Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 08, pp.72876-72878, August, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

SIMPLE CONVENIENT AND EFFICIENT PROCESS FOR REMOVAL OF GENOTOXIC IMPURITY (F IMPURITY) FROM IMATINIB API TREATING WITH BASE USING WATER AS MEDIUM

***[1]Shiva Rama Krishna Samala, [2]Kishore Gokavarapu, [2]Srinivasa Rao B., [3]Sarita Gokavarapu and [4]Sunil Gandhi**

[*1]Research and Development Department, Helios Life sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117
[2]Production Department, Helios Life sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117
[3]QC and ADL Department, Helios Life sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117
[4]Chairman - Helios Life sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117

ARTICLE INFO

Article History:
Received 23rd May, 2018
Received in revised form
14th June, 2018
Accepted 27th July, 2018
Published online 31st August, 2018

Key Words:

Imatinib,
Genotoxic,
Anticancer,
F Impurity.

ABSTRACT

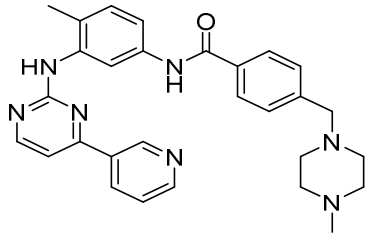
A simple convenient and efficient process of Genotoxic impurity (F impurity) removal from the Imatinib API by treatment with base like sodium hydroxide at 45-50°C about 12hr using water as medium with negligible yield loss , this process can used as a high potential application in commercial scale Genotoxic impurity removal from the Imatinib API.

Citation: Shiva Rama Krishna Samala, Kishore Gokavarapu, Srinivasa Rao B., Sarita Gokavarapu and Sunil Gandhi. **2018.** "Simple Convenient and efficient process for removal of Genotoxic Impurity (F Impurity) from Imatinib API treating with Base using water as medium", *International Journal of Current Research*, 10, (08), 72876-72878.

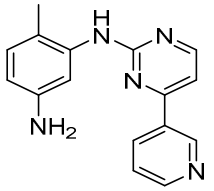
INTRODUCTION

Genotoxic impurities (GTIs) are DNA-reactive substances that may damage DNA, leading to genetic mutations which could potentially cause cancer (Liu, 2010). GTIs, also referred to as mutagenic impurities are unusually toxic. Accurate identification and control of them are critical to ensure product quality and minimize safety risks. Imatinib mesylate is an anti-neoplastic (anti-cancer) drug used for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumor (Arava et al., 2012). Two process impurities, 4-[(4-Methyl-1-piperazinyl) methyl]benzoic acid dihydrochloride (MPBA) and 4-Methyl-N3-[4- (3-pyridinyl) -2- pyrimidinyl]-1, 3-benzenediamine (PNMP), are classified as potential genotoxic impurities based on the structural alerts and must be monitored during the synthesis process. The methods reported in literature for quantitative determination of genotoxic impurities in Imatinib mesylate utilize HPLC instrumentation and columns, which can be long and consume a high volume of solvents (Arava et al., 2012; Madireddy et al., 2011). Early in API development, there is a need for fast, sensitive, and accurate identification and assessment of impurities to provide guidance on identifying and controlling impurities within acceptable levels. Once impurity profiles are characterized, it becomes equally important to implement methods and technologies that are well suited for accurate, robust, routine, and traceable testing that are critical for late stage development. Typically, early stage development is often performed using information-rich tools (e.g. single/tandem quadrupoles, NMRs), which enable confident characterization of analytes.

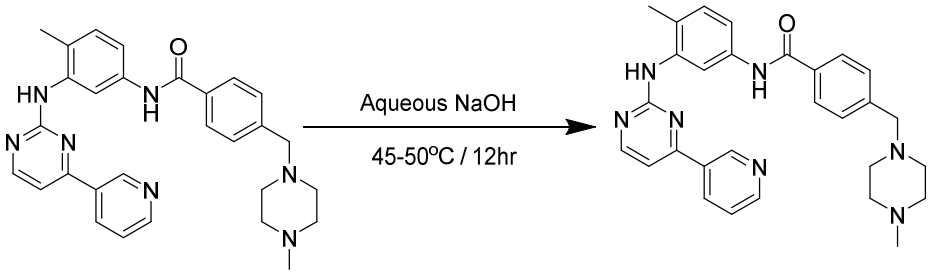
****Corresponding author:*** **Shiva Rama Krishna Samala,**
Research and Development Department, Helios Life sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117.
DOI: https://doi.org/10.24941/ijcr.32142.08.2018



Imatinib

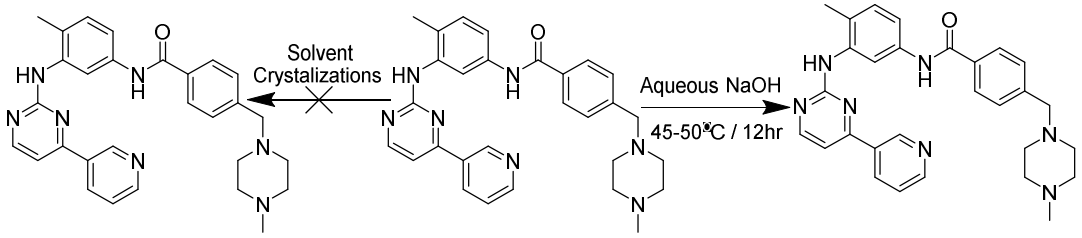


Genotoxic impurity (F)



Genotoxic Impurity level in input 3000-3500ppm

Genotoxic Impurity after base treatment <10ppm



Genotoxic impurity level afer solvent crystalizations 1500-2500ppm

Genotoxic Impurity level in input 3000-3500ppm

Genotoxic Impurity after base treatment <10ppm

Conducted experiments mentioned in below table

Entry	Input Impurity ppm	Solvent/ Base	Process Temperature °C	Output Impurity ppm (HPLC / LC-MS)	Remarks on process
1	3000- 3500	MeOH	Reflux	3100	Not good
2		Acetone-H_2O	Reflux	1800	Not good
3		IPA-H_2O	Reflux	2200	Not good
4		DMF-H_2O	RT	2900	Not good
5		DMSO-H_2O	RT	2700	Not good
6		$NaHCO_3$-H_2O	45-50	1900	Need improvement
7		Na_2CO_3-H_2O	45-50	1200	Need improvement
8		K_2CO_3-H_2O	45-50	1250	Need improvement
9		Cs_2CO_3-H_2O	45-50	750	Better
10		KOH-H_2O	45-50	270	Good
11		NaOH-H_2O	45-50	7	Excellent

These methods are then largely implemented as UV-based methodologies in later stages. As drugs become less amenable to UV methods (lower concentrations, more complex formulations), it is becoming increasingly important to establish rapid, MS-friendly workflows to support the entire development life cycle. The ICH M7 guidance describes several approaches for control of GTIs in drug substances (ICH M7). In the case when routing testing is recommended, an analytical method with "as low as reasonably practicable" (ALARP). Detection limits will enable accurate monitoring of the fate and purging levels of the impurities during the drug development process. In addition, the ICH M7 recommends periodic verification testing to demonstrate that the product consistently meets specifications. In this work, we describe a sensitive and rapid UPLC method coupled with mass detection for the quantitative determination of genotoxic impurity of the Imatinib drug substance. We will investigate the sensitivity and linearity achievable witha tandem quadrupole (Xevo TQ-S micro) mass spectrometer. Then, we will repeat this study on a single quadrupole (ACQUITY QDa) mass detector. We will show that the tandem quadrupole detector is ideal for ultra-sensitive residual detection and quality monitoring of genotoxic impurity the drug substances, while the ACQUITY QDa provides a robust and sensitive platform suited for routine testing in the late stage development through to QC environments and same results observed on HPLC condition optimized system and for this we have optimized a robust process in Research &Development Lab which is given genotoxic impurity free material Imatinib API.

Experimental section: We have used in-house synthesized Genotoxic impurity (F impurity 3000-3500ppm) contained

Imatinib API for our process, commercially available sodium hydroxide and available DM water taken and optimized the process in R&D lab, same implemented and done in production bathes, obtained Genotoxic impurity free Imatinib API analysis done on above explained LC-MS and HPLC system.

Brief process: To remove genotoxic impurity from Imatinib API we have conducted around 11 experiments in this five are solvent recrystallization and other six are aqueous base treatments, in solvent recrystallization methods we did not found impurity removal from API but where as in the case of Aqueous base treatment found some improvement. And finally the best process picked up from table is aqueous sodium hydroxide treatment, in this process we have Genotoxic impurity contained Imatinib taken in clean and dry RBF charged DM water followed by aqueous sodium hydroxide (P^H=10-11) heat the reaction 45-50^oC about 12hr and filtered the material at same temperature given through hot water wash to filtered solid unloaded dried in oven at 60^oC 15hr and sent the sample for Genotoxic impurity content estimation by HPLC and LC-MS.

Conclusion

In summary, a new and novel process of Genotoxic impurity removal from Imatinib API (Active Pharmaceutical Ingredient) using aqueous medium with inorganic base like sodium hydroxide.

Acknowledgment

We gratefully acknowledge the generous support provided by Helios Life sciences Limited as a special project on Imatinib Genotoxic impurity removal process.

REFERENCES

Arava, V.R., Bethi, M.R., Cherukuri, K.R., Thota, G., Cherukupally, S.R. 2013. LC-MS/MS Method for Determination of Potential Genotoxic Impurities in Imatinib Mesylate, *Scholars Research Library,* 5(6) , 47–52.

http://www.ionsource.com/tutorial/msquan/intro.htm

ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, International Conference on Harmonization, 23 June 2014.

Liu, D.Q., Sun, M., Kord, A.S. 2010. Recent Advances in Trance Analysis of Pharmaceutical Genotoxic Analysis. *J Pharm Biomed Anal*., 51 (5), 999–1014.

Madireddy, V., Babu, K.S., Narayanareddy, P. 2011. Stability-indicating, Validated, Fast HPLC Method for Quantification of Two Genotoxic Impurities in Imatinib Mesylate, *Global Journal of Analytical Chemistry*., 2 (5), 198–206.

****