Summary

In our attempt to combine antiinflammatory and antioxidant activities, it has been possible to synthesize indomethacin-antioxidant codrugs by conjugating with the different naturally occurring phytophenols/alcohol and flavonoids as antioxidant promoieties. Further, these agents were found to possess encouraging results of antiinflammatory and analgesic activity with significant reduction in their ulcerogenic side effect.

In order to assess the prodrug potential of these synthesized derivatives, the antinflammatory, analgesic and antiulcer activities have been evaluated in appropriated animal models. The pharmacological activities of physical mixtures of indomethacin and promoieties have been studied.

The direct ester derivatives (407-413) showed equivalent or slightly higher antiinflammatory and analgesic activity with significant reduction in ulcer index. Among these compounds sesamol and eugenol conjugates showed enhanced antiinflammatory and analgesic activity with potential reduction in ulcerogenic side effects. The introduction of \(-\text{CH}_2\text{CO}-\) spacer does not result in better activity but it could retain its antiinflammatory and analgesic activity equivalent to parent drug indomethacin. However, these \(-\text{CH}_2\text{CO}-\) spacer compounds (421-426) showed significant reduction in ulcer index equivalent to that of direct ester eugenol and sesamol (408 & 411) which showed highest analgesic and antiinflammatory activity with maximum reduction in ulcerogenic side effects. The indomethacin-flavonoid codrugs (430-432) resulted in increased antiinflammatory and analgesic activity with maximum reduction in their ulcerogenicity. The absence of gastric damage in all cases is attributed to the antioxidant activity of the phytophenol/alcohol and flavonoids used as promoieties.

Furthermore, simple coadministration of the parent NSAID, indomethacin with phytophenol/alcohol and flavonoids as physical mixture could not effectively reduce the risk of gastrointestinal side effects in comparison to their corresponding conjugates. These results suggest that the absence of carboxylic group is necessary, in addition to their antioxidant promoieties. All these results suggest, there are potential advantages
in giving such coadministered drugs having complementary activities, in the form of single chemical entity. 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 indomethacin, for their antiulcer activity. For this purpose, acetyl derivatives were synthesized. Administration of equimolar doses of these compounds with indomethacin showed significant decrease in ulcer index as compared to indomethacin. This may be due to their improved physicochemical properties.

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