CHAPTER 4

LITERATURE REVIEW

NSAID’s are widely used for treating various inflammatory diseases. The clinical value of many NSAID’s is limited due to their gastrointestinal toxicity, which range in both severity and frequency from relatively mild to more serious and potentially life threatening condition, such as GI ulceration and haemorrhage. It can be attributed to the direct local action on the gastric mucosa particularly of acidic NSAID’s and generalized systemic action that takes place after absorption of these agents. The development of prodrugs to temporarily mask the acidic group of NSAID’s has been considered as a promising means of reducing the GI toxicity due to the local action mechanism. Most prodrugs of NSAID’s have been prepared by derivatization of the carboxyl group and later the parent drug elicits the desired pharmacological response. The history and development, of conjugation with different promoeities, in designing new efficacious NSAID prodrugs is discussed briefly in the following section.

1. Paris G.Y. et.al. synthesized few glycerol prodrugs of Indomethacin and evaluated for anti inflammatory activity by rat paw carrageenan oedema assay. Most active compounds were also tested in rat adjuvant arthritis model and found to be essentially equivalent to Indomethacin. On a molar basis the gastric irritating properties of these were seven to eight times less than Indomethacin.

2. Allen R.C. launched butyl Flufenamate, prodrug of Flufenamic acid and Pnaprofen, the pinacol ester of Ibuprofen, in to market in 1984 in Japan, are used topically for the treatment of eczema, contact seborrheic and atopic dermatitis. Fosfosal is a highly water soluble salicylic acid ester prodrug found useful in the treatment of musculo-skeletal and arthritic pain. Piketoprofen (Fig. 29), an amide derivative of Ketoprofen, is used in the form of aerosol for treating topical inflammatory and painful musculoskeletal disorders.
3. *Allen R.C.* \(^{57}\) marketed Nabumeton; a non acidic NSAID in 1985 in Ireland. It is a bioprecursors type of prodrug that gets converted to 6-methoxy-2- naphthyl acetic acid, which is an active metabolite. Nabumeton (Fig. 30) is reported to be effective in the treatment of rheumatoid and osteoarthritis.

4. *Allen R.C.* \(^{58}\) marketed Osalazine sodium (Fig. 31), a mutual prodrug, comprising two molecules of 5-amino salicylic acid, in 1986 in Sweden and Netherlands, was found to be useful in the treatment of ulcerative colitis.

5. *Cherie L.G. et.al.* \(^{59}\) reported a pivalic ester prodrug of Piroxicam which showed reduced gastric irritant activity. The time course of plasma levels of both the prodrug and the active principle were studied and a correlation of later with synovial fluid levels were made. Good gastric tolerance was achieved along with good clinical results.
6. **Ong H.H. et.al** reported a guaiacol ester of Ibuprofen (Fig. 32) with comparable anti inflammatory activity but greater GI tolerance which was found to be effective in ameliorating symptoms due to common cold and influenza.

![Figure 4: Guaiacol ester of ibuprofen](image)

7. **Nielsen N.M. et.al.** observed rapid hydrolysis of benzoic acid ester of various substituted 2-hydroxyl acetamides in human plasma and it could be largely attributed to the presence of choline esterase. Results showed that it is possible to achieve ester derivatives with desired water solubility by retaining its ability to undergo the enzymatic hydrolysis.

8. **Venuti M.C. et.al.** synthesized (N, N, N-trialkyl ammonium) alkyl ester and thio-ester derivative of various NSAIDs and evaluated for its pharmacological activities. The study revealed that the prodrugs retained anti inflammatory characteristics of corresponding parent drug, exhibited reduced gastrointestinal erosive properties and reduced analgesic potencies.

9. **Kahns A.H. et.al.** studied the hydrolysis kinetics of glycolamide esters of Indomethacin to assess the possibility of designing water soluble and solution stable prodrug of indomethacin suitable for parenteral or ocular administration. Indomethacin and its ester prodrug showed maximum stability at pH 4.9 and 4.7 respectively. The shelf life was observed to be almost two years for Indomethacin but only 43 days for ester prodrug. Very pronounced water catalysed hydrolysis of ester prodrug accounts for its poor water stability and limits its use as ready to use formulation.

10. **Kuriyama K. et.al.** studied the pharmacological properties of LFP83, a prodrug of Flurbiprofen which is its active metabolite and LPF83 showed remarkable analgesic, antipyretic and anti inflammatory activities. Its analgesic potency was more than that of Flurbiprofen, along with rapid onset of action. In addition, LFP83 showed less ulcerogenicity than Flurbiprofen in both single and consecutive (7 days) administration.

11. **Nielsen N.M. et.al.** synthesized a series of glycolamide glycolate, acyloxy methyl, alkyl and aryl esters of Acetyl salicylic acid and evaluated for hydrolysis and
pharmacological profiles. Lipophilicility and water solubility of the esters were also determined. The studies showed N, N-di-substituted glycolamide as rapidly hydrolysable in human plasma.

12. Jeremy J.Y. et.al. 66 studied Nabumetone, a novel NSAID with less cyclooxygenase inhibitor activity has been converted to its active metabolites, which possess more potent COX inhibitor activity by liver. Synthesis of rat gastric prostaglandin as well as in vitro and in vivo comparative studies was carried out on the effect of Nabumetone and 6-methoxy-2-naphthyl acetic acid with indomethacin and naproxen respectively. The results showed inhibition of platelet TXA2 synthesis due to the administration of Nabumetone.

13. Ong H.H. 67 studied Piroxicam cinnamate is a longer active prodrug and is found useful in once daily therapy for rheumatoid and osteoarthritis.

14. Strupczewski J.D. et.al. 68 marketed Aminoprofen, an amide prodrug of Ibuprofen, is a topical anti-arthritic drug with analgesic properties.

15. Oga S.et.al. 69 prepared the Flurbiprofen complex of copper and characterized. The anti inflammatory and analgesic activities were performed in vivo in rats. The study showed similar inhibitory effect for both copper-flurbiprofen complex and parent Flurbiprofen. However, the gastric irritation was found to be less for the prodrug than free Flurbiprofen.

16. Larsen C.et.al. 70 prepared a range of Ketoprofen- Dextran ester prodrugs and administered orally in pigs. The bioavailability of Ketoprofen after administration of prodrugs were determined and compared with that obtained from the administration of an equivalent dose of Ketoprofen alone. The plasma profile for the Ketoprofen- Dextran ester prodrugs demonstrated a characteristic time lag of 2 to 3 hr and the average absorption fractions for the prodrugs vary from 67-100 %.

17. Giammona G. et.al. 71 studied the water soluble and water insoluble polymer derivatives of NSAIDs such as Aceclofenac, Ketoprofen and Ibuprofen for their hydrolysis rate in simulated gastric juice with α, β-poly (N- hydroxyethyl)-DL-aspartamide, a hydrophilic macromolecular prodrug as carrier.

18. Sugimoto M.et.al. 72 synthesized hydrazide derivatives of Naproxen, Diclofenac, Ibuprofen and Indomethacin and evaluated biologically in rodent model.

19. Zorc B. et.al. 73 studied the macromolecular prodrug of Fenoprofen and Probenacid using α poly (N-hydroxy ethyl-DL-aspartamide, a hydrophilic polymer and the release of drug in alkaline medium.

20. Mork N et.al. 74 determined the hydrolysis kinetics of various alkyl, glycolamide, amino ethyl and 2-(l-imidazolyl) ethyl ester of Ibuprofen and Flurbiprofen in 80 % human
plasma using direct HPLC assay for the enantiomers for these acids. The R-isomers undergo faster plasma catalyzed hydrolysis than the corresponding S-isomer.

21. **Shanbhag V.R. et al.** \(^7^5\) carried out the synthesis and evaluation of amide and ester derivative of Ibuprofen and Naproxen for anti inflammatory activity and GI toxicity. Some prodrugs exhibited significantly better reactivity towards hydrolysis and remaining exhibited considerably less irritation to the gastric mucosa in rats.

22. **Otis M.F. et al.** \(^7^6\) synthesized the amide prodrugs of Indomethacin and Diclofenac by condensing methyl and ethyl ester of various amino acids. It was observed that during reaction with peripheral blood leukocyte, blood plasma or liver extract, the parent drugs were not regenerated from the amide substrate at 10-4 M. However the ester protection of some amino acid was hydrolyzed efficiently by leukocyte or liver enzyme. The condensation product of Diclofenac and Indomethacin with phenylalalanine were observed to be less inhibiting than the free drug on Prostaglandin-F\(_2\) release from cultures fibroblasts.

23. **Larsen F. et al.** \(^7^7\) studied the release process of Ketoprofen from Ketoprofen-Dextran ester prodrugs in pigs. The prodrug was given to three pigs at intervals of 12 hr and in seven doses corresponding to 4 mg Ketoprofen/kg body weight. It was concluded on the basis of results that following administration of dextran prodrug, the plasma concentration curve and the dissolution profile are uniform with small inter individual variations.

24. **Tammara V.K. et al.** \(^7^8\) synthesized the morpholinan alkyl ester prodrugs of Indomethacin and Naproxen and evaluated and tested in rats for pharmacokinetics, bioavailability, ulcerogenicity and solid state stability for oral drug delivery. Results showed that the prodrugs were 30 to 60 % more bioavailable orally than parent drugs. In addition, they were found to exhibit irritation at a lesser amount to gastric mucosa than original drug during single dose administration.

25. **Tammara V.K. et al.** \(^7^9\) also attempted *in vivo* and *in vitro* studies of Morpholin alkyl prodrugs of Diclofenac for oral drug delivery. Results showed a 200 fold increase in solubility of prodrugs in SGF and phosphate buffer at pH 7.4 when compared with that of the parent drug. All the esters were reported to exhibit a rapid bioconversion in rat plasma and were significantly less irritating to the gastric mucosa than the parent drug.

26. **Roy S.D. et al.** \(^8^0\) investigated the *in vitro* skin permeabilities of Ketorolac and its two ester analogues ketorolac ethyl ester and [N, N-dimethyl amino carbonyl] methyl esters through cadaver skin. The [N, N-dimethyl amino carbonyl] methyl esters was observed to
be a better ester prodrug than ketorolac ethyl ester as it exhibited relatively higher skin flux and faster enzymatic hydrolysis in human serum to liberate the parent drug.

27. **De Caprariis P. et.al.** 81 synthesized Oligoethylene ester prodrugs of Indomethacin and evaluated for chemical and enzymatic stability, anti inflammatory, analgesic and ulcerogenic activities in rats and mice. All prodrugs demonstrated good chemical stability and were readily hydrolyzed by human plasma. Better and similar anti inflammatory and analgesic activities along with 'hacin levels for 24 hr observation period. Both the prodrug and the drug were able to inhibit the inflammation of carrageenan induced paw oedema.

28. **Bansal A.K. et.al.** 82 studied the effect of substitutes on the physicochemical properties, such as aqueous solubility, octanol-water partition coefficient and hydrolysis kinetics in aqueous buffer and human plasma, of a series of synthesized alkyl ester prodrug of Ibuprofen and concluded that it is possible to get Ibuprofen prodrug that is able to achieve their objectives without compromising on therapeutic activities.

29. **Murtha J.L. et.al.** 83 suggested Phospholipid microemulsions as a drug delivery system for hydrophobic compounds. The cholesteryl Ibuprofen and cholesteryl Flufenamic acid derivatives were synthesized and prepared emulsion of prodrug and phopholipid using various concentrations of prodrug and lipids. The results indicated that a molar ratio of 75:25 and a total lipid concentration of 60 mg/ml consistently gave microemulsions with a mean size of 100-150 nm.

30. **Hayball P.J. et.al.** 84 carried out the protein binding studies of the enantiomers of the non-opiate analgesic Ketorolac using plasma and serum albumin at physiological pH and temperatures. Tritium labelled Ketorolac was synthesized in order to detect the very low levels of unbound enantiomers in protein solution. HPLC column afforded labelled enantiomers of high activity. The *in vitro* use of (R)- and (S) Ketorolac enabled reproducible radiometric detection of enantiomers.

31. **Tsunematsu H. et.al.** 85 synthesized ethyl ester Flurbiprofen based amino acid prodrugs and subsequent release of enantiomers of flurbiprofen, in presence of trypsin and carboxy peptidase, was carried out to assess their use as prodrugs for Flurbiprofen. No significant differences between the kinetic parameters for two diastereomers were observed suggesting that the orientation differences between (S)- FP and (R) FP diastereomers does not have any effect on the tryptic hydrolysis of the ester bond.

32. **Bonina F.P. et.al.** 86 reported the synthesis of Indomethacin polyoxyethylene esters as Indomethacin dermal prodrug. The esters possess good water solubility, rapid chemical
and enzymatic hydrolysis. It was observed that the rate of chemical and enzymatic hydrolysis was not significantly affected by the length of the polyoxy ethylene chain used as a promoiety.

33. **Samara E. et al.**\(^87\) evaluated the pharmacokinetics of diethyl carbonate ester prodrugs of Ibuprofen and Naproxen in dog plasma, SGF and SIF at 37°C significant difference was found between the rate of absorption of prodrug and their respective parent compounds. It was concluded that these prodrugs did not offer any pharmacokinetic advantage over the parent compound and were unstable in the gastrointestinal tract.

34. **Bhosle D. et al.**\(^88\) carried out the histidine conjugate of Diclofenac from Diclofenac acid chloride and histidine ester hydrochloride by modified Schotten Baumann reaction. Compounds were physicochemically characterized and studied for rate of hydrolysis in phosphate buffer (pH 7.4) and 80 % plasma (pH 7.4). Hydrolysis study indicated rapid hydrolysis following first order kinetics. The compound showed less anti inflammatory tendencies in comparison to Diclofenac.

35. **Fukuhara A. et al.**\(^89\) studied the in vivo and in vitro stereo-selective hydrolysis characteristics of mutual prodrug FP-PPA, which is a conjugate of Flurbiprofen, with the histamine H\(_2\)-antagonist piperidinyl methyl phenoxypropyl-2-hydroxy ethyl thio acetamide to reduce gastrointestinal lesions induced by Flurbiprofen. The prodrug was also compared with Flurbiprofen methyl ester (rac-Flurbiprofen-Me) and FP ethylene glycol ester (rac-Flurbiprofen-EG) and it was found that the rac-Flurbiprofen derivatives hydrolyzed preferentially to the (+) S- isomer in plasma and to the (-) R-isomer in liver.

36. **Aboul-Fadl T. et al.**\(^90\) attempted Nalidixic acid amide of amino acid esters as prodrugs to overcome the drawbacks of Nalidixic acid. It was observed that prodrugs were more stable in buffer (pH 1.2 and pH 7.4) and in 80 % plasma. The plasma protein binding potency was studied in vitro and revealed a decrease in the percentage bound in case of glycine and alanine derivatives and increase in the percentage bound of phenylalanine leucine and isoleucine derivatives.

37. **Akgun H. et al.**\(^91\) prepared amide prodrugs of Ibuprofen, Naproxen, Diclofenac and Ketorolac from the corresponding 2-aryl propionic acids and R-(-)-2-amino-1-butanol in the presence of N, N-dicyclo hexyl carbodiimide. The prodrugs prepared in the study showed significant analgesic activity.

38. **Bonina F.P. et al.**\(^92\) synthesized the pharmacokinetic profile of triethylene glycol Indomethacin ester, an Indomethacin and in vitro enzymatic hydrolysis studies showed
that triethylene glycol Indomethacin ester was quantitatively recovered in to Indomethacin at a very fast rate. Triethylene glycol Indomethacin ester oral administration to rats gave lower but relatively constant Indomethacin levels for 24 hr observation period. Both the prodrug and the drug were able to inhibit the inflammation of carrageenan induced paw oedema.

39. *Tabrizi M.H.N. et.al.* \(^{93}\) conjugated in order to minimize sodium Diclofenac side effect and to increase its therapeutic efficiency of Diclofenac polymer prodrug. The hydrolysis of polymer drug conjugate was carried out in cellophane membrane dialysis bags containing aqueous buffer solutions (pH 8) at 37ºC. Compounds were found useful as polymeric prodrug and it was found that polyvinyl chloroacetate is an appropriate carrier for release of drug in human condition.

40. *Bonina F. et.al.* \(^{94}\) studied the chemical stability, enzymatic hydrolysis, anti inflammatory and analgesic activity and GI toxicity of 1-ethyl azacycloalkane-2-one Indomethacin esters. The esters are found stable in pH 7.4 buffer and simulated gastric fluid but showed rapid hydrolysis rate in plasma due to plasma esterases. Esters were found less irritating to gastric mucosa and showed good analgesic activity in the mouse acetic acid induced writhing assay.

41. *Palagiano F. et.al.* \(^{95}\) investigated in another study, terpenoid esters of Indomethacin for topical use were prepared. Chemical and enzymatic stability, solubility, lipophilicity, stability of aqueous formulation of prodrugs and *in vitro* profile to inhibit methyl nicotinate induced skin erythema. All prodrugs showed high lipophilicity, poor water solubility in hydrochloric acid medium and rapid enzymatic cleavage.

42. *Davaran S. et.al.* \(^{96}\) performed hydrolysis study on acryloyl and methacryloxy ethyl ester and amide prodrugs of Ibuprofen and Indomethacin using di-functional spacer group between the drug and acryl moiety that the drug was released by hydrolysis of ester or amide bonds between the drug and spacer group.

43. *Jilani J.A. et.al.* \(^{97}\) synthesized various acyloxy ethyl Mefenamate and hydrolysis kinetics was studied in pH 1.2, pH 7.4 and human plasma at 37ºC. Among the synthesized compounds, α-carboxy propionyl ethyl Mefenamate and pivaloyl oxyethyl Mefenamate showed high stability in aqueous and in enzymatic and non-enzymatic hydrolysis.

44. *Jilani J.A. et.al.* \(^{98}\) conjugated the hydroxyl ethyl ester of Diclofenac and Mefenamic acid and evaluated for stability in aqueous buffer solution of pH 7.4, 1 N HCl and in human plasma. The hydrolytic degradation of Diclofenac ester in aqueous buffer solution was
Chapter-4: Literature Review

slow ($t_{1/2} > 22$ hr) while rapid enzymatic hydrolysis occurred in the plasma ($t_{1/2} = 12$ hr). Mefenamic acid ester showed a relatively higher stability in buffer solution ($t_{1/2} > 38$ hr at pH 10) as well as in the plasma ($t_{1/2} = 7.28$ hr) compared with the Diclofenac ester. It was concluded that Mefenamic hydroxyl ethyl ester would not be considered as prodrug.

45. Rautio J. et.al. 99 carried out synthesis and evaluation of acyloxyalkyl ester and hydroxyl alkyl esters of Ketoprofen and Naproxen as topical prodrug with an aim to improve the dermal delivery of drugs. All prodrugs were found more lipophilic than parent drug. Hydrolysis study showed that prodrugs were stable in aqueous solutions of pH (7.4) but hydrolyzed in human plasma and human skin homogenates.

46. Aborodo E.A. et.al. 100 synthesised and characterized of 2-formylphenyl and 2-acyl phenyl esters of Indomethacin, Ketoprofen, Ibuprofen and Aspirin showed that all compounds, except 2-acetyl phenyl aspirin, act as prodrugs. Study also proved 2-formyl phenyl esters as more potent anti-inflammatory agent than the parent compounds.

47. Omar F.A. et.al. 101 showed N-hydroxy methyl phthalimide esters of Ibuprofen, Naproxen and Aspirin to be useful non-ulcerogenic prodrugs of acidic NSAIDs.

48. Rautio J. et.al. 102 synthesized various aminoacyloxy alkyl esters of Naproxen and naproxenoxyalkyl diesters of glutamic acid and aspartic acid and their use as potential prodrugs for transdermal delivery was evaluated. The prodrugs were shown to have higher aqueous solubilities and similar lipid solubilities in terms of octanol-buffer partition coefficients (log P) at pH 5, when compared with naproxen.

49. Thorsteinsson T. et.al. 103 reported the diacyl glyceryl ester prodrug of Naproxen with potential for improving dermal delivery of the parent drug.

50. Mahfouz N.M. et.al. 104 synthesized two additional analogous cyclic amides, N-hydroxy methyl succinimides and N-hydroxy methyl isatins as alternate promoieties to N-hydroxy methyl phthalimide and found that the parent drugs treated groups as more ulcerogenic in stomach than the prodrugs.

51. Redden P.R. et.al. 105 prepared a series of acyloxy methyl derivative of the NH acidic drugs and carboxylic acid drugs to find out the effect of varying nature of drug on the rate of in vitro hydrolysis catalyzed by procaine liver esterase and human plasma. The derivatives followed first order kinetics in both enzyme systems. The NH acidic derivatives showed a rapid hydrolysis than the carboxylic acid derivatives in both the systems.
52. Abou-Ghali M.H. et.al. 106 examined 12 new non-proteinogenic amino acid conjugates of Diclofenac for various pharmacological properties. The conjugates were found non ulcerogenic as well as were found to retain generalized anti-phlogistic activity.

53. Kourounakis A.P. et.al. 107 studied the anti inflammatory and antioxidant properties of derivatives of Indomethacin, Diclofenac, Tolfenamic acid and Ibuprofen with cystamine, a polar antioxidant.

54. Lastra A. et.al. 108 analyzed their effect on protection against rat hepatic microsomal lipid peroxides and interaction with the stable free radical 1,1-diphenyl-2-picrylhydrazyl. Results revealed all prodrugs as potent antioxidant and found to reduce lipid peroxidation very significantly with IC\textsubscript{50} values ranging from 55 to 510 mm. They also interacted approximately 90% with 1,1-diphenyl-2-picrylhydrazyl at equimolar concentrations. Melatonin, an antioxidant was reported to show protective effects in Indomethacin induced gastric injury by virtue of its radical scavenging activity.

55. Kourounakis P.N. et.al. 109 synthesized the amide derivatives of Diclofenac, Ibuprofen and Indomethacin with a well known antioxidant cysteamine. The prodrugs exhibited good anti-inflammatory and antioxidant activities and a significant reduction in ulcerogenicity.

56. Jung Y.L. et.al. 110 investigated in vitro and in vivo properties of 5-aminosalicyl glycine (5-ASA-Gly) as a colon specific prodrug of 5-ASA in rats. In the study, free 5-ASA was not detected upon incubation of the conjugate with the homogenates of stomach or small intestine.

57. Bansal A.K. et.al. 111 synthesized Glycolamide esters of Ibuprofen and evaluated for various physicochemical, pharmacological and toxicological properties and found that the prodrugs are better in action than the parent drug.

58. Chandrasekar M.J. et.al. 112 showed that the in vitro study of polymerizable drug derivative of Diclofenac sodium the drug release takes place predominantly at a higher pH and in a sustained manner with complete drug absorption from the polymeric prodrug. Also a significant decrease in ulcerogenicity was observed revealing its potential for site-specific and sustained delivery of Diclofenac.

59. Bansal A.K. et.al. 113 reported Alkyl ester prodrugs of Ibuprofen with significant improvement in the oral delivery of Ibuprofen. The prodrugs were evaluated for physicochemical properties and pharmacological activities and found to exhibit enhanced anti-inflammatory activity in carrageenan induced rat paw oedema by topical route and reduced gastro ulcerogenicity.
60. Bonina F.P. et.al. 114 attempted in vitro and in vivo evaluation of polyoxy ethylene of Ketoprofen, Naproxen and Diclofenac as dermal prodrugs. An appreciable and sustained in vivo topical anti inflammatory activity was observed for the ester prodrugs in the erythema model in human volunteers.

61. Bonina F. et.al. 115 studied oligoethylene ester derivatives of Ketoprofen, Naproxen and Diclofenac, the prodrugs showed good stability in phosphate buffer (pH 7.4) and SGF (pH 2), and were readily hydrolyzed by human plasma. Anti inflammatory activity of the esters was found to be similar to the parent drugs and good analgesic activity was exhibited with significantly reduced gastric irritation even at higher doses.

62. Dhaneshwar S.S. et.al. 116 studied glucosamine, an amino sugar is conjugated with flurbiprofen to mask -COOH group temporarily. Glucosamine hydrochloride and sulphate are being used as anti arthritic agents as well as a nutritional supplement in conditions like joint ache, stiffness severely restricted movements and serious pains. These prodrugs have additional advantage of producing non-toxic, nutrient by product, glucosamine on cleavage, which shows the synergistic effect. Glucosamine is also used in wound healing and gastric disorders.

63. Khan M.S.Y. et.al. 117 synthesized the glycolamide ester prodrugs of Ibuprofen, Diclofenac, Naproxen and Indomethacin and evaluated for their GI toxicity in rats.

64. Sheha M. et.al. 118 synthesized the results showed better pharmacological response by the prodrugs. Mutual prodrugs of Naproxen-Propyphenazone for improving the therapeutic properties by preventing the various gastrointestinal toxicities.

65. Wang L.F. et.al. 119 studied esterification of naproxen with different alkyl esters and thio-esters led to prodrugs with retained anti-inflammatory activity and exhibited reduced erosive properties and analgesic potency. But esterification with ethyl piperazine showed that analgesic activity was preserved whereas anti-inflammatory activity was generally reduced. Propyphenazone is converted to its active metabolite, 3-hydroxy methyl propyphenazone, which actually gives the analgesic effect. The NSAIDs such as ibuprofen, Ketoprofen and Naproxen have been co-polymerized with 2-hydroxyethyl methacrylate having high methacrylate content.

66. Sharma V. et.al. 120 found the polymeric prodrug of Ibuprofen to retain the anti inflammatory activity while the prodrugs of Ketoprofen and Naproxen showed greater potency to inhibit acute inflammatory activity than their corresponding parent drugs. Naproxen, Probenecid, Diclofenac, Ibuprofen and Indomethacin were converted to hydrazide derivatives which were further condensed with keto esters to give pyrazolone
derivatives. The hydrazide derivatives of Probenecid and Diclofenac were also reacted with biphenyl acetic acid, an active metabolite of Fenbufen. The prodrugs exhibited comparable anti-inflammatory activity and analgesia when evaluated in rodent models.

67. Hoogstraate J. et al. 121 reported the Nitric oxide (NO) donating groups exhibited some useful properties like local protective actions including mucosal vasodilatation and prevention of neutrophil adhesion in both gastric and intestinal microcirculation and preserved the mucosal cell integrity. It has been tested in various animal models and proved the improved pharmacological activities of the prodrugs.

68. Takeuchi K. et al. 122 reported NCX-530, an NO releasing derivative of Indomethacin to decrease gastric motility, increased mucosal blood flow and caused a marked inhibition of PGE2 formation in intact and ulcerated gastric mucosa.

69. Kaza C.S. et al. 123 Studies carried out revealed that conjugation of NO-NSAIDs could be effective in a variety of diseases including cardiovascular, rheumatological, lung disease and cancer.

70. Jonzon B. et al. 124 studied NO-Naproxen, prodrug of Naproxen, which reduced the GI toxicity of Naproxen and was proved by their efficient anti inflammatory and analgesic activities.

71. Cena C. et al. 125 evaluated the anti-inflammatory and antiplatelet properties of NO donor esters of Aspirin. Aspirin was conjugated with furoxan moieties through an ester linkage, and had the ability to release NO. The prodrugs showed an improved anti inflammatory activity devoid of acute gastro toxicity, mainly due to their ester nature, and an antiplatelet activity due to their ability to release NO.

72. Marshall M. et al. 126 evaluated the efficacy, potency and spectrum of activity of prodrugs of NSAIDs such as Naproxen, Ibuprofen, Flurbiprofen, Ketoprofen and Aspirin by coupling to NO-donating moieties.

73. Downing J.E.G. 127 studied all the prodrugs exhibited better result than the parent drugs. Ibuprofen esterified with NO donor moiety abolished the GI irritation and significantly reduced thinning with no alteration in levels of diaphorase.

74. Velazquez C. et al. 128 reported a novel group of hybrid NO-NSAIDs possessing 1-(pyrrolidin-1-yl) diazen-1-ium-1,2-diolate or 1-(N,N-dimethyl amino) diazen-1-ium-1,2-diolate moiety attached through methylene spacer to the carboxylic acid group of Aspirin, Ibuprofen and. Indomethacin. The prodrugs showed better in vivo anti-inflammatory activities than the parent drugs.
Chapter-4: Literature Review

---

75. **Ranani R.R. et.al.**\(^{129}\) showed a series of NO-donating N-substituted glycolamides of Naproxen to possess anti-inflammatory activity in rat carrageenan paw oedema model.

76. **Khan M.S.Y. et.al.**\(^{130}\) prepared for reducing the gastrointestinal toxicity associated with Ibuprofen, ester prodrugs with 1,2,3-trihydroxy propane-1,3-dipalmitate/stearate and evaluated.

77. **Zhao X. et al.**\(^{131}\) synthesized ester prodrugs of Ibuprofen using methyl, ethyl and propyl gluco pyranosides as promoieties have been reported to undergo rapid cleavage inside the biological system and elicit a pharmacological profile quite similar to that of Ibuprofen on oral administration. But, unlike the parent drug, they displayed reduced gastric ulceration.

78. **Shiang P.Y. et.al.**\(^{132}\) linked Ibuprofen, Naproxen and Ketoprofen to chondroitin sulfate (ChS) via a PEG 1000 as spacer.

79. **Halen P.K. et.al.**\(^{133}\) found the Ketoprofen-ChS conjugate to be susceptible to degradation in presence of esterases and chondroitinase with the liberation of Ketoprofen and ChS. Indomethacin was coupled with amino alcohols having structural resemblance with amino ethanol ester class of anti-cholinergics. The N,N-disubstituted amino alcohol esters were specifically designed to possess a terminal tertiary nitrogen atom with an ethylene bridge between the terminal nitrogen and carbonyl group of bulky ester, which are also the structural features of anti-cholinergics.

80. **Carlos A. et.al.**\(^{134}\) studied gastric toxicity was reduced considerably not only because of blockage of acidic group but also due to the cessation of gastric acid secretion caused by local inhibition. Hydrolysis of such entities leads to the formation anti-cholinergic molecules in intact form. Ester derivatives of Aspirin, Ibuprofen and Indomethacin with 2-acetoxy methyl-1-[N-(2-hydroxy ethyl-N-methyl amino] diazenium diolate were synthesized as NO-releasing prodrugs. The derivatives did not exhibit *in vitro* COX inhibitory activity against cyclooxygenase isozymes but significantly decreased carrageenan induced rat paw oedema showing an enhanced *in vivo* anti-inflammatory activity relative to the parent drugs. All derivatives showed less ulcerogenicity than the parent drugs.

81. **Fiorucci S. et.al.**\(^{135}\) synthesized ester prodrugs of Ibuprofen, Indomethacin, Ketoprofen, Naproxen, Diclofenac and Aspirin with (4-thiocarbamoyl phenol, 5-[4-hydroxy phenyl]-1, 2-dithiole-3-thione and analyzed. It was reported that these moieties release hydrogen sulphide which exerts anti-inflammatory and analgesic activity. Results of the study showed significantly less gastric irritancy of the prodrugs than the NSAIDs alone.
82. *Mishra A. et.al.* \(^{136}\) synthesized ten prodrugs of Ketorolac by amidation with ethyl esters of amino acids glycine, L-phenyl alanine, L-tryptophan, L-valine, L-isoleucine, L-alanine, L-leucine, L-glutamic acid, L-aspartic acid, and alanine. Marked reduction in ulcer index and comparable analgesic, anti-inflammatory activities were obtained in all cases as compared to Ketorolac.

83. *Vyas S.* \(^{137}\) synthesized the Ketorolac-Dextran conjugates and characterized to improve the aqueous solubility and to reduce the gastrointestinal side effects of Ketorolac.

84. *Mohan R. et.al.* \(^{138}\) confirmed the ester bond in Ketorolac-Dextran conjugates by various spectral studies. *In vitro* hydrolysis studies were performed in various aqueous buffers (pH 1.2, 7.4, and 9) and in human plasma (pH 7.4). At pH 9, a higher rate of Ketorolac release was observed as compared to aqueous buffer of pH 7.4 and human plasma. The conjugates followed first order kinetics pattern. The various pharmacological screening carried out in mice and rats showed better analgesic activity, markable anti-inflammatory activity and reduced ulcerogenicity of the conjugates than Ketorolac. Simple ester prodrugs of NSAIDs like Ibuprofen, Flurbiprofen, Ketoprofen with ethanol and isopropyl alcohol have been synthesized and evaluated. This kind of system can easily undergo enzymatic hydrolysis by the action of esterase present abundantly in the small intestine; hence stomach’s mucosa is not exposed to the free carboxylic group. Similarly, simple amide prodrugs of Ibuprofen, Flurbiprofen, Ketoprofen have also been reported, wherein simple amines were used to form amide bond with the carboxylic acid. These are more stable in stomach as amidases that bring upon the hydrolysis of amide bond are present only in intestine.

85. *Sharma R. et.al.* \(^{139}\) studied Polymeric drugs are polymer-conjugated drugs, polymeric micelles and liposomal drugs or solid phase depot formulations of various agents. Polymeric drugs can target selectively, solid tumors by exploiting abnormalities of tumour vasculature, extensive production of vascular permeability factors stimulating extravasation within tumor tissues and lack of lymphatic drainage. Dextrans are polysaccharide polymeric carriers devoid of selective transport properties and may serve as one of the most promising carrier candidates for a wide variety of therapeutic agents like hormones, iron and Methotrexate. Bone targeting by conjugation of drugs with bis phosphates has shown promise in enhancing their effects in bones and reducing adverse drug reactions. Tetracycline-conjugated estradiol and oligopeptide-conjugated estradiol are reported as novel bone-specific drug carriers with high affinity for hydroxyl apatite crystals.
86. **Onishi H. et.al.** studied *In vivo* studies on the polymeric micro and nanoparticles revealed that their particle characteristics are very useful in controlling drug behavior. Recently, research based on the combination of the concepts of polymeric prodrugs and micro or nanoparticles have been reported. Polymeric prodrugs enable drugs to be released at a certain controlled rate based on the features of the macromolecule drug linkage. Various reports proved that the micro and nanoparticles can control *in vivo* behavior based on their size, surface charge and surface structure.

87. **Penugonda S. et.al.** synthesized a novel Dextran- Methyl prednisolone prodrug having peptide linkages and to control the rate of release of Methyl prednisolone in lysosomes were characterized.

88. **Varshosaz J. et.al.** studied methyl Prednisolone succinate was attached to dextran 25 kDa using linkers with 1-5 Gly-residues. The drug release of prodrugs in various buffers, blood, liver lysosomes, and various lysosomal proteinases were carried out. The study revealed that the novel dextran-Methyl prednisolone prodrug can be successfully applied for the controlled delivery of Methyl prednisolone in lysosomes. In another study on the treatment of ulcerative colitis, dextran-budesonide conjugates were attempted as colon specific prodrugs. The previous reports showed budesonide as a potent glucocorticoid for the treatment of inflammatory bowel diseases. Dextran-budesonide conjugates were prepared with different molecular weights of dextran in the presence of dimethyl amino pyridine using succinate spacer. The prodrugs were subjected to various spectral studies and physicochemical characterization. Drug release characteristics of the conjugates were also studied in the presence of the luminal contents of different segments of the rat GI tract. The study revealed the promising use of dextran-Budesonide conjugates for treating various anti inflammatory bowel diseases

89. **Manon B. et.al.** conjugated Diclofenac with natural antioxidants like vanillin, sesamol, umbelliferone using glycolic acid spacer (-OCH2COO-) and found that diclofenac-antioxident mutual prodrugs are better and safer than Diclofenac.

90. **Pugazhendhy S. et.al** oxidized Dextran by sodium periodate, and then free amino group of Lamotrigine was coupled with oxidized dextran in alkali medium to form Schiff’s base. The structure of conjugate was confirmed by UV, FTIR and NMR spectroscopy. *In vitro* hydrolysis study showed a negligible release of Lamotrigine from the conjugate at acidic pH 1.2, but faster release was observed in alkaline pH 9.0 than pH 7.4. Synthesized conjugates were screened for preliminary anticonvulsant activity in rats and showed a comparable activity than Lamotrigine. The histological studies of liver
parenchymal cells in control and Lamotrigine-Dextran conjugate groups were similar and showed no abnormalities whereas, the parent Lamotrigine treated group showed focal scattered coagulative necrosis. The results of study concluded that the prodrug would be a safer and suitable drug for the treatment of partial and generalized epilepsy without hepatotoxic side effect.

91. **Shrivastava P.K. et.al.** studied the colon targeted polymeric prodrugs of Celecoxib were synthesized with dextran having various molecular weight using succinic acid as linker between the drug and dextran. The maximum degree of substitution was observed for dextran conjugate. The results of the *in vitro* hydrolysis studies carried out in simulated colonic fluid (SCF) at pH 6.8 and in simulated intestinal fluid (SIF) at pH 7.4 suggested the successful use of dextran as a polymeric carrier for colon targeting of Celecoxib.