The development of new drugs is one of the fundamental goals in medicinal chemistry. Researchers are always interested to synthesize new molecules from old or pre-existing molecules and screen their pharmacological parameters. The pharmacological active molecule is very beneficial for the exploration of a new class of drug molecule. Pharmacological parameters are widely used for the therapeutic regimen setting and for the clinical study. Literature surveyed revealed that various pharmacological active paracetamol derivatives have been synthesized, which are more efficient than paracetamol. Varying substituent is a common method for drug design in medicinal chemistry.

Paracetamol is a non-steroidal anti-inflammatory drug (NSAIDs). It is mostly used as an analgesic and antipyretic drug. Paracetamol is a weak anti-inflammatory action inspite of member of NSAIDs. It is a weak anti-inflammatory drug due to lack of prostaglandin inhibition peripherally in the body. The main mechanism of action of paracetamol is the inhibition of cyclooxygenase (COX). The recent reports suggest that it is highly selective for COX-3 in the brain and spinal cord. Paracetamol is effective in relieving pain and reducing fever without having unwanted gastrointestinal side effects. However, several reports stated that large overdoses of paracetamol can produce a fulminant hepatic and renal tubular necrosis due to the formation of the toxic metabolite, like N-acetyl-p-benzoquinoneimine (NAPQI). Therefore, there has been a concerned search for the discovery and development of newer pharmacological active paracetamol derivatives.

The simple, efficient, sensitive, accurate and economical analytical technique for quantification of such newly synthesized derivatives is needed in pharmaceutical pasture. The development of novel techniques is used for the estimation of drug in different in-vitro and in-vivo pharmacological parameters such as, in pharmacokinetics, pharmacodynamic and bioequivalence study. A number of methods have been reported for the determination of paracetamol. The determination of paracetamol in biological fluids (blood, plasma, urine) is mainly depended on HPLC techniques, electrochemical method and spectrofluorimetry, while there are
very few spectrophotometric methods in which paracetamol is determined in biological fluids. Different methods are used for kinetic study of the paracetamol, such as, bioavailability data of paracetamol was determined by spectrophotometrically using saliva samples.

In recent years, the throughput of the drug discovery process has improved because of the implementation of high-throughput in pharmacokinetics (PK) parameters such as, Absorption, Distribution, Metabolism and Elimination. Hundreds of compounds can be screened in vitro per week, providing scientists with a wealth of data. In vivo pharmacokinetic studies are included in various steps, study protocol preparation, animal dosing and sample processing and analysis (analytical portion), PK regression and data reporting.

The aim of the present work is to synthesize new condensed paracetamol derivative and to test the antimicrobial and pharmacological activities by in-vivo and in-vitro tests. The acute oral toxicity study is also revealed new effective dose of the synthesized derivatives. The synthesized paracetamol derivatives show analgesic, antipyretic, anti inflammatory, antibacterial and antifungal activities. New spectrophotometric methods are also developed for the estimation of synthesized compounds in biological fluids. Pharmacokinetics study is performed by using animal model and examines various parameters.

THE THESIS IS DIVIDED INTO SIX CHAPTERS

The aim of this work to synthesize new paracetamol derivatives, which are having more potential activities than the present paracetamol drug. The simple, accurate and cost-effective spectrophotometric methods are also developed for the estimation of synthesized compounds in biological fluids. Pharmacological study and pharmacokinetic study of the synthesized derivatives are covered in this research work.

Chapter I: Introduction and Literature Review

This chapter comprises of the information on the scenario of paracetamol drug and lack of pharmacological activities potency. Literature
studies revealed that pharmacological activity, toxicity study and lack of anti-inflammatory activity of paracetamol. Current references along with the previous paracetamol derivatives have been more effective pharmacological activities than the presence paracetamol drug. Various spectrophotometric methods, which are used for biological fluids and pharmacokinetics study have been also reported. The objective and scope of the present work are also included.

Chapter II: Experimental

The materials and synthesis method used during the entire research work are reported in this chapter. The physical parameters, such as %yield, melting point, solubility, TLC and pka value etc. are summarized in this chapter.

Chapter III: Spectral Characterization

The synthesized compounds are characterized by different spectral techniques (UV, FTIR, ¹H NMR, LCMS and Elemental analysis).

Chapter IV: Spectrophotometric Validation Method

This chapter describes the spectrophotometric validation method and quantitative determination of synthesized compound in biological fluids (blood and urine).

Chapter V: Pharmacological Evaluation

The synthesized compounds have been shown various pharmacological activities (antibacterial, antifungal, analgesic, antipyretic and anti-inflammatory). Well plate method was used for the antibacterial and antifungal activities of the synthesized compounds. OECD guideline 423 was used for the evaluation of acute oral toxicity of the synthesized compounds. The analgesic study was carried out by Hot plate and Tail Immersion method; while antipyretic and anti-inflammatory activities were performed by Yeast induce Pyrexia and Carrageenan-induced paw oedema method, respectively. The pharmacokinetic studies were carried out using
Chapter VI  Results and Discussion

The structure of synthesized compounds was confirmed by FT-IR, $^1$H NMR, LC-MS and elemental analysis. The synthesized compounds have shown excellent biological and pharmacological potencies than the present paracetamol drug. The synthesized compounds have been screened for antibacterial and antifungal activities and gives better results than the standard drug. Acute oral toxicity of the synthesized compounds was performed by using OECD guideline 423 and calculates the effective dose ($ED_{50}$) for the synthesized compounds. The results of analgesic and antipyretic activities revealed that the synthesized compounds are shown moderate to excellent potency than the paracetamol. Synthesized paracetamol derivatives of paracetamol are shown moderate to excellent anti-inflammatory activity than that of the standard diclofenac sodium drug. Pharmacokinetic studies were performed by an animal compartmental model method using blood and urine sample of the rats and calculates the different pharmacokinetic parameters such as, $T_{max}$, $C_{max}$, $K_e$, $T_{1/2}$, $(AUMC)_{0-\infty}$, $(AUC)_{0-\infty}$ and $MRT$, maximum rate of excretion ($R_{max}$), Area under the rate of excretion versus midpoint of time interval curve for 0-84 hr and up to infinity $[(AURC)_{0-t}$ and $(AURC)_{0-\infty}]$, cumulative amount of unchanged drug in urine $(Ae)$, fraction of unchanged drug excreted $(fe)$ are discuss in this chapter.

Conclusion

The results and discussion is followed by the concluding remarks derived from this research work.