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Strategies For Controlling Genotoxic Impurities And LCMS/MS Method Development For Quantifying TTC Levels In Rebamipide Synthesis.

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Abstract
The key research investigates strategies for controlling of potential genotoxic impurity (PGI) to the desired limit by reducing the genotoxic functionality to non-PGI functionality and elimination of non-PGI functionality by converting to its acid salt and removing it by dissolving in water/solvent. This investigation work is approached during the synthesis of Rebamipide and it was free from the PGI. The robust LC-MS/MS method was developed for identification and quantification of mentioned PGI at TTC limit. The characterization data and the control of PGI at TTC level are reported
Keywords: *Genotoxic Impurity, Rebamipide, 4-chlorobenzoic acid, LCMS, Solvent effect, water.*

INTRODUCTION

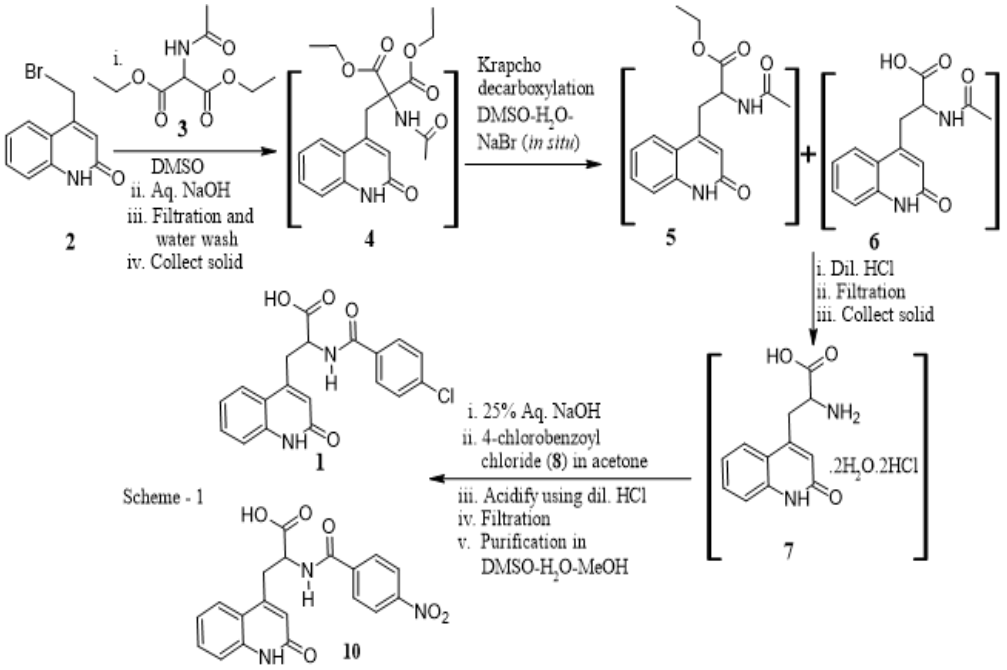
Nowadays, safer drug production received great attention because of stringent rules and regulations of regulatory agencies. Hence it is the responsibility of chemists, engineers and formulators, who involved in the manufacture of drug, to ensure that the developed manufacturing process is efficient for multi kilogram production of API (active Pharmaceutical Ingredients) compared to reported processes and the manufactured drug is safer for the medication.

In safety point of view, in the formulation ensuring the quality and purity of API, play a key role on patient's health. The presence of potential genotoxic impurities (PGIs) in drug substances is common because the final drug substance holds; noxious starting materials, process intermediates, reagents at low level as an impurity, and the by-products of synthetic processes as toxic impurities. But, the presences of PGI's at high enough concentrations and other unintended contaminants present in drug substances could cause adverse health effects in humans, for example elicit cancer to humans[1,2].

Hence, the great demand for identification, characterization of PGIs, their control by derivatization method and a better analytical tool for the detection and quantification of the PGI at TTC limit, purification or change in the synthetic process or isolation process to attain safer drugs and to meet the requirement of regulatory agencies worldwide, especially to comply with ICH[International Conference on Harmonization] [3,4].The process chemist plays a key role in avoiding the generation or control of PGIs during the development of efficient manufacturing process of the drugs.[5] Hence, identification, characterization and control of these PGIs are very important otherwise, it could lead to holding of clinical trials for new drug discovery programs or the delay of approval from regulatory agencies for both new and generic drugs. Rebamipide[6] is a superior drug compared to existing drugs for use in healing of peptic ulcers, gastrointestinal bleeding and dyspepsia and it is also useful as an ophthalmic drug for the treatment of dry eye syndrome[7,8].

The present work is process development and synthesis of Rebamipide, we used a commercial source for one of the key starting material, namely 4-Chlorbenzoic acid (8a). Most of the commercial materials were having an unknown impurity at higher level. The derived impurity of API was not at all eliminating in any purification techniques. It became difficult to meet the ICH guidelines due to presence of the impurity. Thus, it has been decided to identify, isolate and characterize the impurity. Based on the commercial route of synthesis as shown in scheme-2, the reagents used & LCMS data of 4-chlorobenzoic acid(8a), the plausible structure identified as 4-Nitrobenzoic acid (9). The standard of same was procured,

checked and confirmed by HPLC retention time check. Upon confirmation of the impurity structure, the structural alert was checked with DEREK and SARAH found 4-Nitrobenzoic acid (9) as PGI.
Now the biggest task is it must be controlled to the level below the Threshold of Toxicological Concern (TTC),[9] i.e. acceptable daily intake should be not more than 1.5 µg per day as accepted by the ICH, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[10]Based on the calculation the TTC using daily dosage of the drug, the impurity should be controlled to the level at NMT 5 ppm. The synthetic route for the synthesis of Rebamipide on bulk scale is represented in Scheme-1.



Scheme-1. Synthesis of Rebamipide

EXPERIMENITAL

Optimum Process Conditions for the elimination/control of 4-Nitrobenzoic acid (9) in 4-chlorobenzoic acid (8a):

The conversion of nitro group to amine was conducted out as per literature reported process. Accordingly, the compound 8a containing compound 9was reduced using Zinc/formic acid combination in DMF/MeOH solvent. The formed amine derivative was converted to its corresponding salt using hydrochloric acid. Thus, formed salt was eliminated in the MLR and highly pure 4-chlorobenzoic acid (8a) was obtained with very good yield and purity without using the column chromatography and also, we found 4-nitrobenzoic acid (9) content at less than 5 ppm was isolated, the isolated 4-chloro benzoic acid is converted in to benzoyl chloride[11] for the synthesis of 1 (scheme-1).

Detection Method:

The solvents and reagents were obtained from commercial sources and it used without any purification, 4-Chlorobenzoic acid used from commercial source containing different levels of 4-nitrobezoic acid. The obtained product was analysed using LCMS for checking the presence of 4-nitrobenzoic acid.

Example-1: Isolation of 4-Chlorobenzoic acid (8a) with control of 4-nitrobenzoic acid (9) at less than 5 ppm.

In a 5L RBF, DMF (625 mL, 2.5 V), 4-chlorobenzoic acid (250 g, 1.59 mol) containing 4-nitrobenzoic acid was charged at 20-30 °C. Zinc dust (12.5 g, 0.12 mol) and formic acid (50 mL, 0.2 V) was charged sequentially at 20-30 °C. The temperature of the reaction mass was raised to 60-65 °C and maintained for 2h. The reaction mass was filtered at 60-65 °C to remove the zinc dust from the reaction mass. The obtained clear filtrate was charged into 5 L RBF and cooled to 20-30 °C. Mixture of water (2500 mL, 10 V) and Conc.HCl (50 mL, 0.2V) was added into the reaction mass at 20-30 °C. Stirred the reaction mass

for 1h at 20-30 °C. Filtered the reaction mass, washed the wet cake with water (250 mL, 1V). Suck dried and unloaded the material. The obtained solid product was dried in hot air oven at 60-65 °C for 6h to give 230g (92% of yield) of pure compound (8) with HPLC purity of >99.7%. 4-Nitrobenzoic acid content was less than 5 ppm.

Example-2: Isolation of 4-Chlorobenzoic acid (8a) with control of 4-nitrobenzoic acid (9) at less than 5 ppm.

In a 5L RBF, MeOH (1250 mL, 5 V), 4-chlorobenzoic acid (250 g, 1.59 mol) containing 4-nitrobenzoic acid was charged at 20-30 °C. Zinc dust (12.5 g, 0.12 mol) and formic acid (50 mL, 0.2 V) was charged sequentially at 20-30 °C. The temperature of the reaction mass was raised to 60-65 °C and maintained for 2h. The reaction mass was filtered at 60-65 °C to remove the zinc dust from the reaction mass. The obtained clear filtrate was charged into 5 L RBF and cooled to 20-30 °C. Mixture of water (3000 mL, 12 V) and Conc.HCl (50 mL, 0.2V) was added into the reaction mass at 20-30 °C. Stirred the reaction mass for 1h at 20-30 °C. Filtered the reaction mass, washed the wet cake with water (250 mL, 1V). Suck dried and unloaded the material. The obtained solid product was dried in hot air oven at 60-65 °C for 6h to give 230g (92% of yield) of pure compound (8a) with HPLC purity of >99.7%, 4-Nitrobenzoic acid content less than 5 ppm.

Materials, Analytical Method Development and Validation

The rrequired chemicals for the study were purchased from Sigma-Aldrich and were used without further purification. The purity of derivatives was monitored using thin-layer chromatography on silica gel-G. The melting points of the compounds were measured in open capillaries, with digital scientific melting point apparatus and are uncorrected. Infrared spectra were recorded using Perkin Elmer SP-2 spectrophotometer by using KBr. ^{1}H &^{13}C NMR spectra of the derivatives were recorded on Bruker (Advance II, Bruker 400MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in terms of ppm and elemental analyses were conducted on a Perkin-Elmer 2400 elemental analyse.

The analytical method was validated following the International Council for Harmonization (ICH) guidelines, focusing on several critical parameters[10] in terms of specificity, linearity, limit of quantification (LOQ), limit of detection (LOD), accuracy, precision, robustness and solution stability. The LOD and LOQ for Imp-E (compound-9) were determined by injecting diluted solutions with known concentrations as shown in [Fig.1 (a-b) see in supporting Information].

The linearity of the method was evaluated across six different concentration levels, ranging from LOQ to 150% of the impurity concentrations. The specific concentrations tested for PGI (Potential Genotoxic Impurity) were 1.24 ppm, 2.48 ppm, 3.97 ppm, 4.96 ppm, 5.95 ppm, and 7.44 ppm. The objective was to determine whether the method produces results that are directly proportional to the concentration of the impurity within this range. The linearity was satisfactorily demonstrated with a six-point calibration graph between LOQ and 150% of the impurity's concentration. The slope, intercept and regression coefficient values were determined by the least square's linear regression analysis. The accuracy of the analytical method was evaluated by performing tests in triplicate at three distinct concentration levels: LOQ, 1.25 ppm, 5 ppm, and 7.5 ppm. These concentrations correspond to the LOQ (Limit of Quantification) up to 150% of the specification level for PGI (Potential Genotoxic Impurity). The accuracy was assessed by calculating the percentage recovery and the % RSD (Relative Standard Deviation) for the recovery results at each concentration level.

The % RSD of area for each individual impurity was calculated. The intermediate precision of the method was also evaluated using different analyst and performing the analysis on different days and different analyst. Solution stability of the impurities in sample solution was established by analyzing spiked sample solution at different time intervals at 5°C. The robustness of the method was studied with deliberate alteration in the flow rate of the mobile phase and column temperature. The optimized flow rate of the mobile phase was 0.5 mL/min and the same was altered by ±0.2 units i.e. from 0.3 mL/min to 0.7 mL/min. The effect of column oven temperature was studied at 28°C and 32°C instead of 30°C. The optimized ionization energy was 3.5 Kv and same was altered by ±0.5 units i.e. from 3.0 Kv to 4.0 Kv. The optimized sheath gas and auxiliary gas pressure at 40 psi and 10 psi respectively and the same were altered

by ±5.0 units i.e. from 35 psi to 45 psi and 5 psi to 15 psi respectively. Method validation results are summarized in [Table 1,2].

Table 1. Analytical Method Validation Data

Parameter	Result
	REB-S3 Imp-E (compound-9)
Detection Limit (ppm)	0.5
Quantitation Limit (ppm)	1.25
Linearity Range(ppm)	1.25-7.5
Slope	8471.193
Intercept	-1264.146
Correlation Coefficient	1.000
Precision at LOQ Level (% RSD)	0.89
System Precision (% RSD)	1.76
Method Precision (% RSD)	1.25
% Recovery at LOQ Level	88.7-95.0
% Recovery at 100% Level	104.0-105.5
% Recovery at 150% Level	100.1-101.5

Table 2. Robustness

Sl No	Name Of The Component	Actual condition (% RSD)	Flow decrease (% RSD)	Flow increase (% RSD)	Temperature decrease (% RSD)	Temperature increase (% RSD)
1	Impurity-E	1.02	1.10	0.92	0.90	0.85
SI. No.	Name of component	Ionization energy				
		Actual condition 3.5 Kv (% RSD)	Temperature increase 4.0Kv (% RSD)	Temperature decrease 3.0Kv (% RSD)		
1	Impurity-E	0.95	0.84	1.02		

Instrumentation

LC-MS analysis was carried out on LTQ Velos Pro dual pressure linear ion tarp mass spectrometer (Thermo fisher, San Jose, USA) connected with ahigh-pressure liquid chromatography Nexera X2 (Shimadzu Corporation, Kyoto, Japan). MS-data was acquired automatically in positive ionization mode with 3.50 kv ionization potential with a heated electro spray ionization (HESI) probe using Thermo Xcalibur software (Thermo Fisher Scientific, San Jose, USA). A single reaction monitoring (SRM) scan was performed with a parent ion 166Da and product ion 122 ±1Da. The source temperature and capillary temperature were maintained at 350 ˚C. The sheath gas and auxiliary gas pressure were kept at 40 psi and 10 psi respectively.

Chromatographic conditions

The method was carried out using an Inertsil ODS-3V column (150 mm length × 4.6 mm id, 5 µm particle size; Agilent Technologies, CA, USA). The eluent consisted of a 0.1% formic acid solution and methanol in a 30:70 (v/v) ratio, applied in isocratic mode. The chromatographic conditions were as follows: run time of 15 minutes, flow rate of 0.5 mL/min, column oven temperature set to 30°C, and auto-sampler temperature set to 20°C. The injection volume was 20 µL. To minimize source contamination, the eluent flow was diverted to waste from 0.01 to 5 minutes and from 9.3 to 15 minutes.

Sample and standard preparation

To prepare a sample solution of IMP-E at a concentration of 10,000 ppm in (methanol). The standard solutions of PGI's were prepared at concentration of 5 ppm with respect to REB-S3 in diluent for system suitability. The concentration of the standard solutions and samples were optimized to achieve a required

LOD, LOQ and good peak shape. All the standards were sonicate well and then filtered through 0.22 µm membrane filters prior to their analysis.

2. RESULTS AND DISCUSSION

At first the synthetic route for Rebamipide was shown in scheme-1. It was carried out using LR grade (sigma Aldrich) 4-chlorobenzoic acid, so the concerned impurity was not observed. Once we shifted to commercial source of compound-8a the problem started arising and we are getting >0.5% of unknown impurity in the API which upon study and data correlation identified that this impurity is from 4-chlorobenzoic acid (8a) (Table 3 Entry-3).

Table 3. 4-Chlorobenzoic acid received from various chemical companies

Entry	Source	PGI impurity (9) in compound (8a) by HPLC in %
1	Sigma Aldrich	ND
2	Avra synthesis	0.38
3	SD fine chemicals	3.08
4	Commercial source-I	ND
5	Commercial source-II	0.48

Elimination of this impurity at API stage based on ICH limit (NMT 0.1%) studied by various solvent system is represented in Table 4. Based on the obtained results the chosen solvent system is not worked to reduce the impurity to meet the ICH limit and the yield of the product is also decreased and the API cost was increasing.

Table 4. Various solvent system used for the purification of impurity

Entry	Solvent system for purification	PGI impurity (10) present in input compound (1) by HPLC in %	PGI impurity (10) after purification, by HPLC in %	Purity of Compound (1)
1	Methanol+water	1.11	1.07	98.41
2	Methanol	1.06	1.11	97.9
3	Acetonitrile+water	1.11	1.09	98.56
4	DMF+water	1.11	1.10	98.60
5	DMSO+water	1.11	0.92	98.93

Keeping API costing in mind, we started to eliminate the impurity at source level i.e. 4-Chloro benzoic acid (8a) by using various solvent system as shown in Table 5. Even then the starting materials were not purified successfully since the solubility of impurity and starting material were are similar.

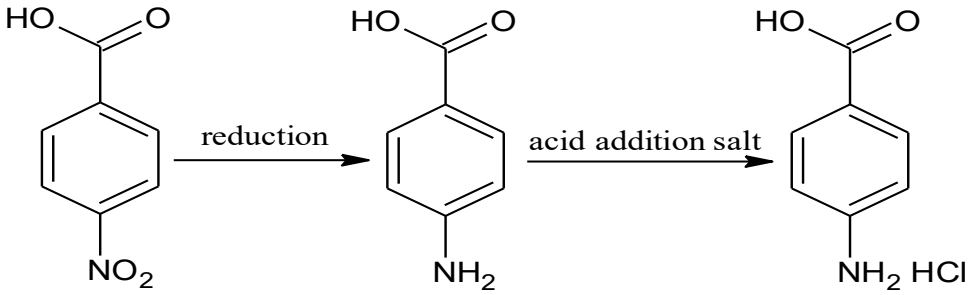
Table 5. Different solvent system used for the purification for 4-chloro benzoic acid

Entry	Solvent system	PGI impurity (10) present in input compound (1) by HPLC in %	PGI impurity (10) after purification, by HPLC in %
1	Acetonitrile	0.50	0.36
2	Anisole+Acetonitrile	0.50	0.36
3	Water+NaOH+HCl	0.50	0.25
4	Methanol+5% NaOH+HCl	0.50	0.50
5	DMSO+toluene+acetonitrile	0.50	0.29
6	Methanol recrystallization	0.50	0.50

7	THF recrystallization	0.50	0.42
8	Ethyl acetate+ DMSO	0.50	0.35

At this difficult situation we have decided to identify what kind of impurity is present to understand the structural property for developing the better purification technique. With the help of vendor ROS and LCMS data we have identified the plausible structure as 4-Nitrobenzoic acid (9). The correlation study involving LCMS, HPLC, and PDA techniques has confirmed that 4-Nitrobezoic Acid (9) is present as an impurity instead of 4-Chlorobenzoic Acid (8a). The formation of this impurity may be related to the use of nitric acid (HNO_3) in the vendor's oxidation step as part of their reported synthesis route (Scheme-2).

Scheme-3



Scheme-3 Conversion of Nitro to Amine and its Corresponding salt

Now, since Aromatic nitro compounds show PGI alert, we have examined for the toxicity of this compound (9) for PGI. It has shown alert in both the software's (DEREK and SARAH). Based on the daily dosage of the drug, Rebamipide, the limit to be controlled for this PGI impurity should be NMT 5ppm.

Since the structural property and solubility for both 4-chlorobenzoic acid and 4-nitrobenzoic acid is same, based on Table 3 results, there is no purification methods for elimination of this impurity. So, we have decided to find out an alternate possibility for eliminating this impurity. A brainstorming session has aided with new ideas as below,

It will be better to eliminate/control the impurity at source i.e, in 4-chlorobenzoic acid instead of carrying it and getting derivatized (compound-10) to API.

Carrying the impurity till API will lead to huge impact on quality and cost of API as the purification loss will be more and we should show control for both impurities such as compound (9) and its derivative compound (10).

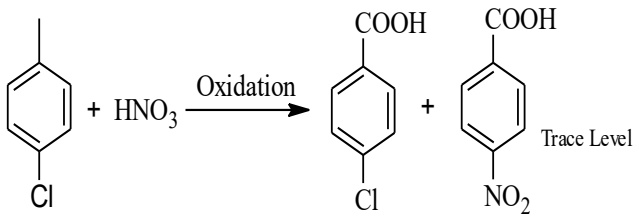
Developing a purification technique will be difficult as the impurity level control is too stringent at NMT 5ppm.

Finally decided to explore a better option for controlling this impurity. Derivatization of Nitro functionality. This will help in converting the potential genotoxic impurity to non-potential genotoxic impurity. The reaction conversion method will be better than the purification.

Decided for a reduction method of Nitro to amine functionality using certain reducing agents and then eliminating the amine functionality by converting to its acid salt. The probability of this technique getting success was more without impacting the main compound (8a) as it is not having any reducing functionality.

The proposed derivatization method is as mentioned in Scheme-3.

Scheme 2



Scheme-2 Synthesis of 4-Chlorobenzoic acid from 4 Chloro Toulene through Oxidation

Table 6. Various reported methods are used for conversion of nitro functionality to its amino functionality.

We reported similar work for the synthesis of Metopimazine *via* Smile's rearrangement[10] The optimization work has been started, Initially, the nitro functionality was reduced to amine group

SI No	Reducing system	PGI impurity (9) present in input compound (8a) by HPLC in %	PGI impurity (9) in reaction mass by HPLC in %	PGI impurity (9) in isolated compound (8a) by LCMS in ppm
1	Fe/HCl/water	0.50	After/10h: 0.31	NA
2	Zn/Acetic acid	0.50	After/10h: 0.32	NA
3	sodium sulphide/ethanol	0.50	After/3h: 0.53	NA
4	Zn/ammonium format/methanol	0.50	After/6h: 0.16	NA
5	Zn/Formic acid/acetone	0.50	After/5h: 0.31	NA
6	Sodium thiosulfate/ammonium format/methanol	0.50	After/2h: 0.54	NA
7	Zn/Formic acid/water	0.50	After/10h: 0.39	NA
8	Zn/Formic acid/methanol	0.50	After/2h: ND	1.57
9	Zn/Formic acid/DMF	0.50	After/2h: ND	2.45

using different types of reducing systems, for example $SnCl_2$in hydrazine hydrate, $SnCl_2$ in HCl, Fe/$CaCl_2$ in ethanol-water.[11]Fe/HCl in ethanol[12]and Pd/C in hydrazine hydrate,[13] Zn/Formic acid in DMF, Zn/NH_4Cl in THF-Water.[14] Among these reported methods, the Zn/Formic acid in DMF provided good results (Table 4entry-9).The formed amine derivative was converted to salt using hydrochloric acid. The salt was easily eliminated in the MLR and highly pure 4-chlorobenzoic acid (8a) with 4-nitrobenzoic acid (9) content at less than 5 ppm was isolated as solid with very good yield. A robust LCMS method has been developed for analysing the presence of Aromatic PGI (compound 9) in compound-8a at NMT 5ppm level. The conversion of compound-9 was monitoring using HPLC and the final isolated material was checked for compound-9 using LCMS at NMT 5ppm level. The obtained results at different conditions are shown in Table 6.

CONCLUSION

In the present work, we have reported a genotoxic impurity and their control strategies in Rebamipide. Also reported the Robust analytical method developed for identification and quantification of PGI at TTC limit. The major advantages of the present work include characterization of unknown genotoxic impurities, development of control strategies to the specified potential genotoxic impurities, helpful in DMF filling of the present reported molecule, able to apply the same control strategies to other than present reported raw materials, intermediates and industrial applications in APIs, Robust analytical tool for identification and detection of PGI at TTC limit.

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