CHAPTER 6:

Scope and conclusion

Impurity profiling helps in quantification and identification of impurities in pharmaceuticals and plays a major role in predicting and maintaining stability and efficacy of pharmaceutical agents. Hydrazine hydrate is genotoxic impurity which is highly reactive in nature and shows various carcinogenic effects to human and other creatures. The developed method is accurate and highly sensitive reversed-phase liquid chromatography-UV derivatization method for the determination of hydrazine in Imatinib Mesylate drug substance.The derivatization effectively shifts the resultant 1,2-dibenzylidenehydrazine product away to higher wavelengths in the UV spectrum where API matrix components &solvents do not interfere with the analysis. The present work described an accurate and highly sensitive reversed-phase liquid chromatography-UV derivatization method for determination of hydrazine in imatinib mesylate drug substance. The method of quantification was developed by attaching chromophores to hydrazine with derivatization, which is helped to increase sensitivity. The LOQ of the method was determined to be 0.0040µg/g (%w/w) and was adequate for sensitive quantification of hydrazine hydrate in imatinib mesylate API.

The organic solvents used in the process of manufacturing requires monitoring and control as the solvents are toxic, have no therapeutic importance and affect the quality and stability of drug substances and drug products. There are six volatile organic solvents are methanol, acetone, dichloromethane, n-hexane, ethyl acetate and pyridine and all these volatile organic solvents are required to be identified and quantified during the manufacturing of the imatinib mesylate drug substance since most of the solvents are under the category of Class II solvents as per ICH guideline. A developed method is selective, sensitive and fast static HSGC method for the determination of methanol, acetone, dichloromethane, n-hexane, ethyl acetate and pyridine in Imatinib Mesylate API through consideration of route of synthesis and solvent nature. The developed method was successfully validated as per regulatory guideline and found to be precise, accurate, linear, and robust and specific. Additionally, the developed method is suitable for analysis of all solvents in a single run. The current developed method can be used for the separation of the residual solvents from the other drugs and used for routine analysis to monitor in-process drying and in quality control for bulk drug manufacturing. Hence, developed HSGC method demonstrated precise, economical and commercially viable quantitative technique for residual solvents determination in Imatinib Mesylate API which will also be advantageous for industrial scale manufacturing.

Impurities present in the dasatinib are needs to characterize as it has genotoxic potential. Total Six impurities present in the dasatinib i.e. Dasatinib Imp-1, Dasatinib Imp-2, 2-Amino-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide, 4-(2-(4-(6-((5-((2-chloro-6-

methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl) ethoxy)-4-oxobutanoic acid, 4-(2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethoxy)-4-oxobutanoic acid, N-(2-chloro-6-methylphenyl)-2-[(6-chloro-2-methyl-4-pyrimidinyl)amino]-5-thiazole carboxamide, 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl acetate. These impurities have been characterized using mass spectrum, 1H NMR spectrum, 13C-NMR spectrum, IR spectrum to confirm its structure. Structures of the impurities are proved helpful in the future scope of the impurity detection and its quantification during commercialization.

A developed robust method shows evaluation of all the process and degradation related impurities of solid dispersion of Dasatinib drug substance. The developed method is capable for quantitative analysis of potential impurities present in bulk drug and in pharmaceutical dosage form of Dasatinib. The method was developed and validate using chromatographic evaluation for determination of process and degradation related impurities in solid dispersion of Dasatinib drug substance by evaluating RF values of each impurity as per validation guideline of ICH. As HPLC is involved in method of detection, method can be performed easily at academic and industrial level due to very cheap solvents and easily available agents are used during method development. The developed method will be of high importance for the commercial production of Dasatinib, an efficient oncological drug, with over $ 2000 million market size. The developed method was validated for its specificity, linearity, range, accuracy and precision to demonstrate that the method is suitable for its intended use as per ICH Q2 (R1) guideline. Reproducibility of method is very high so it can be performed at any facility with basic instrumentation requirements so the method is applicable for routine analysis for determination of impurities in Dasatinib bulk drug and formulation in Quality Control Labs.

From force degradation study of novel compound ZY12201 can elucidate the structure of degradation products along with resolution of stability-related problems. From these types of studies we can produce more stable formulations of drugs and it also helps in determination of expiry date of drugs. Stability studies can be useful in formulation selection, packaging selection and storage conditions for the products. The developed analytical method is rapid, simple, precise, robust, accurate and selective gradient RP-LC method that separates the ZY12201 and its impurities and degradation products with good resolution. The developed method was validated to ensure the compliance in accordance with ICH guidelines. The developed method can be used for routine testing and stability analysis in quality control laboratories to check purity of ZY12201 in bulk and pharmaceutical formulation.

Overall work presented have produced a very useful result and on the verge of the industrial application.