Nonsteroidal antiinflammatory drugs (NSAIDs) belong to one of the most widely prescribed therapeutic agents for treating various inflammation related disease. However their usefulness is limited due to their gastrointestinal toxic side effects. The pharmacological activity of NSAIDs is related to their ability to inhibit the activity of the enzyme cyclooxygenases (COXs) involved in the biosynthesis of prostaglandin H$_2$ (PGH$_2$). It is now well known that COX exists in two isoforms, namely COX-I and COX-II, which are regulated differently. COX-I is constitutively expressed in stomach to provide cytoprotection in the gastrointestinal tract. COX-II is inducible and plays a major role in prostaglandin biosynthesis in inflammatory cells. Since most of the NSAIDs used clinically inhibit both isoforms, long term use of these agents results in appreciable gastric ulcer and there is enough evidence that inhibition of COX-I rather than that of COX-II underlies gastric ulcer formation. As a result, a number of selective COX-II inhibitors, including Celecoxib and Rofecoxib have been introduced for clinical use with exceptional antiinflammatory properties and reduced gastric toxicity. But initial enthusiasm for selective COX-II inhibitors has faded due to emergence of serious side effects on long term use and the search for safer NSAIDs still continues.

Review of literature in preceding section reveals that involvement of various ROS is responsible for the formation of gastric ulcers associated with long term NSAIDs use. These observations indicate that the use of antioxidants may be useful to prevent the NSAIDs induced gastric ulcer. As a result, a number of phytophenolics have been identified with antiulcerogenic activity due to their antioxidant properties, It has been proposed that concomitant use of an antioxidant and NSAID may decrease the risk of gastrointestinal toxicity and make the therapy safer. However, there is an added advantage in giving such agents in the form of a single chemical entity. Such hybrid molecules consisting of two different therapeutic agents having complementary pharmacological activities are named as mutual prodrugs, which are
designed with improved physicochemical properties and at the same time release the parent molecules at the site of action. On these lines, a number of NSAID–antioxidant mutual prodrugs devoid of their ulcerogenic side effects have been reported. In the University Institute of Pharmaceutical Sciences, also, a number of NSAID–antioxidant prodrug have been synthesized and these agents have been found to be devoid of ulcerogenic side effects.

These observations prompted us to work in this area of drug research for the design and development of safer NSAIDs. In the present study, the well known and most widely used NSAID ibuprofen (31) has been selected which is the first non aspirin NSAID to be allowed for OTC sale since 1984. Today, consumption of OTC ibuprofen accounts for approximately one third of the market for OTC analgesics, and over 100 billion 200mg tablets of ibuprofen have been sold OTC in the United States alone.

This agent has been in clinical use for the last three decades all over the world and therefore it has reasonable safety except gastrointestinal side effect similar to other NSAIDs and therefore there is merit to extend the therapeutic utility of this potential therapeutic agent by designing and development of ibuprofen - antioxidant mutual prodrugs as gastrosparing NSAIDs. For this purpose, a number of antioxidant phytophenols including thymol, guaiacol, eugenol, vanillin, quercetin, naringenin and hesperetein have been selected as promoieties for conjugation with ibuprofen. These naturally occurring compounds have been traditionally in use as food additives and therefore have well documented safety profile.
Based on these facts, it was decided to conjugate ibuprofen with these phytophenols through ester and amide linkages, directly, as well as through spacer. The structures (32-34) of the model compounds are given in figure (Figure 21).

![Figure 21: Illustration of structures of the model compounds of ibuprofen-phytophenols/alcohol (32); ibuprofen-phytophenols/alcohol (32, 33) with spacer.](image)

It was also decided to evaluate these derivatives for their pharmacological activities including antiinflammatory, analgesic and antiulcer activities to access their prodrug potential.