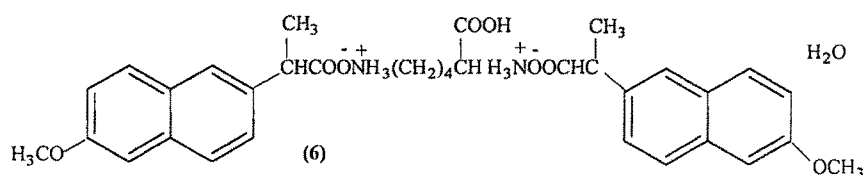


were synthesized and evaluated⁴² for their ulcerogenic activity and hepatic injury after oral administration in rats. The ulcerogenic activity and hepatic injury, expressed by

decreased hepatic microsomal enzyme activities, were hardly seen after repeated oral administration of prodrugs, in contrast to the severely irritating effects of indomethacin alone.

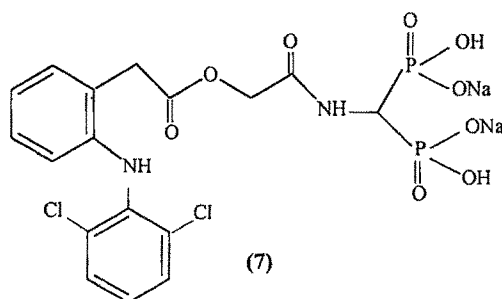
Indomethacin farnesil (**5c**), an ester prodrug of indomethacin has been reported⁴³ to cause less gastric damage than indomethacin and loxoprofen due to its lower potency for inhibiting the gastric mucosal prostaglandins.

Naproxen lysinate (**6**) was synthesized by Lalla *et al*⁴⁴ to obtain enhanced solubility of the drug in water in order to enable its formulation into a parenteral dosage form.



Hydrazide derivatives of naproxen, diclofenac, ibuprofen and indomethacin were synthesized⁴⁵ and evaluated for their anti-inflammatory and analgesic activities in rodent models.

Disodium 2-(2,6-dichloroanilino)phenylacetoxycetaminomethylene biphosphonate (**7**) a biphosphonic prodrug of diclofenac was synthesized based on the concept of Osteotropic



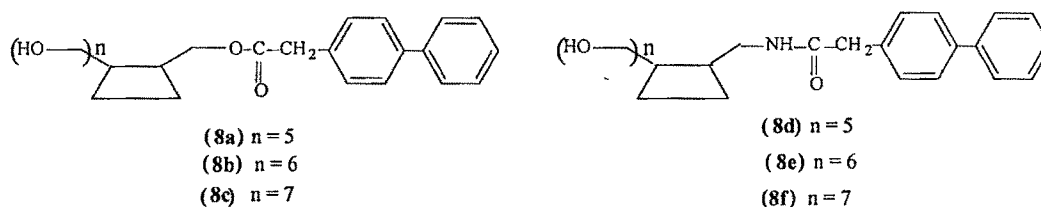
Drug Delivery System and was investigated⁴⁶ for its potency and controlled delivery of the parent drug diclofenac to the bones in rats. No side effect of gastrointestinal damage, typical of NSAIDs was observed, for this prodrug (**7**).

A new polymerizable drug derivative of diclofenac sodium was synthesized and characterized by Chandrasekar *et al*⁴⁷. The *in vitro* study showed that the drug release takes place predominantly at higher pH and in a sustained manner, as hypothesized, with complete drug absorption from the polymeric prodrug and a statistically significant decrease in ulcer scores was observed demonstrating the potential for site-specific and sustained drug delivery.

Ethyl esters of flurbiprofen-*L*-arginine, flurbiprofen-*L*-lysine and flurbiprofen-*p*-guanidino-*L*-phenylalanine were synthesized and were evaluated⁴⁸ for their availability as prodrugs for flurbiprofen.

The hydrolysis kinetics of various alkyl, glycolamide, aminoethyl, and 2-(1-imidazolyl)ethyl esters of ibuprofen and flurbiprofen in 80% human plasma were investigated⁴⁹ and in each case the *R*-isomer ester was found to undergo faster plasma catalysed hydrolysis than the corresponding *S*-isomer ester.

Six 4-biphenylacetic acid prodrugs coupled to alpha, beta and gamma-cyclodextrins through an ester or amide linkage, 6-O-[(4-biphenyl)acetyl]- $\alpha/\beta/\gamma$ -cyclodextrins (**8a-c**) and 6-deoxy-6-[(4-biphenyl)acetyl]- $\alpha/\beta/\gamma$ -cyclodextrins (**8d-f**) were prepared and the *in vivo* drug release behaviour of these prodrugs in rat gastrointestinal tracts after oral



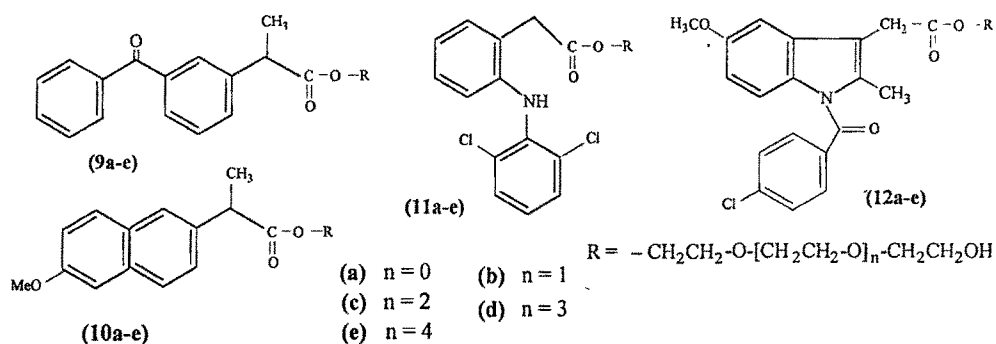
administration was investigated by Minami *et al*⁵⁰. The results suggested that the cyclodextrin prodrug approach can provide a versatile means for construction of not only colon-specific delivery systems but also delayed-release system of certain drugs.

4-Biphenylacetic acid selectively conjugated to one of the hydroxyl groups of β -cyclodextrin through an ester or amide linkage to give (**8b**) and (**8e**) conjugates respectively, were investigated⁵¹ for the physicochemical properties (aqueous solubility

and hydrolysis), and the results suggested that the ester-type conjugate of beta-cyclodextrin (**8b**) may serve as colon-targeting prodrug.

Jung *et al*⁵² reported a simple synthetic route for the preparation of amino acid conjugates of 5-aminosalicylic acid (5-ASA) and prepared 5-aminosalicyl-glycine (5-ASA-Gly) in good yield. *In vitro* and *in vivo* properties of 5-ASA-Gly as a colon specific prodrug of 5-ASA were investigated using rats as the test animals. Incubation of 5-ASA-Gly with cecal or colonic contents at 37°C released 5-ASA in 65 or 27% of the dose in 8 h, respectively. No 5-ASA was detected from the incubation of 5-ASA-Gly with the homogenates of stomach or small intestine.

Polyoxyethylene esters of ketoprofen (**9a-e**), naproxen (**10a-e**) and diclofenac (**11a-e**) were tested⁵³ *in vitro* to determine their stability in pH 7.4 phosphate buffer and in simulated gastric fluid (pH 2.0 buffer) and their susceptibility in undergoing enzymatic cleavage in human plasma. All the prodrugs showed good stability in both the buffers and were readily hydrolyzed by human plasma. Anti-inflammatory activity of the esters was found to be similar to their respective parent drugs although at higher doses and



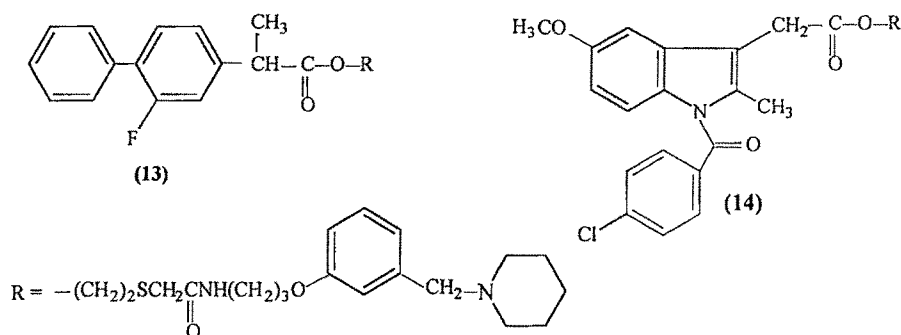
good analgesic activity was exhibited following acute administration with significantly reduced gastric irritation even at higher doses than the respective parent drug.

Polyoxyethylene esters of ketoprofen (**9a-e**), naproxen (**10a-e**) and diclofenac (**11a-e**) were also evaluated⁵⁴ as dermal prodrugs. The aqueous solubilities, lipophilicities and hydrolysis rates of esters were determined in buffered solution and in porcine esterase, and the *in vitro* permeation studies through human skin were also studied. The esters showed good water solubility, good stability in buffer and rapid enzymatic cleavage,

with increased flux through stratum corneum and epidermis membranes compared to their respective parent drugs. An appreciable and sustained *in vivo* topical anti-inflammatory activity was observed for the ester prodrugs in the erythema model in human volunteers.

Five indomethacin oligoethylene ester derivatives (**12a-e**) were synthesized and evaluated⁵⁵ for their anti-inflammatory, analgesic and ulcerogenic activity after oral administration. The esters showed an anti-inflammatory activity similar to parent drug and all the prodrugs exhibited better or similar analgesic activity compared to indomethacin and were significantly less irritating to the gastric mucosa than the parent drug, after oral administration of doses even higher than that of indomethacin.

The drug conjugate (**13**) of flurbiprofen with a histamine H₂ receptor antagonists, N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]-2-(2-hydroxyethylthio)acetamide was synthesized and investigated by Imai *et al*⁵⁶ for the reduction in gastric damage, and for the enzymatic hydrolysis in 10% rat plasma. A significant reduction in gastric toxicity in

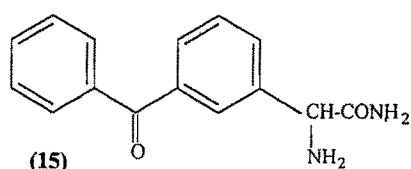


comparison with an equivalent dose of flurbiprofen was observed with rapid plasma catalysed hydrolysis.

The ester prodrug 2-[N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]carbamoylmethylthio]ethyl 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (**14**) was prepared⁵⁷ from a new histamine H₂-receptor antagonist, N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]-2-(2-hydroxyethylthio)acetamide and indomethacin. The ester was shown to be essentially similar to indomethacin in its anti-inflammatory potency and

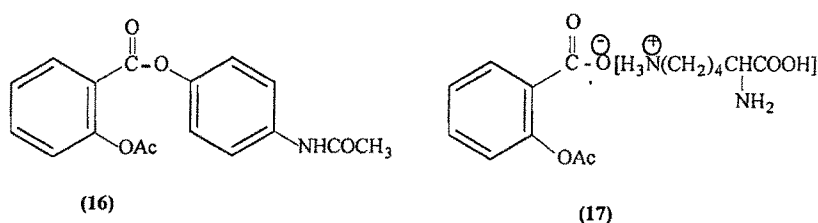
almost completely inhibited carrageenan-induced hind-paw edema in the rat at a high dose of 230 mg/kg, which is comparable to 100 mg/kg of indomethacin, without producing gastric lesions. On a molar basis, the acute gastric lesioning properties of the ester were nearly hundred times less than those of indomethacin resulting in over a twenty-fold improvement in the ratio of antiedema activity to ulcerogenicity.

Nepafenac (**15**), the amide analog of the NSAID amfenac, was examined⁵⁸ *in vitro* for its bioactivation by ocular tissue components and for its ability to permeate through external ocular barriers. Rabbit tissues catalysed a concentration dependent conversion of nepafe-



nac to amfenac and enhanced permeability of nepafenac (**15**), combined with rapid bioactivation to amfenac by the iris or ciliary body and retina or choroid, suggesting it as a target specific NSAID for inhibiting prostaglandin formation in the anterior and posterior segments of eye.

Decreased gastrointestinal irritation was claimed by Croft *et al*⁵⁹ for both benorylate (**16**)

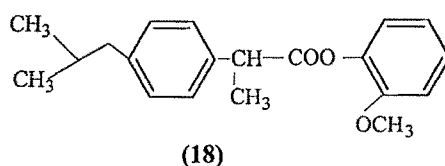


and the lysine salt of aspirin⁶¹ (**17**), the latter producing three times less gastrointestinal bleeding than its parent acetyl salicylic acid.

Succinimide esters and glycine amides of naproxen, ibuprofen, ketoprofen, aspirin, diclofenac and indomethacin have been synthesized by Singh *et al*⁶⁰. The succinimide esters retained their anti-inflammatory property whereas the glycine amides exhibited

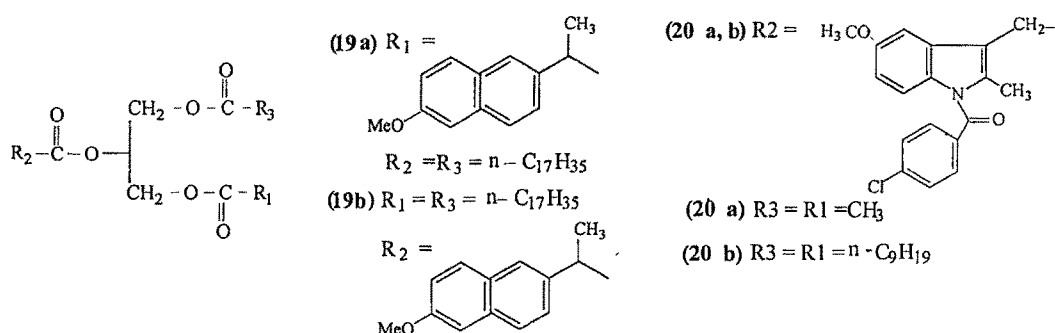
lower activity as compared to those of the parent drugs. The glycine amides showed no hydrolysis at lower pH and in gastric fluid till 2 hours and had less GI toxicity than succinimide esters which exhibited complete hydrolysis within 15 minutes in the gastric fluid.

Cioli *et al*⁶² have investigated the toxicological and pharmacological profile of ibuprofen guaiacol ester (18). The gastrointestinal toxicity, behavioural disorders and acute toxicity of the ester were much reduced in comparison to ibuprofen. The ester and



the parent drug at equimolar doses, were equally effective in edema and fever. The ester was found to be better tolerated than its parent drug because of its peculiar pharmacokinetics i.e. the slow release of the parent drug, which reduced its local and general toxicity.

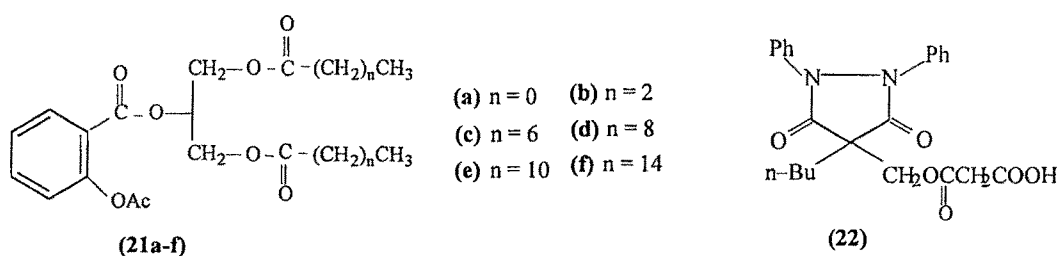
Triglyceride derivatives^{63, 64} of naproxen (19a-b) and indomethacin (20a-b) along with various other heterocyclic anti-inflammatory agents have been prepared. Comparison of the 2-glyceride of naproxen (19b) with naproxen for gastric irritation, as determined by



the minimum chronic dose producing occult blood in either faeces or urine in dog, gave a dose ratio of 3 in favor of the 2-glyceride (19b), and the 2-glyceride (20b) of indomethacin showed a 2.5 to 3.0 fold improvement in the therapeutic index

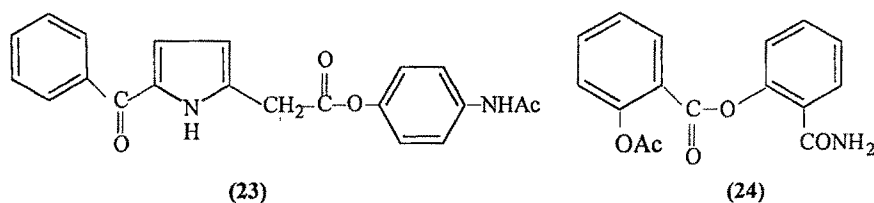
(ulcerogenic dose causing lesions in 50% of the animals/anti-inflammatory dose to give 50% inhibition in rats).

Paris *et al*⁶⁵ prepared a series of 1,3-bis(alkanoyl)-2-(O-acetylsalicyloyl) glycerides, (triglycerides of aspirin) (**21a-f**) having aspirin at 2 position of glycerol and fatty acids at 1 and 3 position. The studies for presence of lesions in stomach showed that the derivatives, in which fatty acids are of intermediate chain length (C_4 - C_{12}), did not cause gastric lesions and had essentially all the systemic activity associated with aspirin.



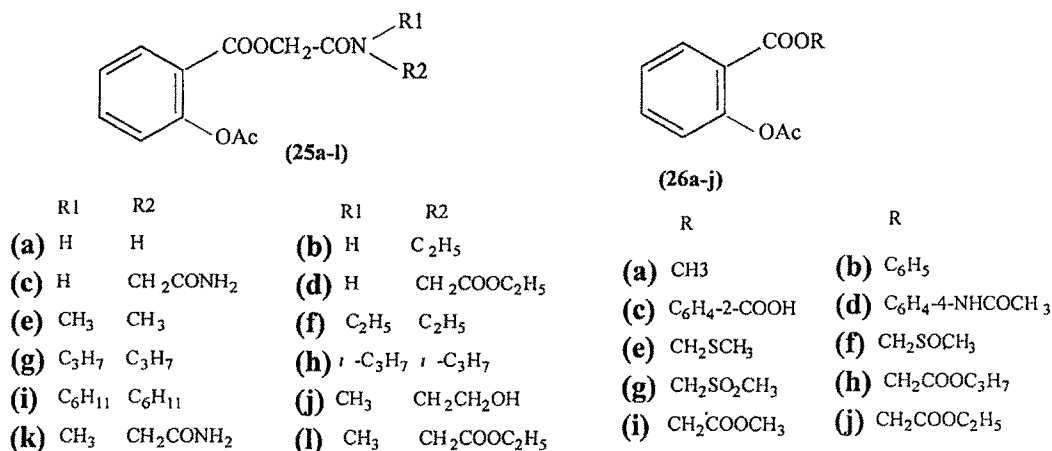
Suxibuzone (**22**), a prodrug of phenylbutazone, has been reported by Bianchi *et al*⁶⁶ to exhibit extremely low ulcerogenicity, although its anti-inflammatory, analgesic and antipyretic properties remain intact when compared to the parent drug at equimolar dose level.

Some mutual prodrugs^{67, 68} of tolmetin with paracetamol (**23**), and of aspirin with salicylamide (**24**) have been evaluated with the aim of abolishing the gastrointestinal toxicity of these drugs.

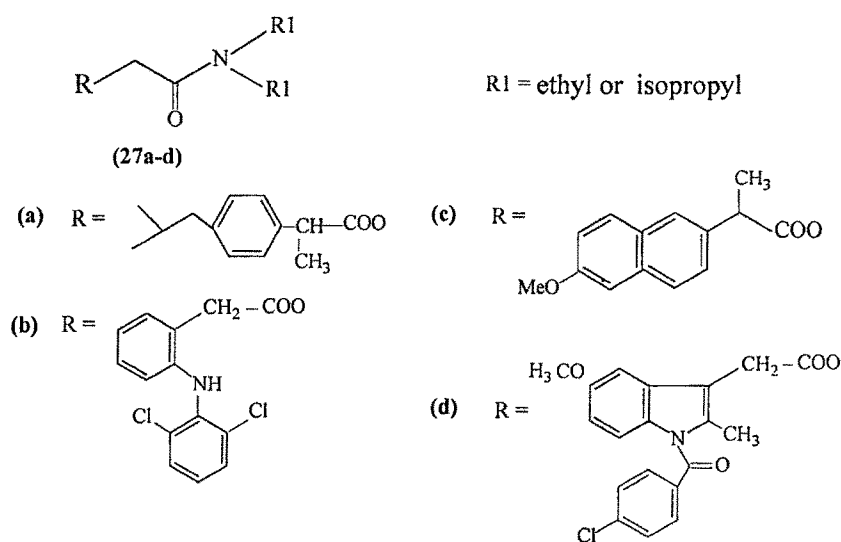


A series of glycolamide (**25a-l**), glycolate, (acyloxy)methyl, alkyl and aryl esters (**26a-j**), of acetylsalicylic acid were synthesized and evaluated⁶⁹ as potential prodrug forms of aspirin. The N,N -disubstituted glycolamide esters were found to be rapidly hydrolysed in

human plasma resulting in the formation of aspirin as well as the corresponding salicylate esters and these in turn hydrolyzed rapidly to salicylic acid.



Khan *et al*⁷⁰ have evaluated the glycolamide ester prodrugs of ibuprofen (**27a**), diclofenac (**27b**), naproxen (**27c**) and indomethacin (**27d**) for their GI toxicity in rats.

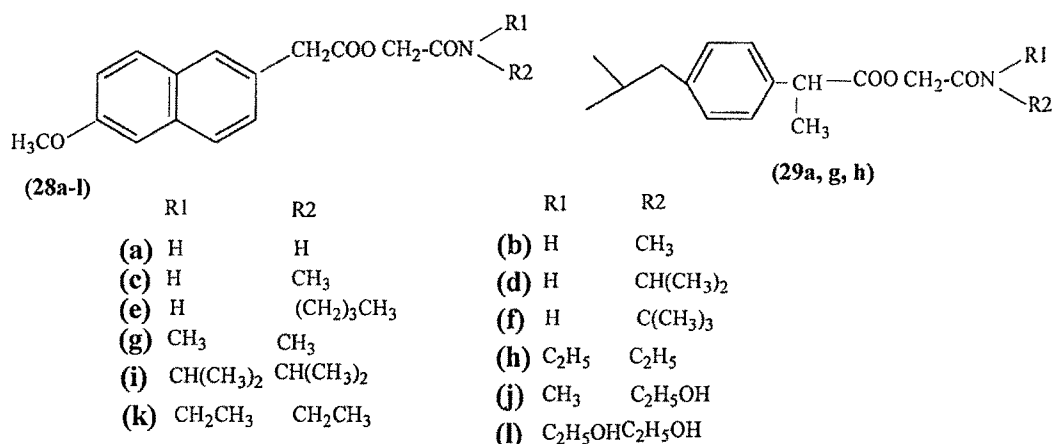


The results showed that all the synthesized glycolamide esters were considerably less gastric toxic and possessed comparable anti-inflammatory and analgesic potencies with respect to the parent compounds.

Various glycolamide ester prodrugs (**28a-l**) of 6-MNA were synthesized and evaluated⁷¹ for their physicochemical properties, chemical stability and enzymatic hydrolysis in 80%

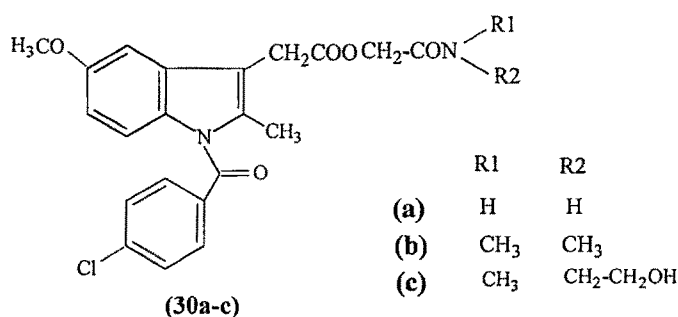
human plasma. The disubstituted glycolamide esters (**28g-l**) were more stable than monosubstituted glycolamide esters in pH 7.4 buffer. All the esters rapidly converted to 6-MNA in human plasma at 37°C. The chemically more stable N,N-disubstituted glycolamide esters proved to be better substrates for plasma enzymes (half-lives 7-83 s) when compared to the monosubstituted glycolamide esters (half-lives 168-809 s)

Glycolamide esters (**29a, g, h**) of ibuprofen were synthesized and studied⁷² for their physicochemical, pharmacological and toxicological properties. They were comparable



with ibuprofen in respect of anti-inflammatory and analgesic activities but did not exhibit reduction in ulcerogenicity on oral administration.

The kinetics of hydrolysis of glycolamide esters (**30a-c**) of indomethacin was studied⁷³ to assess the possibility of designing a water-soluble and solution-stable prodrug of indomethacin suitable for parenteral or ocular administration. The prodrugs degraded

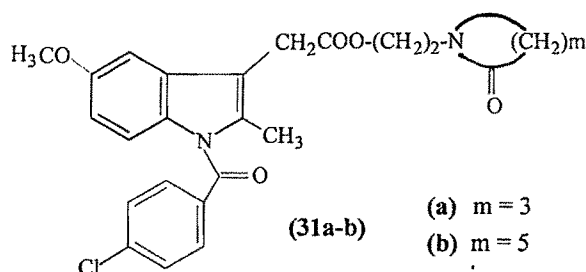


both, at its ester group linkage and at the indole amide linkage of indomethacin, and

showed a very pronounced water catalysed hydrolysis leading to the conclusion that designing of a stable indomethacin ester prodrug, for the purpose of a ready-to-use aqueous formulation may be difficult.

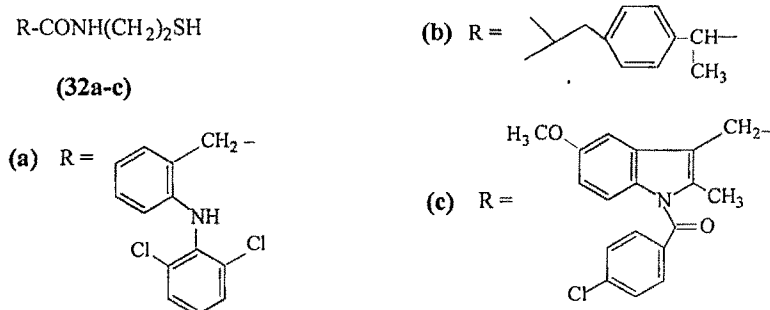
The methyl esters of salicylic acid, diflunisal, flufenamic acid, indomethacin, diclofenac and tolmetin were synthesized⁷⁴ and found to be effective in reducing interaction of the irritant NSAIDs in the acidic milieu of the stomach with drug sensitive mucosal and parietal cells.

Bonina *et al*⁷⁵ evaluated two esters (**31a-b**), 1-ethylazacycloalkan-2-one of indomethacin for their potential use as prodrugs for oral delivery. The evaluation indicated that the



esters represent potentially useful indomethacin prodrugs for oral administration since they were found stable in aqueous solution as well as in simulated gastric fluid with a fast enzymatic hydrolysis in rat plasma. Moreover, the anti-inflammatory and analgesic activity of the parent drug was retained and both the esters notably inhibited the gastrointestinal irritation induced by indomethacin.

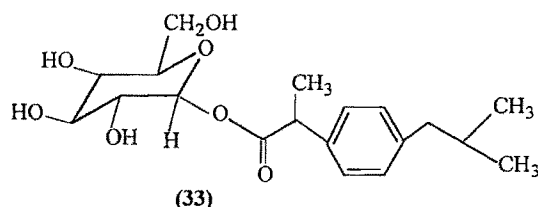
Amide derivatives⁷⁶ of diclofenac (**32a**), ibuprofen (**32b**) and indomethacin (**32c**) with a



well known antioxidant cysteamine, exhibited good anti-inflammatory and antioxidant

activities and showed a significant reduction in ulcerogenicity.

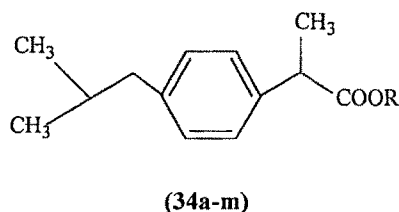
Ibuprofen β -D-glucopyranoside (**33**) was synthesized by Khan *et al*⁷⁷ and reported to



have superior anti-inflammatory and analgesic activities over the parent drug with significantly less ulcerogenicity.

Many alkyl ester prodrugs of ibuprofen (**34a-l**) with the aim of reducing GI toxicity were synthesized and evaluated by Bansal *et al*⁷⁸. The n-propyl and n-butyl esters were found to have significant improvement in the oral delivery of ibuprofen in terms of reduced gastroulcerogenicity and maintenance of anti-inflammatory potency.

The alkyl esters (**34a-l**) of ibuprofen were also evaluated⁷⁹ for their physicochemical properties and anti-inflammatory activity in carrageenan induced rat paw edema by topical route. Favourable shifts in the lipophilicity and in the penetration effect of prodrugs were reflected in improved topical activity over the parent drug ibuprofen.



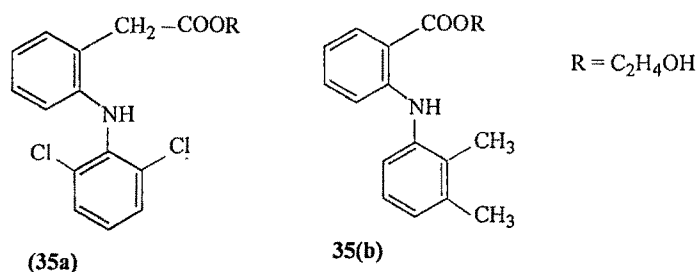
	R	R
(a)	methyl	(b) ethyl
(c)	n-propyl	(d) isopropyl
(e)	isobutyl	(f) tert-butyl
(g)	n-pentyl	(h) hexyl
(i)	heptyl	(j) octyl
(k)	cetyl	(l) octadecyl
(m)	benzyl	

Benzyl ester prodrug of ibuprofen (**34m**) was evaluated by Bansal *et al*⁸⁰. It showed a significantly reduced gastric ulcerogenicity at equimolar doses with comparable anti-inflammatory and analgesic activities to the parent drug, ibuprofen.

The synthesis of three water soluble NSAID polymeric prodrugs, using copolymerization

of ibuprofen-, ketoprofen- or naproxen-linked 2-hydroxyethylmethacrylate (HEMA) with high methacrylic acid content, was carried out by Wang *et al*⁸¹. The polymeric prodrug of ibuprofen retained the anti-inflammatory potency of ibuprofen whereas the prodrugs of ketoprofen and naproxen displayed greater potency to inhibit acute inflammatory processes than the free drug.

Hydroxyethyl esters (**35a**, **35b**) of diclofenac and mefenamic acid were prepared by Jilani *et al*⁸² with the aim of obtaining enzymatically labile prodrugs. The hydrolytic degradation of diclofenac ester in aqueous buffer solutions (pH 7.4 and 1N HCl) was



slow while rapid enzymatic hydrolysis occurred in the plasma. However, the mefenamic acid ester showed a relatively higher stability in buffer solutions as well as in the plasma and was considered to be a poor prodrug in terms of release of the parent moiety.

Mahfouz *et al*⁸³ synthesized ester prodrugs of aspirin, ibuprofen, naproxen and indomethacin using N-hydroxymethylsuccinimide and N-hydroxymethylisatin as promoeities to reduce their GI toxicity and improve bioavailability. *In vivo* ulcerogenicity studies revealed that the synthesized ester prodrugs were significantly less irritating to gastric mucosa than the parent drugs.

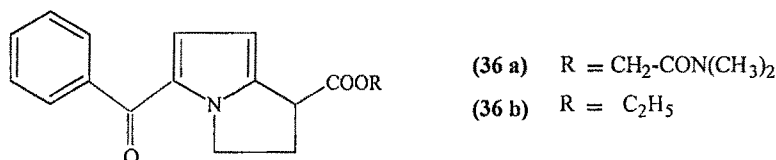
A series of novel ω -(N,N,N-trialkylammonium)alkyl ester and thioester derivatives of eleven non-steroidal anti-inflammatory agents (naproxen, ketorolac, indomethacin, ibuprofen, sulindac, ketoprofen, flufenamic acid, mefenamic acid, zomepirac, etodolac and tifurac) were prepared and evaluated⁸⁴ for their anti-inflammatory, analgesic and gastrointestinal erosive properties. In general, each prodrug was reported to retain the anti-inflammatory activity characteristic of the corresponding parent drug but exhibited

moderately to greatly reduced gastrointestinal erosive properties and significantly reduced analgesic potencies.

Carty *et al*⁸⁵ evaluated ampiroxicam, a non-acidic ether carbonate prodrug of piroxicam and demonstrated that, in contrast to piroxicam, ampiroxicam does not possess detectable prostaglandin synthesis inhibitory activity *in vitro*. Ampiroxicam, however, had similar *in vivo* potency to piroxicam in suppressing paw swelling in rat adjuvant arthritis model.

The pharmacokinetics of ibuprofen diethylcarbonate and naproxen diethylcarbonate, two new diethylcarbonate prodrugs of ibuprofen and naproxen in dogs, was reported by Samara *et al*⁸⁶. The rationale for their development was that esterification of the carboxylic moiety of the parent compounds would suppress gastrotoxicity without adversely affecting their anti-inflammatory activity. In addition, the biotransformation of the prodrugs to the parent compounds may be utilized to achieve rate and time controlled drug delivery of the active entities.

The *in vitro* skin permeabilities of ketorolac and its two ester analogs (**36a-b**) as prodrugs through human cadaver skin were investigated⁸⁷. The [N,N-dimethylamino)car-



bonyl]methyl ester (**36a**) appeared to be better ester prodrug than the simple ethyl ester (**36b**) prodrug since it exhibited relatively higher skin flux and faster enzymatic hydrolysis in human serum to liberate the parent drug.

Various novel morpholinyl- and methylpiperazinylacyloxyalkyl esters of naproxen were synthesized by Rautio *et al*⁸⁸ and evaluated *in vitro* for topical delivery of naproxen.

Rautio *et al*⁸⁹ synthesized and evaluated various aminoacyloxyalkyl esters of naproxen and naproxenoxyalkyl diesters of glutamic acid and aspartic acid as potential dermal prodrugs of naproxen. The aminoacyloxyalkyl prodrugs were shown to have higher

aqueous solubilities and similar lipid solubilities in terms of octanol-buffer partition coefficients at pH 5.0, when compared with naproxen.

A series of acyloxyalkyl esters of ketoprofen and naproxen were synthesized and investigated by Rautio *et al*⁹⁰ as topical prodrugs with the aim of improving the dermal delivery of the parent drugs.

Various acyloxyethyl mefenamates were synthesized by Jilani *et al*⁹¹ and were evaluated for their potential application as prodrugs. Among the synthesized compounds, the β -carboxypropionylethyl mefenamate and the pivaloyloxyethyl mefenamate were reported to have high stability against enzymatic and non-enzymatic hydrolysis. Preliminary *in vivo* study showed that acetoxymefenamate gave plasma concentration of mefenamic acid lower than that of control after oral administration.

Diacylglyceryl ester derivatives of naproxen were synthesized by Thorsteinsson *et al*⁹² and were tested for transdermal and dermal applications. The prodrugs were slowly hydrolysed to naproxen inside the skin. The release of naproxen to the receptor compartment of diffusion cells showed that this type of prodrug could be used for controlled drug delivery.