5. **SUMMARY**

NSAIDs are widely prescribed for the management of pain and inflammation, but their deleterious effects on the stomach, like gastric irritation, ulceration, bleeding and perforation, are eminent. This is probably attributed to the free carboxylic group of NSAIDs, and to the local inhibition of prostaglandins on gastric mucosa. Therefore the present study was undertaken in order to temporarily mask the free carboxylic group of the conventional NSAIDs by means of the prodrug approach, to overcome the GI injury associated with their long term use.

Numerous ester and amide prodrugs of NSAIDs were prepared by condensation of NSAIDs with different organic compounds in the presence of phosphorous oxychloride in dry pyridine.

Mutual prodrugs of various NSAIDs and paracetamol were prepared to mask the free carboxylic group of the NSAIDs as well as to give a synergistic anti-inflammatory and analgesic response.

Mutual prodrugs of NSAIDs with different sulfonamides, including Dapsone, were synthesized with the intention of improving their efficacy, decrease their side effects, and produce a dual pharmacological response.

Ester prodrugs of some NSAIDs using different alcohols were also prepared and evaluated for their *in vitro* penetration through rat’s skin.

Synthesis of mutual prodrugs, prodrugs and some novel derivatives of fluoroquinolones were undertaken with a view to enhance their antibacterial spectrum.

73 Prodrugs and 33 mutual prodrugs were synthesized and their structures were established on the basis of IR, $^1$H-NMR and Mass spectral data results. The prodrugs were evaluated for their ulcerogenic potential, anti-inflammatory and analgesic activity. The *in vitro* hydrolysis profile of some selected prodrugs was also studies in acidic buffer (pH 1.2), basic buffer (pH 7.4), 80% human plasma, 10% rat liver homogenate and 10% rat intestine homogenate in phosphate buffer (pH 7.4). Some compounds were also
evaluated for their in vitro antibacterial action against *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*.

The ulcerogenic potential of the compounds was evaluated at three different doses in rats. As expected, all the tested compounds showed 50-70% reduction in gastric ulceration at the dose equivalent to their parent compounds, which is indicative of increased margin of safety with these compounds.

Most of the compounds showed better anti-inflammatory activity as compared to that of their respective parent drugs. However, a slight decrease in activity was observed in some cases. Analgesic activity results showed that the tested compounds were very good in their action with maximum activity displayed by 22 and 61 with 71.06 and 69.72% protection respectively.

Some of the compounds were also evaluated for their in vitro antibacterial action against *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*. The prodrugs did not show appreciable in vitro activity against all the bacterial strains, but are expected to exhibit excellent in vivo activity following oral administration due to regeneration of the parent drugs. Conversely, mutual prodrugs of sulfamethoxazole (1, 2, 3, 4 and 20), and compounds 100-105 showed moderate to good activity against these bacterial stains.

Some of the synthesized prodrugs were subjected to in vitro hydrolysis and skin permeation studies. The hydrolysis studies were carried out on prodrugs 18, 22, 61 and 81 in acidic buffer (pH 1.2), basic buffer (pH 7.4), 80% human plasma, 10% rat liver homogenate and 10% rat intestine homogenate in phosphate buffer (pH 7.4). The hydrolysis profile of prodrugs signifies that the target compounds hydrolyzed to release the parent drugs. Negligible hydrolysis was observed at pH 1.2, suggesting that very less of all the prodrugs would hydrolyze in stomach. In aqueous basic buffer (pH 7.4), around 40% of all the prodrugs hydrolyzed to the parent compound, indicating that prodrugs will undergo hydrolysis in the system easily. The ester prodrugs hydrolyzed more in 10% liver homogenate may be due to the presence of esterases. This is evident from the half life ($t_{1/2}$) (2.96hrs.) observed in prodrug 22 (Ester-based mutual prodrug of Paracetamol and Aceclofenac).
The skin permeation studies were performed on prodrugs 44, 47, 49, 53, 56 and 58. Maximum permeation rate was observed in prodrugs 47 and 56 with a flux of 21.21 and 19.86μg/cm²/hr respectively.

These results confirmed the importance of exploring old drugs as safer templates to build new prodrug and mutual prodrug candidates. It can be concluded the newly synthesized prodrugs and mutual prodrugs hold promise towards the pursuit to develop agents with improved pharmacological profile.