Prodrug has been the concept of retro metabolic drug design that incorporates targeting, metabolism and duration of action consideration into the design process. The literature survey reveals that the synthesis of prodrugs of non-steroidal anti-inflammatory drugs results in the reduction of gastrointestinal toxicity as observed by the conventional NSAIDs. The general objective of the present study was to design, synthesize and evaluate novel prodrug structures, which could improve the physicochemical, pharmaceutical or biopharmaceutical properties of drug molecules.

In view of above, novel prodrugs of selected NSAIDs were synthesized and their animal activity was performed in order to obtain better and safer NSAIDs with improved pharmacological activities. Indomethacin, mefenamic acid, aceclofenac, aspirin, ibuprofen, diclofenac, ketoprofen, propyphenazone were used as model drugs in this study. Prodrugs of selected NSAIDs were synthesized by direct coupling and by using spacer technique (amino acid was taken as a spacer). Prodrugs were synthesized in two parts with two different aims. In part-A, mutual prodrugs of NSAIDs were successfully synthesized with synergistic effects. NSAIDs- propyphenazone esters were synthesized as prodrugs with the aim of improving therapeutic index through prevention of GI irritation and bleeding. In part-B, mutual Prodrugs of NSAIDs with additional effects were synthesized. NSAIDs - Allopurinol mutual prodrugs were synthesized with antigout activity additional to anti-inflammatory and analgesic activity of NSAIDs. The synthesized compounds were characterized by determining the physicochemical properties (melting point, solubility, T.L.C., partition coefficient). The structure of synthesized compounds were confirmed by spectral (IR, $^1$H NMR, Mass spectroscopy) and elemental analysis. Hydrolysis studies (In vitro release studies) were carried out in aqueous buffers (SGF of pH 1.2 & SIF of pH 7.4). NSAID-propyphenazone esters were tested for analgesic activity by acetic acid induced writhing method; for anti-inflammatory activity by carrageenan induced rat paw edema method and for ulcerogenicity. On the other side, NSAIDs-allopurinol esters were screened for hypouricaemic / Anti-Gout Activity by serum urate level determination using standard uric acid kit; for anti-inflammatory activity by TNF-$\alpha$ Elisa kit and for ulcerogenicity. Histopathological studies of mice stomach were also carried out to observe the gastric lesions.
The results of present work indicated that the prodrugs of NSAIDs synthesized had better analgesic, anti-inflammatory and reduced / negligible ulcerogenic potential when compared to their parent NSAIDs. All prodrugs were successfully synthesized and the structures were confirmed by spectral analysis. These newly synthesised prodrugs showed encouraging hydrolysis rate in SIF and excellent pharmacological response. Increased anti-inflammatory as well as reduction in ulcer formation of the prodrugs were observed when compared to the parent drug. The histopathological findings revealed that there is limited ulcer formation in stomach by the prodrugs. *In vitro* and *in vivo* evaluation indicated that these prodrugs were more lipophilic than the parent drugs and exhibited better stability in SGF. No change in physical form was observed when these prodrugs were stored at room temperature. Pharmacologically also, when severity of gastric mucosal injury were determined on rodents after chronic oral administration, it was observed that these prodrugs were found to be less irritating than the parent drugs.

Statistical analysis of the pharmacological activity of the synthesized prodrugs on animals was evaluated using a one-way analysis of variance (ANOVA). The results were found to be statistically significant.

**Future Scope**

1) The synthesized compounds can be subjected to enzymatic hydrolysis study.
2) *In vivo* bioavailability study can be undertaken in animals and can be correlated in humans.
3) *In vitro* plasma hydrolysis of the compounds can be done.
4) Stability studies of the compounds as per ICH guidelines can be performed.
5) This approach can be applied to other NSAIDs having free carboxyl functional groups.