CONCLUSION

In our attempt to combine antiinflammatory and antioxidant activities, it has been possible to synthesise ibuprofen-antioxidant mutual prodrugs using different naturally occurring phytophenols/alcohol and flavonoids as antioxidant promoieties. Further, these agents were found to possess encouraging results with retention of antiinflammatory and analgesic activity with significant reduction in their ulcerogenic side effects.

In order to assess the prodrug potential of these synthesized derivatives, the antiinflammatory, analgesic and antiulcer activities have been carried out in appropriate animal models. The pharmacological activities of physical mixtures of ibuprofen and promoieties have also been studied.

The ibuprofen-phytophenols/alcohol mutual prodrugs (41-45) showed comparable antiinflammatory activity with that of the parent drug ibuprofen and significant reduction in ulcer index. The mutual prodrugs with –OCH₂COO- spacer (50-53) and glycine spacer (56-59) showed retention of antiinflammatory activity with significant reduction in ulcer index. All these synthesized derivatives showed significant analgesic activity in acetic acid induced writhing model.

Ibuprofen-glycine-phytophenols/alcohol (56-59) and ibuprofen-phytophenols/alcohol (41-45) derivatives showed significant antiinflammatory activity than ibuprofen –OCH₂COO- phytophenols/alcohol derivatives (50-53). However, these compounds (50-53) showed comparable antiinflammatory activity and significant reduction in ulcer index with that of the parent drug ibuprofen.

Among these compounds, guaiacol and eugenol conjugates of directly (41-45) as well as through spacer (50-53, 56-59) derivatives showed highest antiinflammatory and analgesic activity with maximum reduction in ulcerogenic side effects. The amidation of carboxylic group of ibuprofen with glycine is well tolerated and in most cases, results in compounds with increased antiinflammatory and analgesic activity. The ibuprofen-flavonoid mutual prodrugs (63, 65, 67 & 68) showed significantly increased antiinflammatory and analgesic activity with maximum reduction in their
ulcerogenicity. The absence of gastric damage in all these cases may be attributed to the combined effect of antioxidant activity of the phytophenols/alcohol and flavonoids promoieties as well as masking of the −COOH group of the NSAID.

Furthermore, ibuprofen with phytophenols/alcohol and flavonoids physical mixture did not effectively reduce the risk of gastrointestinal side effects in comparison to their corresponding conjugates. These results suggest that there is a potential advantage in giving such drugs having complimentary pharmacological activities, in the form of single chemical entity i.e. mutual prodrugs which are designed with improved physicochemical properties.

Further work is required to study their physicochemical properties including solubility, partition coefficient, chemical stability and enzymatic hydrolysis to correlate the observed pharmacological activities.