SUMMARY

In our attempt to combine antiinflammatory and antioxidant activities, it has been possible to synthesize diclofenac-antioxidant mutual prodrugs using different naturally occurring phytophenols/alcohol as antioxidant promoieties. For conjugation, glycolic acid spacer and ether spacer were used. Furthermore, 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 evaluated in appropriate animal models. The pharmacological activities of physical mixtures of diclofenac and promoieties have also been studied.

The mutual prodrugs with glycolic acid spacer and ether spacer showed retention of antiinflammatory and analgesic activity with significant reduction in ulcer index. This may be due to the combined effect of masking of carboxyl group, contribution of the antioxidant promoieties and improved physicochemical properties of synthesized derivatives.

Among these compounds, sesamol and eugenol conjugates showed enhanced antiinflammatory and analgesic activity with potential reduction in ulcerogenic side effects. These results suggested that there is a potential advantage in giving such drugs having complementary pharmacological activities, in the form of single chemical entity, i.e. mutual prodrugs, which are designed with improved physicochemical properties.

Studies on physicochemical properties indicated encouraging hydrolysis rate both in phosphate buffer (pH 7.4) and in 80% human plasma. Moreover diclofenac-antioxidant mutual prodrugs showed fair solubilities in buffer (pH 7.4) and greater lipophilicity than the parent drug indicating that the mutual prodrugs are suitable for oral administration.

Furthermore, diclofenac and phytophenols/alcohol physical mixture did not effectively reduce the risk of gastrointestinal side effects in comparison to their corresponding conjugates. This may be due to the instability, poor solubility and low bioavailability of the antioxidants. Therefore, prodrugs of various antioxidants were synthesized and
investigated in the form of their physical mixture with diclofenac, for their antiulcer activity. For this purpose, acetyl derivatives were synthesized. Administration of equimolar doses of these compounds with diclofenac showed significant decrease in ulcer index as compared to diclofenac. This may be due to their improved physicochemical properties. Attempts to obtain diclofenac-antioxidant mutual prodrugs without spacers were not successful.