External Examiner’s report for the thesis entitled, “Development and validation of chromatographic techniques in pharmaceutical matrices: a novel approach” submitted by Mr. T. Kaleemullah for the award of Degree of Doctor of Philosophy in CHEMISTRY, Thiruvalluvar University, Vellore, Tamil Nadu, India.

In this Doctoral Research study Mr. Kaleemullah developed simple, reliable, cost effective Chromatographic methods for the quantitative measurement of several contaminations present different spectrum of pharmaceutical drugs. These impurities or contaminants were the trace amount residual solvent and stabilizer present in the active compounds. These solvents and stabilizer were left behind in the final product during the manufacturing process.

The introductory part is highly relevant, Kaleemullah systematically elaborated on the drug manufacturing process, various impurities, acceptable impurity guide lines given by several agencies. Overview of various spectrum of commonly used drugs and the possible contaminates were discussed in this thesis. The threshold of various contaminates and their side effects such as carcinogenetic and genotoxicity were strengthening argument for the development of these methods. This research may open up new methodology for pharmaceutical industries quality control development and to develop manufacturing process contamination free and to safe to use in patients.

This examiner finds this research study is an outstanding piece of innovative research. This research is well thought-out and executed with a great extent. Also, the thesis is well written and articulately composed with adequate background information which is well said in the introduction chapter. The methodology applied is clear and organized in a sequence to address the goal of the planned research study. Results were presented well to establish the need for new methods for the quantitative measurement of impurities left behind the final product, particular emphasis to the contaminates such as α- hydroxyl acid, brominating agents, chiral resolving agents, formylating agents and solvents present in the commonly used drug product belongs to therapeutic agent categories, antihypertensive , antibiotic, antipsychotic, anti-depressants by simple chromatographic techniques.

I **RECOMMEND** that this thesis to be accepted and Mr. T. Kaleemullah be awarded the degree of Degree of Doctor of Philosophy in CHEMISTRY, Thiruvalluvar University, Vellore, Tamil Nadu, India. I congratulate both the doctoral Scholar Kaleemullah and the PhD advisor Professor Dr. Mansur Ahmed for their contribution to the science.

The thesis is, therefore, **HIGHLY COMMENDED**. A few specific comments may, however, be directed at the candidate during viva interface.

Particular focus to the following drugs,

1. Reversed phased-HPLC method was developed for quantitative determination of N-Bromosuccinimide in Valsartan, Irbesartan, Candesartan and Telmisartan.
2. HPLC method developed for quantitative determination of lactic acid in Cefuroxime sodium
3. simple methodology for quantitative determination of DPTTA in Escitalopram oxalate drug substance
4. gas chromatographic method has to evaluate reliable and economical result for the simultaneous determination of Methyl chloride, Ethyl chloride and Isopropyl chloride residue present in the Ziprasidone Hydrochloride, Valganciclovir Hydrochloride, Fluoxetin Hydrochloride.
5. The method was found to be best for Risperidone and Alfuzosin hydrochloride drug substances, which contain Isopropyl chloride and Ethyl chloride in the drug matrix.
6. simple ion chromatographic method was proposed for the determination of sodium citrate in Nafcillin for injection and penicillin G potassium for injection in parenteral preparations and validated as per the ICH guidelines.
7. simple ion chromatographic method was proposed for the determination of Formic acid content in Ampicillin trihydrate drug substance, the method was validated as per the ICH guidelines.

**CHAPTER-5**

**CONCLUSION**

This Chapter describes the conclusion for the overall chromatographic development and validation for various pharmaceutical matrices.

**a) Conclusion for the N-Bromosuccinimde determination in Candesartan, Telmisartan, Irbesartan and Valsartan drug substance:**

The proposed new reversed phased-HPLC method developed for quantitative determination of N-Bromosuccinimide in Valsartan, Irbesartan, Candesartan and Telmisartan drug substance is accurate, Precise and selective. The method has produced satisfactory validation data for the tested parameters as per the ICH guidelines. The proposed method is simple and cost effective as it uses commonly used C1a column under gradient elution, with moderate run time. Hence the proposed method is conveniently used for the determination of NBS during bulk manufacturing of Valsartan, Telmisartan, Irbesartan and Candesartan in quality control laboratories.

**b) Conclusion for the Lactic acid determination in Cefuroxime sodium drug substance:**

The proposed HPLC method developed for quantitative determination of lactic acid in Cefuroxime sodium drug substance is rapid, accurate, precise and selective the method was showing satisfactory validation data for the tested parameters as per the ICH guidelines. The proposed method is simple and cost effective as it uses commonly used ODS column under gradient elution, with moderate run time. Hence the proposed method is conveniently used by quality control department for the determination of lactic acid content in Cefuroxime sodium drug substance.

**c) Conclusion for the Di-p-Toluoyl-D-Tartaric acid determination in Escitalopram oxalate drug substance:**

The proposed simple methodology for quantitative determination of DPTTA in Escitalopram oxalate drug substance is rapid, accurate, precise and selective. The method provided satisfactory validation data for the tested parameters as per the ICH guidelines. Hence the proposed method may be conveniently used in bulk manufacturing for the quantification of DPTTA content in Escitalopram oxalate drug substance.

**d) Isopropyl chloride determination in Ziprasidone Hydrochloride, Valganciclovir Hydrochloride, Fluoxetin Hydrochloride drug substance:**

The developed gas chromatographic method has to evaluate reliable and economical result for the simultaneous determination of Methyl chloride, Ethyl chloride and Isopropyl chloride residue present in the Ziprasidone Hydrochloride, Valganciclovir Hydrochloride, Fluoxetin Hydrochloride.

The results of various validation parameters confirmed that the method is specific, robust, linear, precise and accurate. The method has been applied to various drug substances containing possible alkyl chloride moiety in the drug matrix. The experimental data shows that the method has potential application for the quantitative determination of alkyl chloride moiety present in the drug substances.

The method was found to be best for Risperidone and Alfuzosin hydrochloride drug substances, which contain Isopropyl chloride and Ethyl chloride in the drug matrix. The recovery data also proves the repeatability and robustness of the developed method.

**e) Conclusion for the Citrate determination in Nafcillin for injection and Pencillin for injection (Parenteral&):**

A new, accurate and simple ion chromatographic method was proposed for the determination of sodium citrate in Nafcillin for injection and penicillin G potassium for injection in parenteral preparations and validated as per the ICH guidelines. All statistical results (Percentage, Mean, RSD, Percentage difference and recovery %) were within the acceptance criteria.

**f) Conclusion for the Formate** determination **in Ampicillin Trihydrate sterile drug substance:**

A new, accurate and simple ion chromatographic method was proposed for the determination of Formic acid content in Ampicillin trihydrate drug substance, the method was validated as per the ICH guidelines. All statistical results (Percentage, Mean, · RSD, Percentage difference and recovery %) were within the acceptance criteria.