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Scientific Study for Content of N-Nitrosodimethylamine in Valsartan by GCMS Technique

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Abstract: *Active pharmaceutical ingredients are making vital role in preparation or formulation of any medicines. It is the prime duty of ourselves to monitor the overall quality of pharmaceutical drugs as well as products for safety and efficacy. With the advancement in science of chemistry and other branches of instrumental devices including analytical sciences and biotechnology, the scope of analytical chemistry has reached to, much higher extent. The main focus in current usage of analytical methods advance analytical technology has made it possible not only to evaluate the potency of active ingredients in dosage forms and API's but also to get deep knowledge in characterization, structural elucidation, identifying and quantifying stereo isomers active moiety, possible impurities, metabolism, chirality of API and anticipation of possible degradations likely impurities being generated. Pharmacopoeias rely more on instrumental techniques rather than the classical wet chemistry method. In my research work a scientific attempt, I am going to adopt strategy of development, validated analytical methods for the determination of API single dosage form using GCMS technique.*

Keywords: Content of N-Nitrosodimethylamine

I. INTRODUCTION

According to WHO, Active pharmaceutical ingredient (API) may be defined as," A substance used in finished pharmaceutical product intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings." The other common terms used for an API are Bulk Pharmaceutical chemicals, Drug substances.

To be effective on commercial scale, a drug substance when administered to patient by any route of administration in any finished pharmaceutical product dosage forms, should, Provide desired effect only at desired site of action i.e. effect should be localized. Desired effect at desired site of action should be consistent in terms of how quickly It is observed and its magnitude and it should not provided any surprise side effects It should not provide any severe toxicity. It should be stable under prescribed conditions of storage. APIs are rarely administrated in as such form and are mostly administered as part of finished pharmaceutical product along with excipients.

In a finished pharmaceutical product, an API represents biologically active form, while the inactive ingredients are usually excipients. They generally are added to finished pharmaceutical product, with specific purpose like stabilization during self life, enhancing therapeutic activity of API by increasing their absorption, reducing viscosity etc. Since APIs render finished pharmaceutical product their therapeutic activity, control over their quality is of utmost importance. Their quality in terms of purity and also safety should be controlled to avoid any harm to civil society's health at large. Hence role and responsibility of global health regulators, quality inspectors as well as Pharmaceutical industry is of at-most importance. Continuous, coordinated joint efforts are required by all these 3 major stake holders to ensure that only medicines of highest standards in terms of Quality, safety, reach major part of global population at affordable prices.

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Hence identification and quantification of impurities is a crucial task in pharmaceutical process development for quality and safety.

Any material that can affect the purity of an API or finished pharmaceutical product is considered an impurity. ICH defines impurity as "Any component of the new drug substance that is not the chemical entity defined as new drub substance." Impurities are not introduced in the manufacturing process accidently or maliciously. Since they are not of any therapeutic value and may have toxicity concerns, they must be controlled.

Development of Related substances method is the common name of a group of analytical activities, the aim of which is the detection, identification and quantitative determination of impurities in API and pharmaceutical formulations.

II. METHODOLOGY

Following is the short summary for the research methodology work of Valsartan molecules. Valsartan is in a class of medications called angiotensin II receptor antagonists. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently. Valsartan is used to treat high blood pressure and congestive heart failure. , FDA announced a recall of valsartan tablets because of the potential for certain product to contain an impurity, N-nitrosodimethylamine (NDMA). This impurity is classified as a probable human carcinogen and is believed to have been introduced into the finished products as a result of the manufacturing process of the drug substance. Hence develop a gas chromatography-mass spectrometry (GC-MS) headspace method and to detect the presence of NDMA content in valsartan drug substance and drug products.

2.1 Instrument

A Gas Chromatograph Mass Spectrometer capable of temperature programming equipped with a capillary column, split / split less Injector, a Quadra pole Mass Detector and liquid auto sampler with a suitable software.

2.2 Chromatographic condition (GC-MS)

Column type	:	60m x 0.32 mm ID, 1.8 µ, VF-624 is suitable.
Carrier gas	:	Helium
Carrier gas flow rate	:	1.8 ml/minute
Injection mode	:	Split
Split Ratio	:	1:2
Detector	:	Quadra pole Mass Detector
Injector Temperature	:	160
Interface temperature	:	250
Detection mode	:	SIM
Ion Selection m/z for, N-Nitrosodimethylamine	:	74m/z
Ion Voltage	:	Relative tuning 0.4kV
Ion source	:	250 ºC
Oven Temperature	:	Initially at 90°C and hold for 2.0 minutes then increase at the rate of 12°C/minute to 155°C and hold for 1 minutes. Then increase upto 250°C with the rate of 25°C/minute and hold for 10 minutes.
Injection volume	:	3µl

2.3 Liquid Operating Condition:

Injection volume	: 3µl
Air volume(µl)	: 1
Pre clean solvent 1	: 5
Pre clean solvent 2	: 5

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Pre clean with sample	: 3
Filling volume(µl)	: 5
Filling speed(µl/sec)	: 2
Filling stroke	: 5
Pull up delay(ms)	:300
Inject to	: Appropriate injector
Injection speed(µl/sec)	: 50
Pre injection delay(ms)	: 500
Post injection delay(ms)	: 500
Post clean solvent 1	: 5
Post clean solvent 1	: 5

Diluent: 30% Ammonia solution: purified water (25:75 v/v).
Standard Stock solution of NDMA: Weigh about 100 mg each of N-Nitrosodimethylamine standard in a 100 ml volumetric flask containing about 50 ml of diluent. Dilute up to the mark with diluent and mix well. Dilute 1 ml of above solution to 10 ml with diluent. Further dilute 1 ml to 100 ml with diluent. Further dilute 5.0 ml to 100 ml with diluent and mix well.
Standard solution: Transfer 2 ml of standard stock solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.
Blank: Transfer 2 ml of diluent to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.
Test solution: Weigh accurately about 556 mg of Valsartan sample and transfer to a 15 ml centrifuge tube. Add 2 ml of diluent and vortex immediately to dissolve the sample. Sonicate if needed. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.
Procedure: Separately inject Blank, Standard solution (1) (6 replicates), Standard solution (2), Blank, Test preparation (1), Test preparation (2), Blank and Standard Solution (1) into the chromatographic system. Record the chromatogram and check system suitability parameters. Disregard peak area due to blank interference.

System Suitability Parameters:

1. The Relative Standard Deviation for the peak area response of N-Nitrosodimethylamine for replicate injections of Standard solution (1) and replicate injections of Standard solution (1) including Bracketing Standard should not be more than 15.0% and Relative Standard Deviation for Retention Time for the peak of N-Nitrosodimethylamine for replicate Injections of Standard solution and replicate injections of Standard Solution (1) including bracketing standard are not more than 2.0%.
2. The similarity factor for N-Nitrosodimethylamine between

Calculation: Content in ppm

$$= \frac{(A - B) \times \text{weight of Impurity (mg)} \times 1 \times 1 \times 5 \times 2 \times 10^6}{(C - D) \times 100 \times 10 \times 100 \times 100 \times W_2}$$

Where, A = Peak area response of respective impurity in test solution.
B = Mean peak area response of respective impurity as interference from blank for test Solution.
C = Mean peak area response of respective impurity in standard solution (1).
D = Mean peak area response of respective impurity as interference from blank for standard Solution (1).
W_1 = Weight of respective impurity taken for Standard Stock Solution (1) in mg.
W_2 = Weight of sample taken in mg.
P = Purity of respective impurity standard on as such basis.
Limit: For N-Nitrosodimethylamine **:** Not more than 0.18 ppm
NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches.

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These findings suggest that the consumption of NDMA contaminated valsartan is associated with a slightly increased risk of hepatic cancer; Purpose of study is to develop method of NDMA content in Valsartan with shorter run time duration.

III. Literature Review

We had performed literature search on work performed on these molecules in field of Method development and validation for tests of related substances. Based on this following literatures were identified of having significant value addition for my research work,

1. Monograph of Valsartan API in United States Pharmacopeia DOI Ref. 5ue1i
2. Test method for the determination of NDMA by LC/MS/MS in Valsartan finished products Contact: Oliver el-Atma Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Germany (OMCL BW) Tel. 0049-721-926-3609 Oliver.el-Atma@cvuaka.bwl.de Dr. Birgit Gutsche Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Germany (OCCL BW) Tel. 0049-721-926-5628 Birgit.Gutsche@cvuaka.bwl.de
3. GC/MS Headspace Method for Detection of NDMA in Valsartan Drug Substance and Drug Products, Division of Pharmaceut ical Analysis, US FDA
4. https://www.ema.europa.eu/documents/press-release/update-nitrosamine-impurities-ema-continues-work-preventimpurities-medicines_en.pdf
5. https://www.ema.europa.eu/en/news/ema-review-ranitidine-medicines-following-detection-ndma
6. https://www.USFDA.gov/news-events/press-announcements/statement-alerting-patients-and-health-careprofessionals-ndma-found-samples-ranitidine

I had evaluated all these literatures and came to conclusion that out of these literatures. There is substantial shortfall of current/existing available source of literature.

Based on evaluation of this literatures following was the crux of present work available in research area Regulatory authorities emphasizing on determination of genetoxic impurities content in API. Several methods available for NDMA content of valsartan but no method available with short run time. Also some of the method use of internal standard ,diluents incompatibility ,matrix effect. Hence there is scope to develop short run time method without use extraction technique which can allows only concern impurity to determine and quantify it with much more accuracy. It will not only save cost of each analysis by using less quantity of resources, but will also have positive impact on cost of medicine and useful for society.. Also it will lead to less drainage of solvent waste and hence will have positive outcome from environmental pint of view also.

IV. Results and Discussion

Table 1: Relative standard deviation of NDMA

Sr. No	Sample name	Area	Retention time
1	Standard-A	84614	7.035
2	Standard-A	89425	7.035
3	Standard-A	92297	7.033
4	Standard-A	88235	7.033
5	Standard-A	80564	7.035
6	Standard-A	83759	7.031
Mean		86482.3	7.0
Std. Dev		4277.3	0.0
%RSD		4.9	0.0

Limit of Detection and Limit of Quantitation:

- **Limit of Detection:** Chromatographic conditions, Mass spectrometer conditions, and Blank preparation same as given in Method details.
- **LOD Stock Solution:** Weigh about 100 mg of N-Nitrosodimethylamine standard in a 100 ml volumetric flask containing about 50 ml of diluent. Dilute up to the mark with diluent and mix well. Dilute 1 ml of above solution

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to 10 ml with diluent. Further dilute 1 ml to 100 ml with diluent. Further dilute 1.5 ml to 200 ml with diluent and mix well.

- **Preparation LOD Solution:** Transfer 2 ml of LOD stock solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Table 3: Limit of Detection

Level	Concentration of LOD level solution (ppm w.r.t spl)	Signal to Noise ratio
NDMA	0.015	15

Procedure: Inject blank solution and LOD solution in three replicates.

Acceptance criteria:

1.	The signal to noise ratio for limit of detection level for the peak of N-Nitrosodimethylamine should be equal to or more than 3.

Figure 6: Limit of detection chromatogram

Limit of Quantitation

Chromatographic conditions, Mass spectrometer conditions, and Blank preparation same as given in Method details.

- **LOQ Stock Solution:** Weigh about 100 mg of N-Nitrosodimethylamine standard in a 100 ml volumetric flask containing about 50 ml of diluent. Dilute up to the mark with diluent and mix well. Dilute 1 ml of above solution to 10 ml with diluent. Further dilute 1 ml to 100 ml with diluent. Further dilute 1.5 ml to 100 ml with diluent and mix well.
- **Preparation LOQ Solution:** Transfer 2 ml of LOQ stock solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Table 4: Limit of Quantitation

Level	Concentration of LOD level solution (ppm w.r.t spl)	Signal to Noise ratio
NDMA	0.03	26

Procedure: Inject blank solution and LOQ solution in three replicates.

Table 5: Relative standard deviation of NDMA

Sr. No	**Sample name**	**Area**	**Retention time**
1	LOQ-1	23228	7.037
2	LOQ-2	24384	7.035
3	LOQ-3	23427	7.036
Mean		23679.7	7.0
Std. Dev		618.0	0.0
%RSD		2.6	0.0

Linearity and Range

Chromatographic conditions, Mass spectrometer conditions, and Blank preparation same as given in Method details.

- **Linearity Stock Solution:** Weigh about 100 mg of N-Nitrosodimethylamine standard in a 100 ml volumetric flask containing about 50 ml of diluent. Dilute up to the mark with diluent and mix well. Dilute 1 ml of above solution to 10 ml with diluent. Further dilute 1 ml to 100 ml with diluent.

Preparation of linearity levels:

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Preparation Linearity-I (Lin LOQ) Solution: Dilute 1.5 ml of Linearity stock solution to 100 ml with diluent and mix well. Transfer 2 ml of above solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Preparation Linearity-II (Lin 50%) Solution: Dilute 2.5 ml of Linearity stock solution to 100 ml with diluent and mix well. Transfer 2 ml of above solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Preparation Linearity-III (Lin 100%) Solution: Dilute 5.0 ml of Linearity stock solution to 100 ml with diluent and mix well. Transfer 2 ml of above solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Preparation Linearity-IV (Lin 150%) Solution: Dilute 7.5 ml of Linearity stock solution to 100 ml with diluent and mix well. Transfer 2 ml of above solution to a 15 ml centrifuge tube. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Table 6: Preparation of Linearity levels

Level	Concentration of NDMA Linearity level solution (ppm w.r.t spl)
LIN I (LOQ)	0.03
LIN II	0.05
LIN III	0.10
LIN IV	0.15

Procedure: Inject Level 1 (LIN I/LOQ) (Six replicates), Level 2 (LIN II) to Level 3 (LIN III) (duplicate) and Level 4 (LIN IV) (six replicates).

Table 7: Data for linearity (NDMA)

Level	**Concentration (ppm)**	**Area**	**Response Factor**
Level-I/I	0.03	23228	1515792.2
Level-I/II	0.03	24384	1591229.4
Level-I/III	0.03	23427	152877.4
Level-I/IV	0.03	27186	1774079.9
Level-I/V	0.03	27677	1808121.1
Level-I/VI	0.03	28087	1832676.5
Level-II/I	0.05	41171	1812020.4
Level-II/II	0.05	48380	1933437.7
Level-III/I	0.1	91039	1782282.7
Level-III/II	0.1	91108	1783633.5
Level-IV/I	0.15	131388	1714800.3
Level-IV/II	0.15	132088	1723836.3
Level-IV/III	0.15	140548	1834351.3
Level-IV/IV	0.15	130667	1705390.2
Level-IV/V	0.15	130858	1707863.1
Level-IV/VI	0.15	140671	1835956.7
Average			1730190.8
Correlation coefficient		**0.998**	
%Y intercept		**-1.07**	

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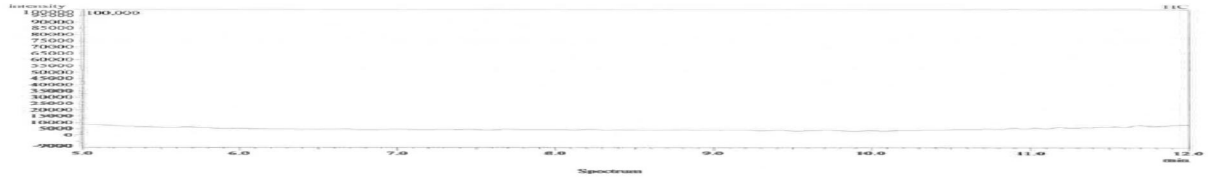
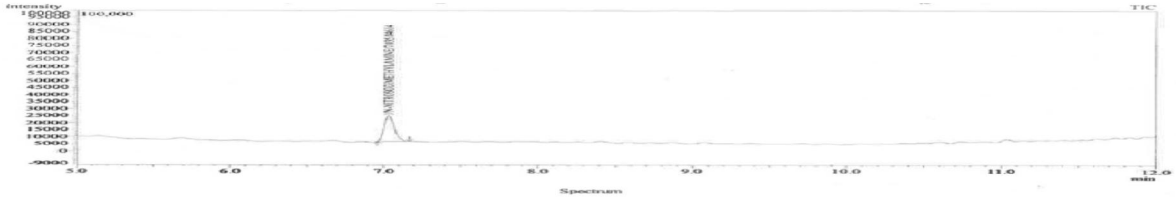
Blank chromatogram



NDMA Chromatogram



Valsartan Sample Chromatogram

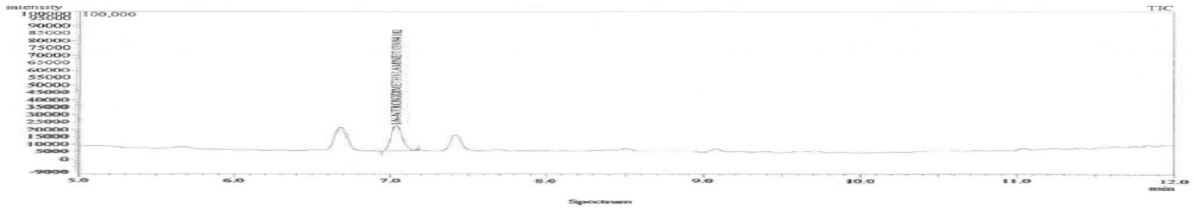


Figure 9: Liearity of Level-I (LOQ)Fig. Liearity of Level-III (100%)Fig. 12 Liearity of Level-IV (150%)

Acceptance criteria:

1.	The Linearity Correlation Co-efficient should not be less than 0.99.
2.	The % Y- intercept for should be within ± 5.0.
3.	The % RSD of Retention time for three replicates of Linearity Level 1 and Level 4 should not be more than 2.0%.
4.	The % RSD of peak area response for three replicates of Linearity Level 1 and Level 4 should not be more than 15.0%.
5.	The % RSD of Response factor should not be more than 10.0%.

Precision

Chromatographic conditions, Mass spectrometer conditions, Standard solution A and Standard solution B and Blank preparation same as given in Method details.

Sample Preparation: Weigh accurately about 1.0g of sample and transfer to a 15 ml centrifuge tube. Add 2 ml of diluent and vortex immediately to dissolve the sample. Sonicate if needed. Add 2 ml Dichloromethane to it and vortex for 10 minutes. Allow the layers to be separated for about 1 hour. Separate the lower organic layer and use for analysis.

Note: Six different Samples to be prepared.

Procedure: Separately inject Blank preparation, Standard solution A (6 replicates), Standard solution B, Blank, each of sample preparation (1 to 6) and Blank preparation into the chromatographic system. Record the chromatogram and check system suitability parameters. Disregard peak area due to blank interference.

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Table 9: Similarity factor accuracy table for NDMA and NDEA

	Area of standard	Area in accuracy	Accuracy (%)
Level	NDMA	NDMA	NDMA
Level-I (LOQ)	25665	26027	101.4
		26418	102.9
Level-II (50%)	44776	38678	86.4
		38713	86.5
Level-III (100%)	91074	79857	87.7
		79423	87.2
Level-IV (150%)	134370	118386	88.1
		118346	88.1

Acceptance criteria:

Sr. No.	**In the chromatogram of Working solution.**
1	The Similarity factor between Standard solution A (six replicates) and Standard solution B (separately prepared and injected) for the peak of N-Nitrosodimethylamine should be between 0.85 and 1.15.
2	The Relative standard deviation for the peak area response of N-Nitrosodimethylamine for six replicate injections of Standard solution A should not be more than 15.0 %.
3	The Relative standard deviation for the retention time of N-Nitrosodimethylamine for six replicate injections of Standard solution A should not be more 2.0 % .

V. CONCLUSION

The GCMS method developed for NDMA Content is simple, specific, linear, sensitive, precise and efficient and is suitable for its intended purpose. The method developed has shorter run time, thus ensuring optimum utilization of the GCMS Instrument system. It avoided use of any internal standard and hence it was cost effective as well as user friendly.

Run time of this method is very short due to shorter retention time of peak due to NDMA (i.e. about 7 minutes) Hence the proposed method is on GC MS with shorter run time obtained using advance and cost effective techniques is fulfil. Also shorter run time ensured lesser consumption of solvents in turn reducing further cost per analysis and also generating lesser solvent waste. The shorter run time also enabled analysis of multiple batches in short duration thus enhancing the out-put of batch analysis.

The method was validated by critical principles stated in ICH guidelines, showing satisfactory data for all the method validation parameters tested. Evaluation of validation data confirmed that method had comparable system suitability parameters as well as precision as those specified in literature reference. Also its linearity range was established to confirm linear response across the concentration range. Further during robustness study, it was established that variations in temperature, flow, column length, column ID, did not have significant impact on Chromatographic pattern.

Hence, the proposed method can be employed for assessing NDMA Content of Valsartan. This study provides an idea how to perform validation process to prove that the method is accurate for its intended purpose and to assure the capabilities of the test method. The definitions of method validation parameters are well explained. Document the experimental design study, the approach to validation is varied and opened to interpretation, and validation requirements differ during the development process of pharmaceuticals. Validation is an important procedure in the API Study and it is utilized to ensure that inbuilt quality is there in to the processes supporting drug development and manufacture to get expected outcome of research study.

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