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STRUCTURE DETERMINATION OF IMPURITY IN MEMANTINE

HYDROCHLORIDE BY ANALYTICAL TECHNIQUES

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ABSTRACT

Impurity related to the synthesis of pharmaceutical ingredient Memantine hydrochloride bulk drug was detected by GC and was subjected to GCMS for identification. The proposed impurity was prepared synthetically and was injected on GC for comparison of retention time with that of the unknown impurity in Memantine. The GCMS spectra of synthetically made impurity and that of process related impurity in the Memantine hydrochloride were found to be the similar. The postulated structure was unambiguously confirmed with the help of NMR and IR analysis. Based on GCMS, NMR and IR data the structure of the impurity was proposed to be 1,3-diacetamido-5,7-dimethyl Tricyclo decane (Diacetamido impurity). This impurity which was elucidated was not found to be previously reported in any synthetic or analytical literature pertaining to Memantine hydrochloride.

KEYWORDS: Memantine Hydrochloride, Impurity, GC, GCMS, NMR, IR Structural Elucidation

INTRODUCTION

Memantine hydrochloride, designated as 1-amino-3, 5 dimethyl- adamantane hydrochloride, belongs to a small group of drugs known as Tricyclic Antivirals (TAVs), and provide good and persistent activation of central nervous system N-methyl-d-aspartate (NMDA) receptors, and hence can be used in the treatment of Parkinson's and Alzheimer's diseases[1].

We have screened the literatures for impurities which were produced from different synthetic processes and have found that this unknown impurity was not reported in any of the synthetic processes related to Memantine. Methods based on GC, GCMS, NMR, IR related to impurities were studied in the present article. However, so far there is no published report, describing the complete characterisation of this unknown process related impurity in Memantine hydrochloride active pharmaceutical ingredient (API).

The impurity profile of the drug substance is critical for its safety assessment and manufacturing process. It is mandatory to identify and characterize the impurities in a pharmaceutical product, if present above the accepted limit of 0.10% [2]. 3' carbon of adamantane derivative undergoes conversion to form the 1-acetamido-3,5-dimethyl tricyclo decane (AC-NHDMAD) [3]. There are few methods which are reported for synthesis of AC-NHDMAD, which is an intermediate used in the synthesis of Memantine hydrochloride. These methods are very facile, safe and can be easily scaleable [1].

The present communication deals with the identification and structural elucidation of a process related impurity which was found in the product Memantine hydrochloride. This process is reported to give high purity product. However the same does not give any detail regarding the unknown impurity [1]. The present GC method is used for identification of unknown impurity in Memantine prepared by synthetic rout given in figure 1.

EXPERIMENTAL

Materials and Reagents

Sample of the Memantine hydrochloride and its intermediate were prepared and obtained from chemical research division, Ipca Laboratories Ltd. (Mumbai, India). HPLC grade acetonitrile was purchased from Merck India Ltd. Deionised water was prepared using MilliQ plus purification system. (Millipore, Bradford) USA, Potassium bromide was purchased from Merck KKGaA, Darmstadt Germany (FTIR Grade), deuterated Dimethyl sulphoxide (DMSO) and D_2O were purchased from Merck KKGaA, Darmstadt Germany, dichloromethane, Sodium Sulphate, and Methanol was purchased from, Merck India Ltd.

Gas Chromatography

Samples were analyzed on Agilent Technology 7890A with Auto sample equipped with flame ionisation detector, a HP-5 capillary column length 30 meter, internal diameter 0.320mm and film thickness 0.25μ, purchased from Agilent technologies USA was used for chromatographic separation [4-7]. The integrator used is Ezchrom-Elite. The chromatographic parameters are as follows:

For oven temperature, the Initial temperature is 50°C with hold time of 5.0 minutes then temperature is increased at the rate of 10°C per minute to 280°C and at 280°C it is kept hold for 15 minutes. Injector temperature is kept constant at 240°C. Detector temperature is kept at constant 280°C. The carrier gas used is nitrogen gas. Split ratio used is 20:1. Carrier gas flow is 1.0ml/min. Injection volume used is 1.0μL. Sample preparation is 1.0% solution, basified by adding 4ml of 5N sodium hydroxide 1.0ml methanol and 5.0 ml of dichloromethane mix and shake for 5.0min. The organic layer was separated and then injected.

Mass Spectroscopy

The Mass analysis was carried out on Thermo Scientific Polaris-Q ion trap mass spectrometer with software Xcalibur (USA). The mode of ionisation is Electron ionisation at 70eV and type of analysis is by Direct Insertion probe. The probe temperature was programmed at 100°C@20°C to 300°C 10 minutes hold. Emission current was at 250mv.

NMR

The ^1H, ^{13}C, DEPT Measurement were recorded on Bruker Advance 400 MHz NMR spectrometer (Fallanden, Switzerland) instrument at 300K. The exchangeable protons were identified by D_2O experiment. The ^1H and ^{13}C chemical shift value also reported on δ scale in ppm relative to DMSO (2.49ppm) and (39.4ppm) respectively.

IR Spectroscopy

IR Spectroscopy of isolated impurities was reported on solid state potassium bromide powder reflectance as Spectrum One-FTIR spectrometer. (Perkin- Elmer-Beconshield-UK)

Formation and Isolation of Unknown Impurity

Synthesis of Memantine is shown in the figure 1, during reaction of 1, 3-dimethyl adamantane (DMAD) to 1-acetamido 3, 5-dimethyl tricyclodecane (AC-NHDMAD) in the presence of acetonitrile and Sulphuric acid -NHCOCH$_3$ group gets attached to 3° carbon to form AC-NHDMAD. But there is also a simultaneous reaction in which -NHCOCH$_3$ gets attached to DMAD which is having two 3° carbon, thus giving rise to unknown impurity [8]. During this reaction some portion of sample is withdrawn with clean and dry pipette and quenched in chilled deionised water in separating funnel. The separating funnel is shaken for 2-3 minute and then small amount of dichloromethane is added to it, emulsion is formed in between water and dichloromethane layer, and this emulsion contains the process related unknown impurity. The emulsion layer is collected, filtered and re-crystallized by methanol. This re-crystallized product contains unknown impurity.

3. RESULTS AND DISCUSSIONS

Detection of Impurity by GC

Sample was analyzed by GC method described in section 2.2 refer figure 2a. The analysis revealed the presence of two marked impurities at the retention time about 14.32min, 24.55mins and Memantine peak at about 14.1min. Impurity at 14.32 min was 1-hydroxy-3,5-dimethyl adamantane (1-OH impurity) refer figure 2b and the unknown impurity was at retention time 24.55min Thus this impurity was isolated using section 2.6 and was injected for GC purity refer figure 2c and further analyzed by GCMS, NMR and IR for structure elucidation.
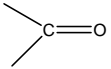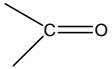
Structural Elucidation of Impurity by GCMS

Mass spectra obtained by subjecting the peak of unknown impurity, using conditions described above showed molecular ion peak at m/z 278 (refer figure 3) The theoretical expected peak for unknown impurity is 278 Da for molecular formula $C_{16}H_{23}N_2O_2$. The sample containing unknown impurity was subjected to GCMS for study. MS study of impurity showed intense peaks of molecular I on at m/z value 278, base peak of m/z value 235 and daughter ions of m/z 263, 235 220,207,176,164 (refer figure 3a). The molecular ion peak is in accordance with the nitrogen rule containing even number of nitrogen in the molecule i.e. having two nitrogen atoms [9]. Before characterisation of unknown impurity, it is important to understand fragmentation of unknown impurity in detail. The unknown impurity peak of m/z 278 on loosing CH$_3$CO˙ (-43 Da), gives peak at m/z 235 for molecular formula $C_{14}H_{23}N_2O$˙˙When CH$_3$ (-15 Da) group is lost from 278 a peak of m/z of 263 is obtained for $C_{15}H_{23}N_2O^{.}_2$. After loosing –NH from 235 peak it shows m/z 219,220,221 which is nothing but 1-acetamido 3,5-dimethy adamantane. 1-acetamido 1,3 dimethyl adamantane of 221m/z on loosing –NHCOCH$_3$ (-57Da) group gives peak at 164m/z. This concludes the presence of 1,3-dimethyl adamantane. The plausible fragmentation of unknown impurity is shown in figure 4. The GC of unknown impurity

Structural Conformation of Impurity by NMR and IR

It is easy to understand the NMR spectra of unknown impurity forming during synthesis of Memantine hydrochloride. The complete assignment given below is based on the proton NMR and IR done after synthesizing the unknown impurity. Proton NMR spectral data shows that singlet at 0.79 δ due to 6H indicates presence of 2CH$_3$ group which are shielded in nature and attached to carbon which has no proton CH$_3$-C[8][9]. The NMR singlet at 1.0 δ due to –CH$_2$- group which is adjacent to –C- which is having no proton i.e. tertiary carbon atom. The multiplet at 1.49 to 1.58 due to 8H indicates presence of 4-CH$_2$- group of adamantane ring which are having the same chemical environment.

NMR singlet at 1.78 δ is due to 6H indicates presence of $2CH_3$ group attached to –C-atom which is having no proton figure 5. It is slightly shielded than above $2CH_3$ group. They are slightly desheilded because they are closer to –NH group. A proton at 2.03 δ due to 2H gives singlet gives $-CH_2-$ group of adamantane. The most desheilded 2H gives single at 6.29 δ and indicates presence of 2H directly attached to –NH group. Chemical shift value (δ/ppm) for C-13, Chemical shift value (δ/ppm) for 1H is also discussed in table 1. C-13 spectra showed prominently carbonyl grouping at 169.2 ppm, remaining values are discussed refer figure 7. D_2O experiment shows that unknown impurity structure contains two exchangeable protons. DEPT data shows the presence of CH_2, CH and CH_3 groups in structure of unknown impurity refer figure 6.

IR band at 3304 cm-1 indicates presence of –NH stretching of amine, or amide. IR peak at 1648cm-1 indicates presence of $\diagup\!\!\!\diagdown C = O$ group attached to -NH. $\diagup\!\!\!\diagdown C = O$ Stretching frequency at 1648cm-1 indicates strong electron withdrawing effect refer figure 8 [9, 10, 11]. Considering the above GC, NMR IR data it was concluded that above impurity molecule contains two $NHCOCH_3$ groups. During the synthesis of Memantine hydrochloride, an intermediate AC-NHDMAD is formed and simultaneously formation of unknown impurity also takes place. Thus IR data confirms acetamido functional group in this unknown impurity.

CONCLUSIONS

The present investigation revealed a major process related impurity while analyzing Memantine hydrochloride by the GC method. GCMS provided the molecular formula information and structural information of this impurity. NMR and IR spectroscopic analysis confirmed the structure as 1,3-diacetamido 5,7-dimethyl tricyclodecane. The present study therefore clearly indicates that intermediate 1-Acetamido 3,5 dimethyl adamantane on acetamidation gives rise to this impurity. Elucidation of the structure of such a process related impurity can certainly be effective for control during manufacturing in pharmaceutical development process to comply with the regulatory norms for impurity levels.

ACKNOWLEDGEMENTS

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APPENDICES
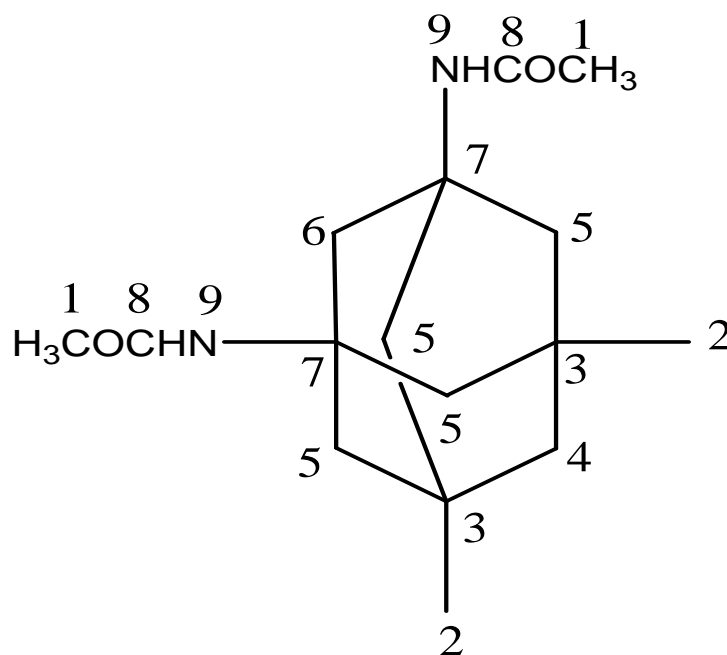
Diacetamido Impurity

Table 1: Structure and Interpretation of 1, 3-Diacetamido-5, 7-Dimethyl Tricyclo Decane (Diacetamido Impurity) by NMR

Position	Chemical Shift Value (δ/ppm) for [1]H	Assignment for [1]H (Multiplicity[#], Number of Protons)	Chemical Shift Value (δ/ppm) for [13]C	Multiplicity J Hz
1	1.73	(s,6H)	24.1	S(12-15)
2	0.83	(s,6H)	29.9	S(12-15)
3	-	-	33.0	
4	1.04	(s,2H)	43.6	S(12-15)

5	1.45-1.57	(m,8H)	46.7	S(0-1)(12-15
6	1.99	(s,2H)	49.9	
7	-	-	53.5	
8	-	-	169.2	
9	7.37	(s,2H)	-	

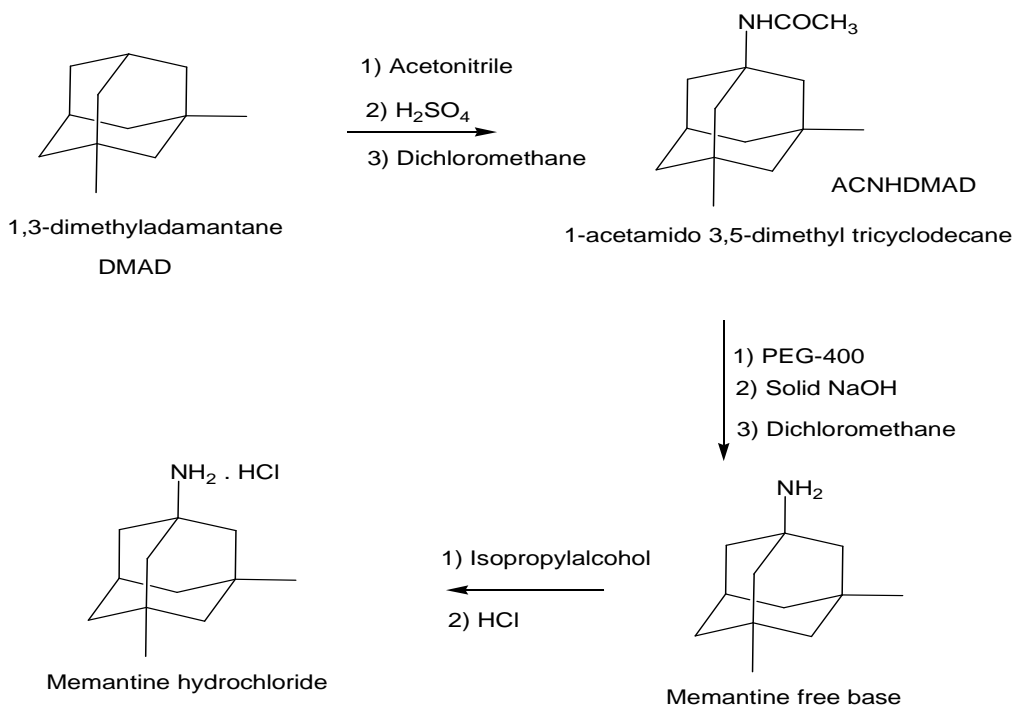# m- multiplet, s-singlet.

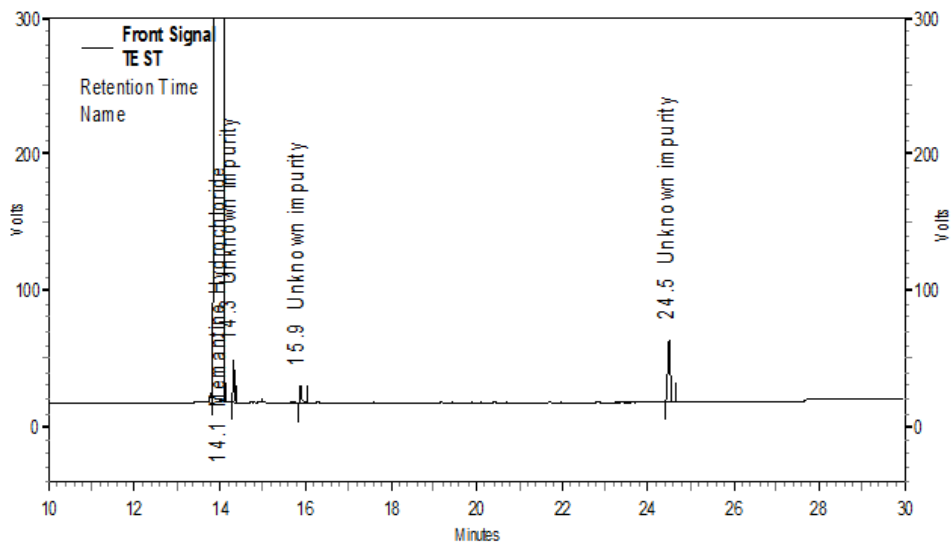**Figure 1: Synthetic Process of Memantine Hydrochloride**

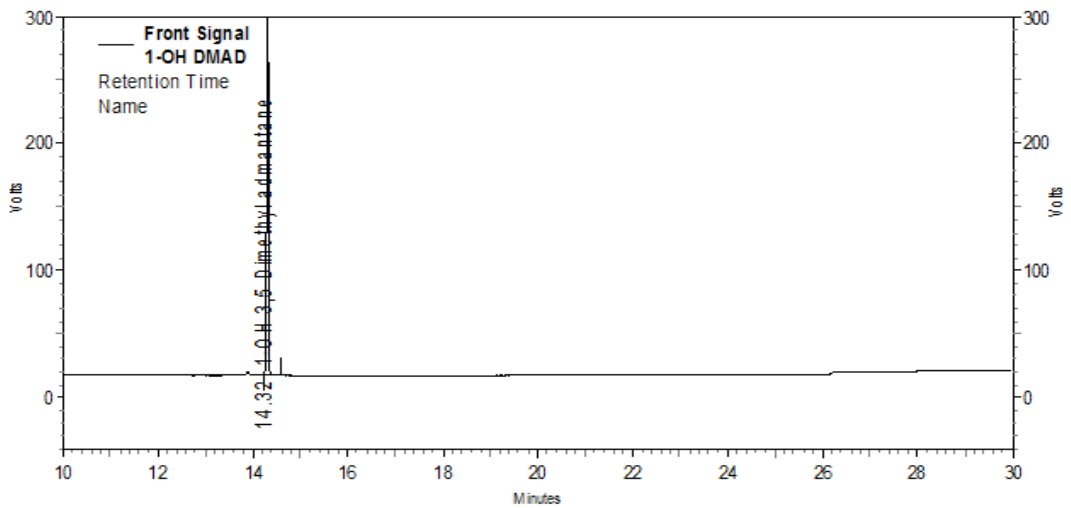**Figure 2a: A Typical GC Chromatogram of unknown Impurity in Memantine**

Figure 2b: A Typical GC Chromatogram of 1-OH DMAD Impurity for Confirmation of Unknown Impurity in Memantine GC Method
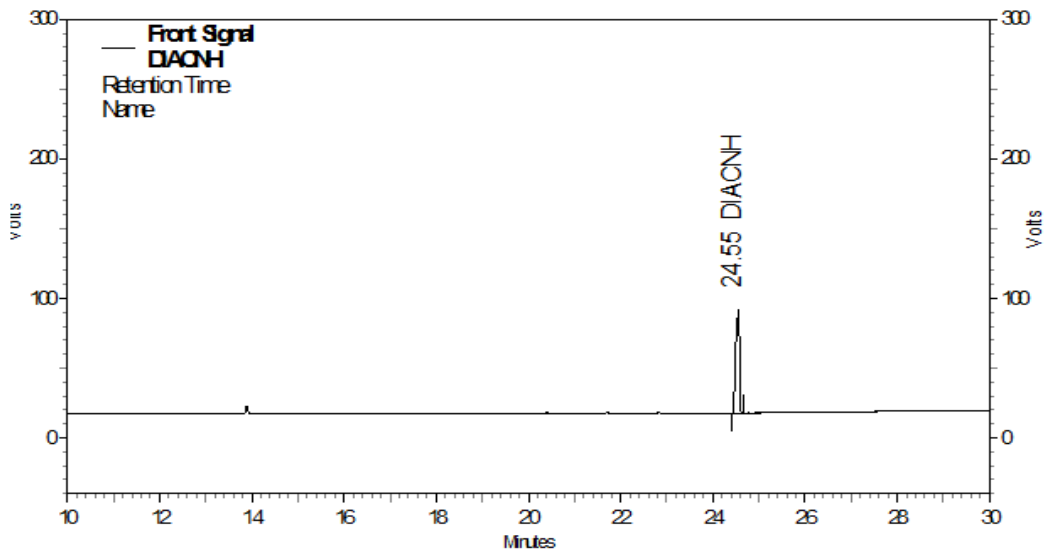

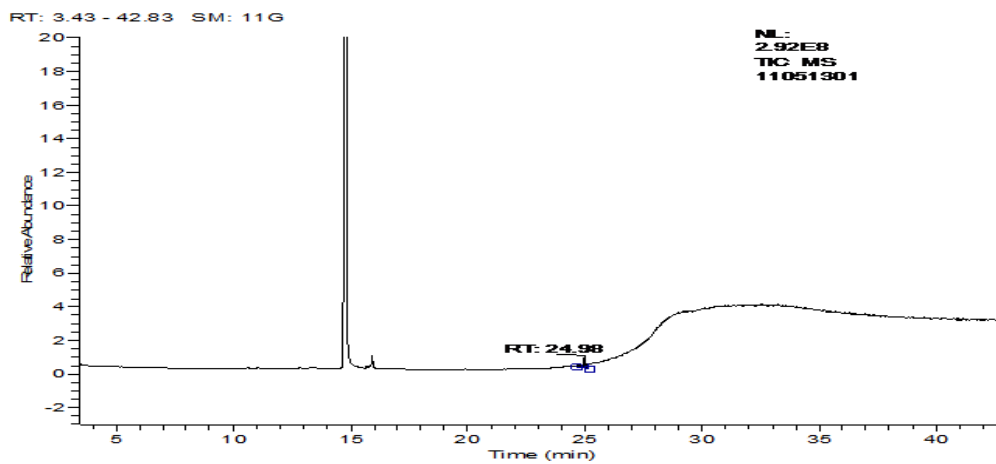**Figure 2C: GC Chromatogram for Diacetamido impurity Prepared Synthetically**

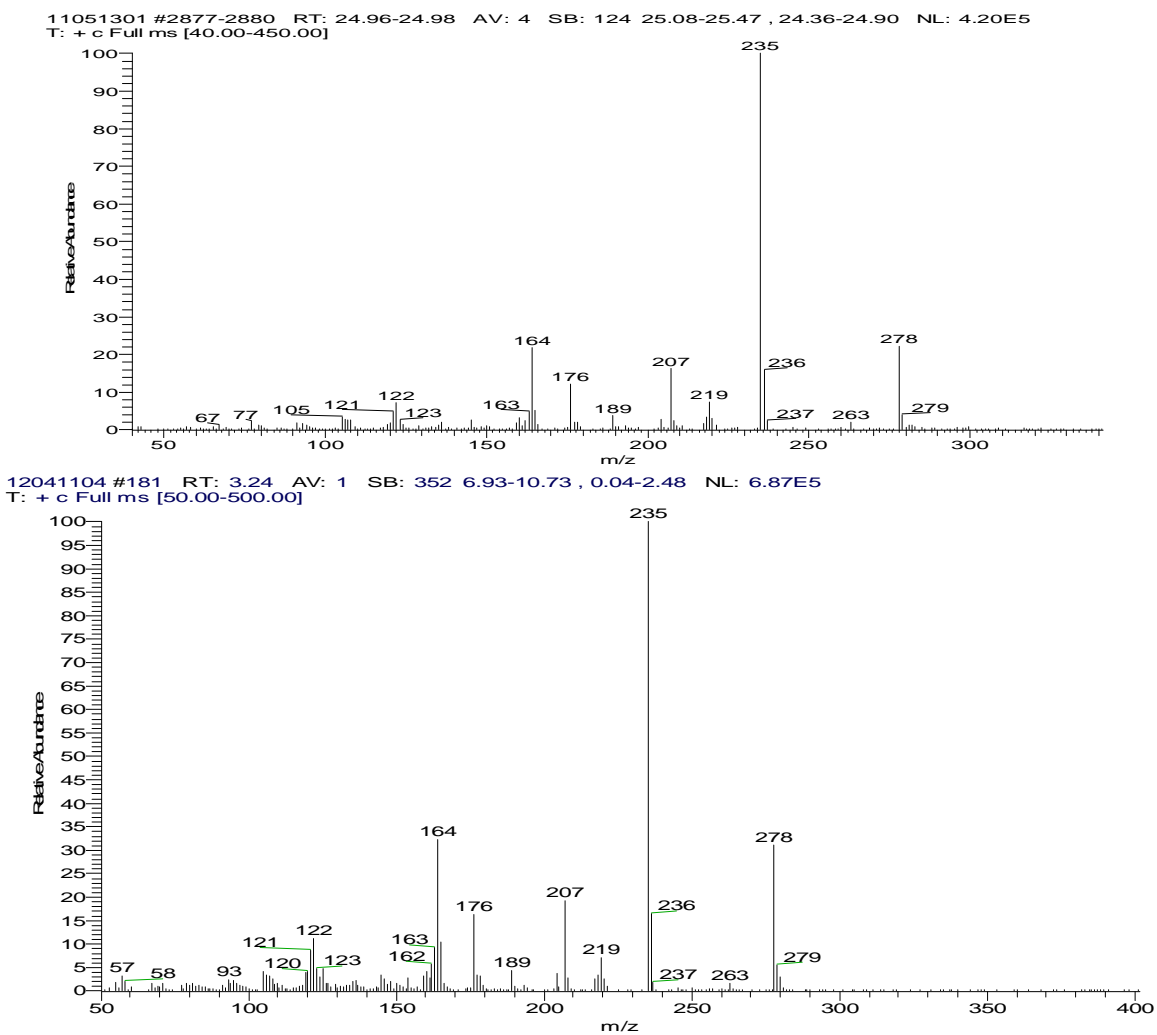**Figure 3: GCMS TIC and Spectra Found in Memantine Hydrochloride Containing Impurity at Retention Time about 24min**
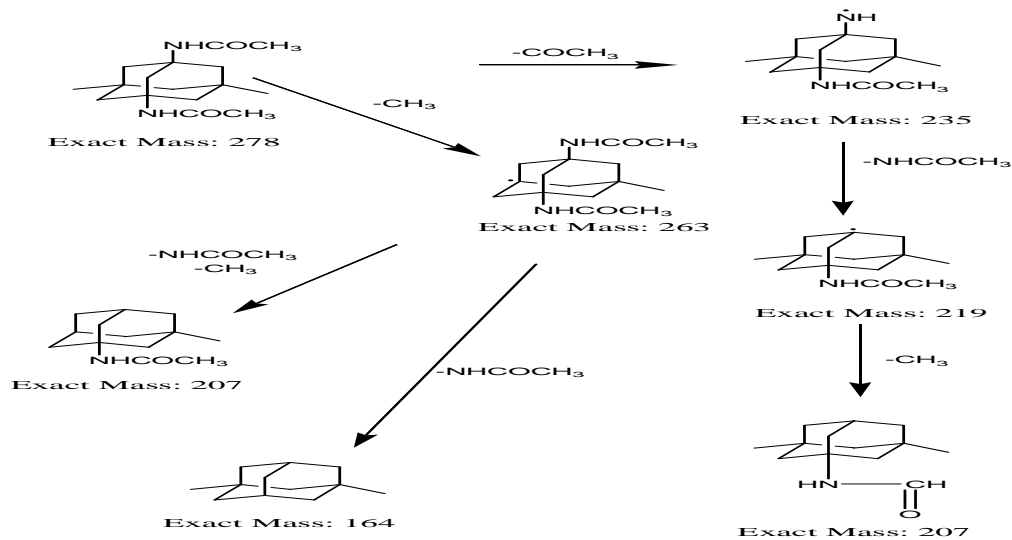
Figure 3a: GCMS Spectra for Diacetamido Impurity

Figure 4: Plausible Fragmentation Pattern in GCMS

Figure 5: Proton NMR for Diacetamido Impurity

Figure 6: 13-C NMR for Diacetamido Impurity

Figure 7: IR Spectra of Diacetamido Impurity