5. Summary and Conclusion

- The class of NSAID represents an important group of drugs indicated for treatment of pain and inflammation. The drugs suppress inflammation by inhibiting prostaglandins synthesis.

- Chemistry and structure activity relationships of palmitoylated derivatives show that all the derivatives have two basic chemical entities: an acidic functional group and a highly lipophilic tail.

- In the present study, palmitoyl ester and amide prodrugs were successfully synthesized and their structural data was characterized and confirmed by IR, $^1$H NMR and $^{13}$C NMR analysis. The efficiency of synthesis and general applicability of palmitoylated derivatives offers a good route for large scale preparation with a good purity and yield. Derivatives of palmitic acid viz. palmitoyl salicylic acid (PSA), palmitoyl anthranilic acid (N-PAA) palmitoyl para amino phenol (PPAP) and palmitoyl para amino benzoic acid (N-PPABA) were synthesized by condensation reaction, taking corresponding parent compound viz. Salicylic acid (SA), anthranilic acid (AA), para amino phenol (PAP) and para amino benzoic acid (PABA) in the presence of pyridine as base. The selection of the fatty acid moiety is done in such a manner that the prodrugs showing lipophilic behavior with varying degree of lipophilicity are obtained.
Synthesized palmitoyl derivatives were found to be more pharmacologically active in terms of analgesic, anti-inflammatory and anti-pyretic activities and quantitatively less ulcerogenic and stable compared to parent drug aspirin and paracetamol.

Palmitoyl moiety was chosen to mask the free carboxylic, hydroxyl and amino group. Since it is condition for prodrug that the pro moiety should be non toxic and a highly lipid soluble, so that drug can readily penetrate cell membrane. The prodrugs showed varying degree of lipophilicity with reduced side effects and not harmful to living system. Thus, a considerable decrease in the solubility of drugs in the aqueous phase including acid medium, can be achieved through chemical modification of these drugs by conjugating with lipid molecules. Lipid formulation can reduce the inherent limitation of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilized phases containing the drug.

At physiological pH the gastric tolerability of NSAIDs may be markedly improved by decreasing their solubility. Hence conversion of salicylic acid, anthranilic acid, para amino phenol and para amino benzoic acid into palmitoyl derivatives through an ester and amide bond to the -OH and NH$_2$ groups of the latter may reduce their acidic nature. Thus the results of this study suggest that PPAP possess promising anti-inflammatory, analgesic properties compared to paracetamol and PSA compared to aspirin. The N- PAA and N- PPABA exhibited
potent pharmacological properties after derivatisation. Thus, the conjugation of palmitic acid to parent compound of NSAID or to their structural analogues leads to new compounds with improved and efficient biological properties. Hence, derivatives with lipids can attribute to eliminate side effects inherent in the initial compounds.

- The prepared palmitoyl ester and amide derivatives were sufficiently chemically stable in SGF and SIF. Additionally, the increased lipophilicity has helped in attaining intact absorption at a higher rate than the parent drugs. Moreover, the enzymatic stability of the amide derivatives also indicated that the activities observed with these molecules were not due to the parent NSAIDs. Therefore, we can conclude that the preparation of suitable ester and amide derivatives of contemporary NSAIDs will represent a potentially useful method for developing compounds with potent analgesic, anti-pyretic and anti-inflammatory activities than their parent compounds.

- The area of design and synthesis of novel NSAIDs is being explored for drugs with better efficacy and safety profile. The discovery of COX-2 inhibitors generated great enthusiasm and competition to design more effective drugs to eliminate major adverse effect of gastro toxicity. Perhaps COX-2 specific palmitoylated SA, AA, PAP and PABA may provide the solution. Molecular docking using auto dock has proved to be useful in finding possible lead compounds. The palmitoylated compounds which were identified and tested
successfully \textit{in silico} and \textit{in vivo}, have given more insights on the attachment of long chain fatty acid moiety to the parent compounds.

\begin{itemize}
  \item In conclusion, the present study provided useful information about novel palmitoyl prodrugs, especially the ester and amide derivatives of palmitic acid holds a great promise for further development of lipid prodrugs. \textit{In vitro} and \textit{in vivo} evaluation of the synthesized palmitoyl derivatives PSA, \textit{N}-PAA, PPAP and \textit{N}-PPPABA revealed improvement in the therapeutic index compared to parent drugs. The derivatives are characterized by adequate chemical and enzymatic stability, reduced ulcerogenic liability, enhanced lipophilicity compared with the corresponding parent drugs. The \textit{in silico} study was supported and complemented by the \textit{in vivo} studies.

  \item It is clear from the foregoing that the design of drug cannot be based just on chemical synthesis. Drug discovery, prodrug and soft drugs development appears to be complementary for generation of target specific medicine now and in the future.
\end{itemize}

On the basis of the above observations, it is concluded that lipid derivatives can be successfully applied to attain the goal of minimized gastro-intestinal toxicity with enhanced anti-inflammatory, anti-pyretic and analgesic activities. The above results confirmed the importance of exploring old drugs as safer templates to built new drug candidates.