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Impurity Analysis of Gentamicin Sulphate Injection UsingLiquid Chromatography/Mass Spectrometry LC / MS

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Abstract:

Gentamicin sulfate (GEN) is a broad-spectrum belonging to the group of aminoglycosides (AGs). The objective of the current study is the analysis of GEN injection impurity using reverse-Phase liquid chromatography and mass spectrometry. Five samples of GEN injection were selected from Abb governorate, and analyzed by LC/MS. The result showed that the Inj-I sample contained nineteen known impurities; m/z163 deoxystreptamine, m/z 322 garamine, m/z 319 gentamine C1, VII-2, XK-62-5, Y-02077H- δ, gentamicin C1a in m/z 450, Y-02077H-γ, XK-62-3, VII-1, gentamicins C2, C2a, and C2b in m/z 464 and m/z 478 gentamicin C1,garosamine m/z 177, m/z 448 sisomicin, at m/z 492 Y-02077H-β, XK-62-7and XK-62-8. In Inj-II sample showed fourteen impurities same impurities as in the Inj-I sample except for gentamineC1 m/z 319 and impurities in m/z 492, and garosamine in m/z 177. While Inj-III samples showed fifteen impurities same impurities as in the Inj-I sample except for impurities in m/z 492 and m/z 177. In Inj-IV sample showed nineteen impurities same impurities as in the Inj-III sample except for m/z 448 sisomicin and impurity m/z482 J1-20A. In Inj-VI sample showed eighteen impurities same impurities as in the Inj-I Rehaf sample except for garosamine in m/z 177. In addition of two unknown impurities in 490 and 110 except the Inj-II sample did not show these impurities.

Keywords: *Impurity analysis; Gentamicin; LC-MS; Liquid chromatography*

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1. Introduction

Gentamicin sulfate (GEN) is a water-soluble, broad-spectrum antibiotic belonging to the class of aminoglycosides (AGs) that is produced by fermenting micromonospora purpura. It is used to treat a variety of bacterial infections including meningitis, pneumonia, urinary tract infections, sepsis, and bone infections. It is ineffective for gonorrhea or chlamydia infections. It can be given intravenously, by injection into a muscle, or topically. Topical formulations may be applied for burns or infections of the outside of the eye. It is frequently only used for two days till bacterial cultures detect what specific antibiotics the infection is sensitive to. The required dose should be monitored by blood testing [1,2].It is made up of a mixture of the major components GEN C_1,C_{1a},C_2,C_{2a}, and minor one C_{2b}, in addition to the related substances such as (Sisomicin, Garamine ,GEN A,GENB, and 2-deoxystreptamine, etc) are formed in small amounts during fermentation[3,4]. The profiling of pharmaceutical products' impurities has greatly increased in the modern era. The majority of medications are chemically produced, therefore in order for them to be safe, they mustbe devoid of any *unintended chemicals that might be left over from the synthetic procedures, aswell as any degradants that may have been* generated during the process or over long periods of storage. The presence of impurities in trace quantity in drug substances or drug products is inevitable, therefore, their level should be controlled and monitored [5,6]. One constant in the pharmaceutical industry is that the product should be as pure as possible. The pharmaceutical industry is expanding daily to create new medications derived from natural products that may contain impurities that can reduce or increase the pharma ecological effect of the active pharmaceutical ingredient. Occasionally, the effect produced by impurities can be carcinogenic, endangering human health by affecting the quality, safety, and efficacy of the product. Consequently, there is a growing interest in regulating and tracking contaminants found in pharmaceutical products [5,7]. The most common impurities present in GEN are listed in Table 1.

Table 1. Name and molecular weight of impurities in Gen C. Zheng et. al [8].

Name of impurity	Molecular weight
Sisomicin	448/mol

Garamine	322g/mol
Gentamine C_1	319g/mol
Garosamine	177g/mol
Deoxystreptamine	163g/mol
JI-20A	482g/mol
Y-02077H-δ	450g/mol
VII-2	450g/mol
XK-62-5	450g/mol
XK-62-3	464g/mol
Y-02077H-γ	464g/mol
VII-1	464g/mol
XK-62-7	492g/mol
XK-62-8	492g/mol
Y-02077H-β	492g/mol
GEN C_1	478g/mol
GEN C_{1a}	450g/mol
GEN C_2,C_{2a},C_{2b}	464g/mol

Many studies conducted on the impurities of GEN injection showed the presence of the same impurities in the current study in a variety of countries, for example, In the States of America a study conducted by (Jariwala et al., 2020) entitled Rapid determination of aminoglycosides in Pharmaceutical preparation by electrospray ionization mass spectrometry, one of it's the most important results present impurity was garamine, the study used liquid chromatography LC-MS **[9]**. In another study conducted in India to detect impurities in GEN injection by using acquity UPLC with QDa Mass Detector, the results revealed the presence of sisomicin, garamine, GENB, G-418, GENA, A1, A3 **[10]** in California the study used Dionex IonPac AmG-3µm C18 consisted of two samples, sisomicin impurity was detected in samples**[11]** in California assay by HPLC with charged aerosol detection investigated of found sisomicin and garamine impurities[12]**.** A study in Syria used Reversed-phase liquid chromatography LC-MS for analyzing five samples of GEN injection, nine impurities (garamine , sisomicin , gentamine C1, gentamine C2, Gen A, Gen B, JI20-B, JI-20A, and Gen B1 were identified **[13].** As well as, a study in Syria for analyzing GEN impurities applied (RP) C18 column the detector was MS with an ESI source in the positive ion mode, and the result revealed the presence of two impurities G-418 and sisomicin [14]. In Poland, a study that used LC-CAD with charged aerosol detection, found three impurities sisomicin, garamine, and gentamicin A[15]. In another study in Slovenia to determine impurities in GEN by liquid chromatography-tandem mass spectrometry, the result indicated the presence of garamine, GENA,A1, A3, GENC1a, GENB, II-2, III-1, GENC2, JI-20A, VII-2, GENB1, GENC2a, sisomicin, J1-20B, gentamine C1,Y-01077H-b, GENC2b, VII-1 and Y-02077H-g **[16]**. This study aims to analyze the impurities of GEN injection from five different brands.

2. Materials & Methods

2.1. Samples collection and distribution

Five samples of GEN injection were selected from Abb governorate, Yemen, and analyzed by LC/MS.The information related to the samples is listed in Table 2.

Table 2. Samples of information about the GEN injection

Name of company	Strength samples	Manuf.date	Expired date
Inj-l(China)	80/2mg/ml	03/2019	03/2022
Inj-ll(Greek)	80/2mg/ml	01/2019	01/2022
Inj-lll(Yemen)	80/2mgml	02/2019	02/2022
Inj-lV(Slovonia)	80/2mg/ml	03/2019	03/2022
Inj-V(Korea)	80/2mg/ml	07/2019	07/2022

2.2. Chromatographic condition

Liquid chromatography coupled (Dionex, Sunnyvale, CA, USA) with mass spectrometry was used todetermine the components of GEN, and identification of its impurities, the method was achieved using cap cell PAK C18 AQ column (250×4.6mm ID,5µm; Shiseido, Japan), the column temperature was 40°C, a manual injector with a 5 µl loop was used for injection of the sample solution. Nitrogen was used as a sheath and auxiliary gas. Helium was used as collision and damping gas in the ion trap. Liquid chromatography quadrupole (LCQ, Thermo Finnigan, San Jose, CA, USA) ion trap mass spectrometer was equipped with an ESI interface operated in the positive ion mode. MS parameters were optimized as follows: capillary voltage, desolvation temperature, and source temperature were 3.9kv, 275°C, and 150°C respectively, and tube lens voltage was set -30v [8].

2.3.Preparation of mobile phase

The mobile phases were used in this study: (A) 50 mM Trifluoroacetic acid (TFA) solution, (B) 50mM TFA /methanol (10: 90 v/v). The TFA was adjusted to the required pH of 2.4 with ammonia,isocratic elution was performed at a flow rate of 1.0 ml/min (A: B, 85: 15 v/v).

2.4.Preparation of samples

All solutions were prepared in the mobile phase at a concentration of around 2.0 µg/ml. The instrument has a built-in library, and the impurities in GEN were identified by molecular weight without the need for a standard.

3. Results & discussion

3.1. Fragmentation behavior of Gen components

Glycoside bond cleavages were the main fragmentation behaviors of the protonated GEN molecule and its related substances. Glycoside bond cleavage between rings B and C yieldsthe ion m/z 160 as the garosamine residue, with a loss of 159 Da in the GEN spectrum. Further fragmentation of the $[M+H-159]^+$ ion results in the ion m/z 163 (ringB, 2-deoxystreptamine) by the loss of ring A (e.g. 142 Da for GEN C2, C2a, C2b). Another typical fragment formed by the loss of 117 Da from the garosamine sugar.The $[M+H-117]^+$ ion could be further fragmented to the ion at m/z 205 by the loss of ring A. Glycoside bond cleavage between ring A and B yields the ion m/z 322 (ring and C, garamine) by the loss of ring A (e.g. 128 Da for GEN C1a).Fragmentation of ion *m/z* 322 yield the product ion *m/z* 163 and 205 by th loss of 159 and 117 Da, respectively. A summary of the fragmentation pathway of GEN components is shown in Figure1, which was the basis for further interpretations of related substances in bulk GEN samples. The loss of ring A from sisomicin and JI-20B is 126 and 174 Da respectively which is different from ring A of major GEN components.

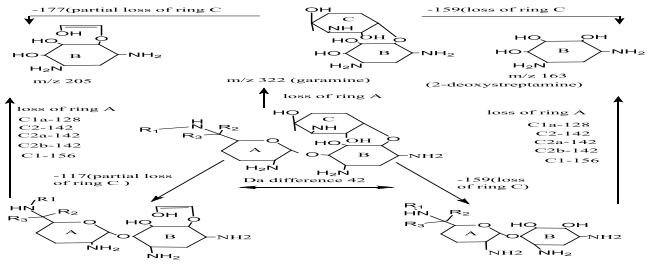


Figure 1. *Summary fragmentation pathway of GEN components.*

3.2. Interpretation of the compounds present in samples

3.2.1. Interpretation of the compounds present in Inj-l sample.

The HPLC chromatogram of the Inj-I sample is shown in Figure 2 and the TLC chromatogram in Figure 3 the LC-MS spectrum of peak at the time (0.16min) is represented in Figure 4 (a), the protonated molecule m/z 322 fragmented into the product ions m/z 205, 163(2-deoxystreptamine) indicate presence impurity garamine. As well as the impurity m/z 319 indicates the presence of gentamine C_1. Impurities VII-2, XK-62-5, Y-02077H-δ, and GEN C_{1a} in m/z 450. Impurities XK-62-3, Y-02077H-γ, VII-1, GEN C_2, C_{2a}, and C_{2b} in m/z 464 and impurity GEN C_1 in m/z 478. Losing ring A (128), (124), and (156) from GENs C_{1a}, C_2, and C_1 respectively indicated the presence of garamine, and losing ring c (159) from *m/z* 322 indicates the presence of deoxystreptamine. This is in line with work done by N. Al-Jammal. and M., Al-Mardini [13] the result indicated the presence of impurities in gentamicin (garamine, sisomicin , GEN C_1, and GEN C_2).

The LC-MS spectrum of peak at the time (0.27min) is shown in Figure 4 (b) shows the ions *m/z* 322, m/z 205, *m/z* 163, and *m/z* 160 that indicated the presence of impurity garamine in one of these components. The *m/z* 163 was impurity deoxystreptamine. Moreover, the impurity is shown at *m/z* 448 indicating the presence of sisomicin which was not shown in the same sample at time 0.16 min. The protonated molecule *m/z* 178 was identified as garosamine. The impurity *m/z* 319 indicates the presence of gentamineC_1. As well as, the same impurities that appeared in time 0.16 min in *m/z* 450,464 and 478 appeared at this time. The study carried by C. Zheng et.al revealed the the presence of garamine in *m/z* 322 and JI-20A in *m/z* 497[8]. The spectrum in Figure 4 (c) at the time (4.47 min) shows impurity garamine. Figure 4 (d) at the time (4.77 min) shows the ions *m/z* 322, *m/z* 163, and *m/z* 205 indicate the presence of garamine in these components and impurity 2-deoxystreptamine in *m/z* 163 and impurity garosamine in *m/z* 177.Moreover, the impurity *m/z* 448 was sisomicin, and the peak at *m/z* 319 indicates the presence of gentamine C_1.Which are the same impurities that appeared at the time 0.16 min and 0.27 min in *m/z* 450,464, and 478. The spectrum in Figure 4 (e) at the time (5.76 min) shows the ions *m/z* 322 and m/z 160 which indicates the presence of garamine in one of these components. Moreover, protonated molecule *m/z* 449 indicates impurity sisomicin in Figure 4 (e), and Figure 4 (f) in time (8.27min). The results study by J. Hu and J. Rohrer. Showed the presence sisomicin impurities in m/z 448[11].

The spectrum in Figure 4 (g) at the time (9.31 min), shows the ions *m/z* 322 and *m/z* 160 indicatethe presence of garamine in one of these components. Moreover, shown impurities GEN C_{1a}, VII-2, XK-62-5, and Y-02077H-δ in *m/z* 450 and impurities XK-62-7, XK-62-8 and Y-02077H-β in *m/z* 492, and protonated molecule *m/z* 449 indicated the presence of sisomicin. The total number of impurities in the Inj-I sample was nineteen, deoxystreptamine, garamine, gentamine C_1, VII-2, XK-62-5, Y-02077H-γ , Y-02077H-β, Y-02077H-δ, garosamine, VII-1, XK-62-3, sisomicin, GENs C_1, C_{1a}, C_2, C_{2a}, and C_{2b}, XK-62-7, and XK-62-8. In addition to two unknown impurities in 490 and 110.

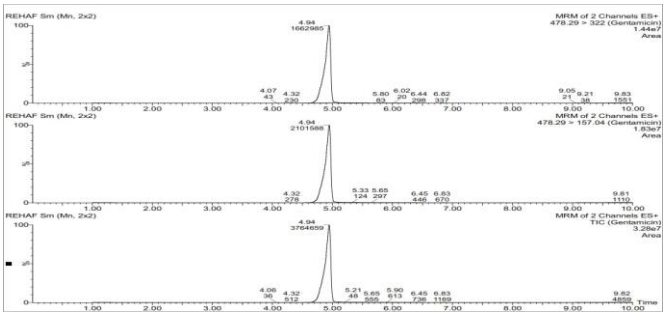


Figure2. HPLC chromatogram of Inj-l sample.

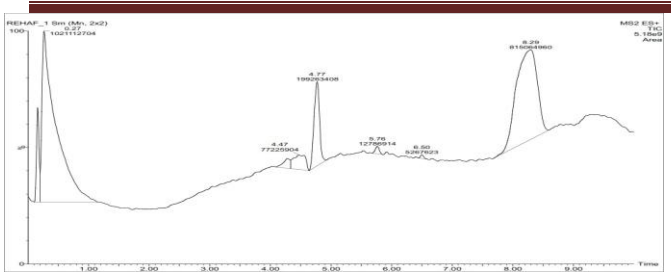
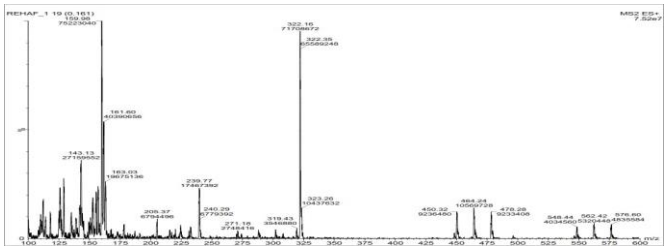
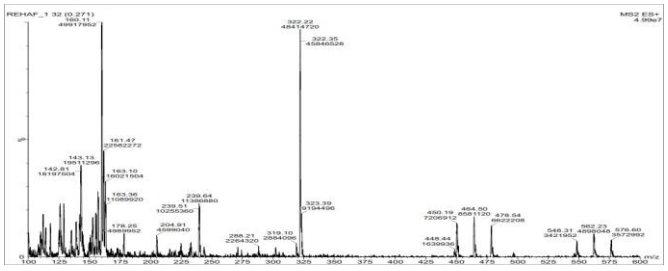


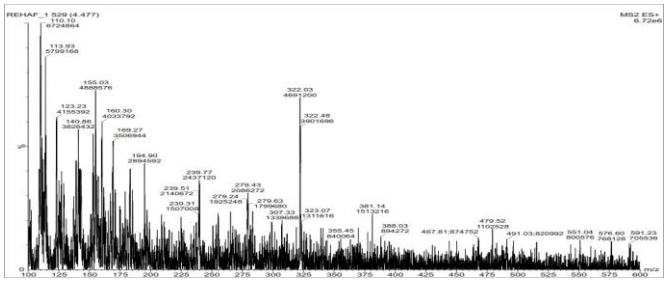
Figure 3. TICchromatogram of Inj-l sample.



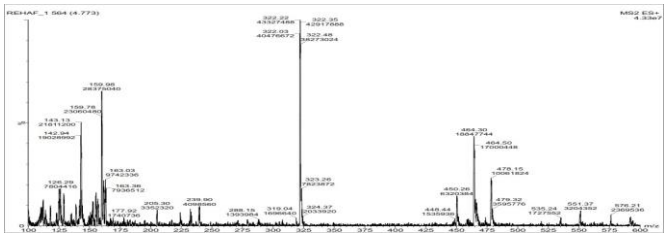
(a)



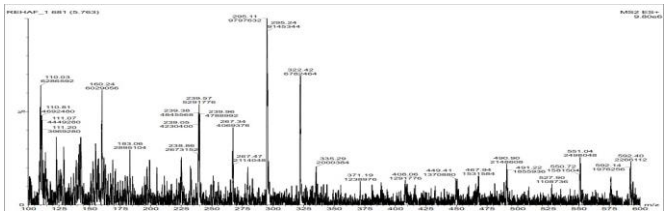
(b)



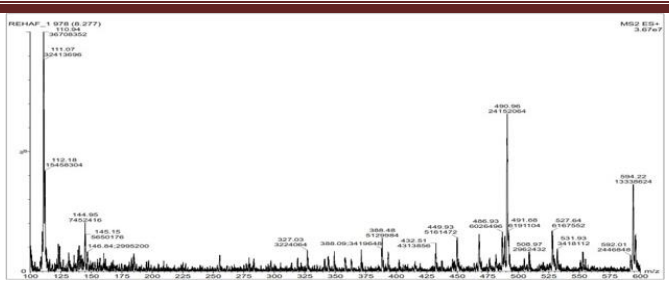
(c)



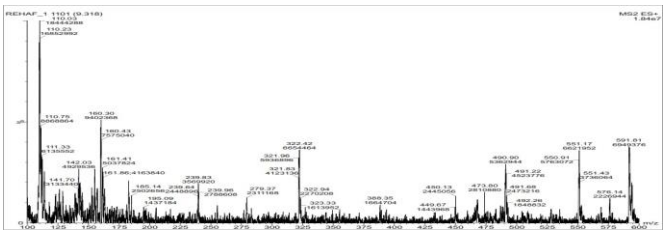
(d)



(e)



(f)



(g)

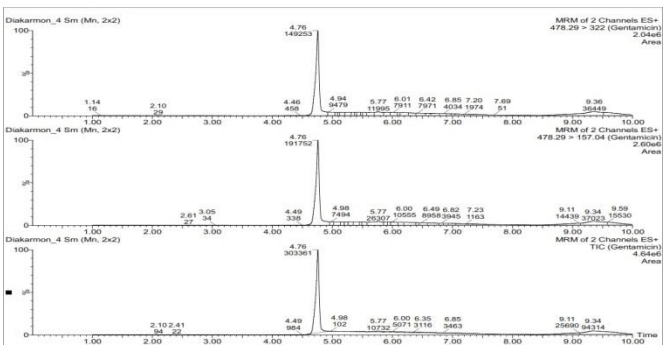
Figure 4. LC-MS spectrums of components in Inj-l sample. (a) 0.16;(b) 0.27; (c) 4.47; (d) 4.77; (e) 5.76; (f) 8.27(g) 9.31 min.

3.2.2. Interpretation of the compounds present in Inj-ll sample.

The HPLC and TIC of the Inj-II sample are represented in Figures 5 and 6 respectively, the fragmentation behavior of GEN and the LC-MS spectrum Figure 7 (a) for a peak at the time (0.16 min), the protonated molecule *m/z* 322 fragments into the product ions *m/z* 205, 163 indicated the presence of garamine in these components, *m/z* 163 was deoxystreptamine, impurities Y-02077H-δ, VII-2, XK-62-5, GEN C_{1a} in *m/z* 450 and impurities XK-62-3, Y-02077H-γ, VII-1, and GENs C_2, C2a andC_{2b} in *m/z* 464 and GEN C_1 in *m/z* 478. The result is parallel with the study performed by K. Stypulkowska et.al. that confirmed the presence garamine in *m/z* 322, and sisomicin in *m/z* 448[15]. The mass spectrum in Figure 7 (b) for

a peak at the time (0.27 min), shows the ions *m/z* 322, *m/z* 205, m/z 163, and *m/z* 160 that indicate the presence of garamine in these components. The *m/z* 163 was impurity deoxystreptamine. However, the impurity in *m/z* 448 is sisomicin. The impurities are shown in *m/z* 450, 464, and 478 in Figure 7 (b). 322, and *m/z* 160 indicate the presence of garamine in one of these components. The *m/z* 448 was impurity sisomicin. The same impurities in m/z 450, 464, and 478 are similar to Figure 7 (a), (b). The result is similar to the study carried out by N. Al-Jammal, M.et.at, which indicated the presence of sisomicin impurity in *m/z* 448**[14].**

The total number of impurities in the Inj-II sample was fourteen, garamine, deoxystreptamine, XK-62- 3, Y-02077H-γ, Y-02077H-δ, VII-1, GEN C_2, GEN C_{2a}, GEN C_{2b}, GEN C_1. Sisomicin, *VII-2, XK-62-5, and GEN C_{1a}.*



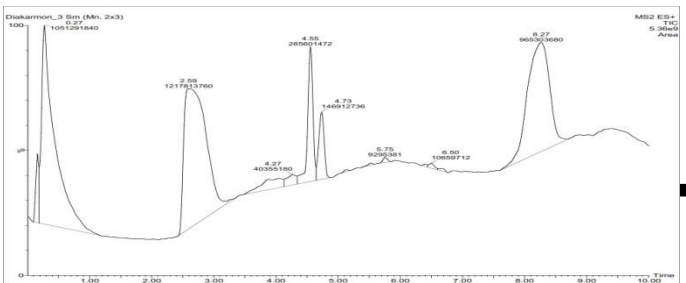
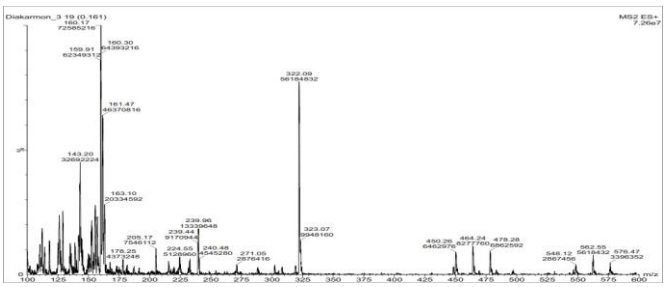
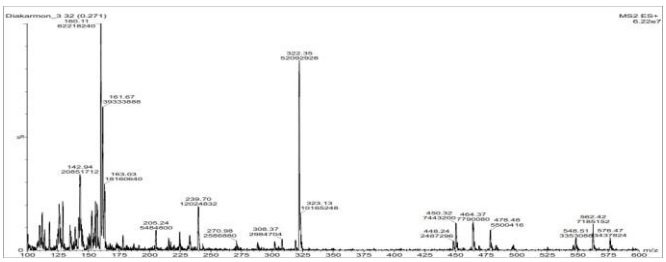


Figure5. HPLC chromatogram of Inj-ll sample.

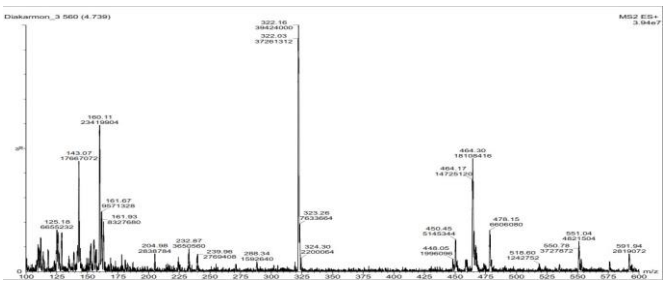
Figure 6. TIC chromatogram of Inj-ll sample.



(a)



(b)



(c)

Figure 7. LC-MS spectrums of components Inj-ll sample (a) 0.16; (b) 0.27;(c) 4.73 min.

3.2.3. Interpretation of the compounds present in Inj-lll sample.

The HPLC chromatogram of the Inj-III sample is shown in Figure 8 and TIC in Figure 9, the

ions *m/z* 160, and m/z 163 in Figure 10 (a) for a peak at the time (0.16 min) indicates the presence of garamine in this compound, the *m/z* 163 was impurity deoxystreptamine, the *m/z* 319 was impurity gentamine C_1 . The impurities VII-2, XK-62-5, Y-02077H-δ, and GEN C_{1a} in *m/z* 450. Also, impuritiesXK-62-3, Y-02077H-γ, VII-1 and GENs C_2, C_{2a} and C_{2b} *in m/z* 464 and impurity GEN C_1 in *m/z* 478. Figure 10 (b) for a peak at the time (0.26 min) shows the same impurities in Figure 10 (a). Figure 10(c) for a peak at the time (4.76 min) shows the same impurities in Figure 10 (a) and (b) except the impurity gentamine C_1 was not presented. Figure 10 (d), (e), and (f) for a peak at the time (4.58 min), (5.77 min), and (9.24min) respectively show impurity garamine. Moreover, protonated molecule *m/z* 449 indicated impurity sisomicin in Figure 10 (f). The presence of garamine in *m/z* 322 and sisomicin in *m/z* 448 was also indicated in the study performed by R. Li., et.al [12].

The total number of impurities in the Inj-III sample was fifteen, garamine , deoxystreptamine, gentamine C_1, VII-2, XK-62-5, Y-02077H-δ, Y-02077H-γ, GEN C_{1a}, XK-62-3, VII-1, GEN C_2, GEN C_{2a}, GEN C_{2b}, GEN C_1, and sisomicin. As well as, two unknown impurities in 490 and 110.

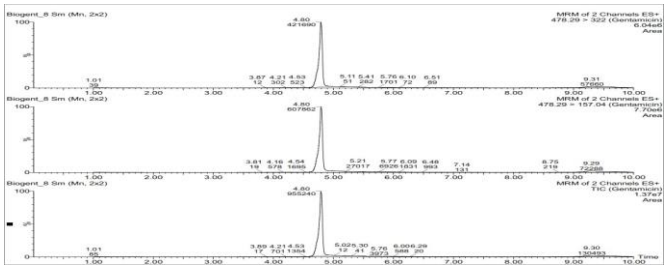


Figure 8. HPL Cchromatogram of Inj-lll sample.

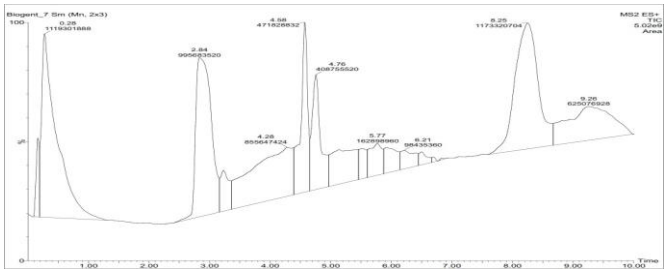
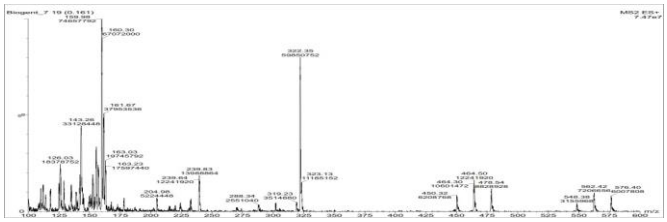
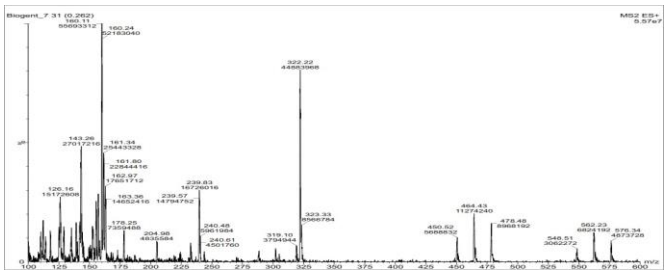


Figure 9. TIC chromatogram of Inj-lll sample.



(a)



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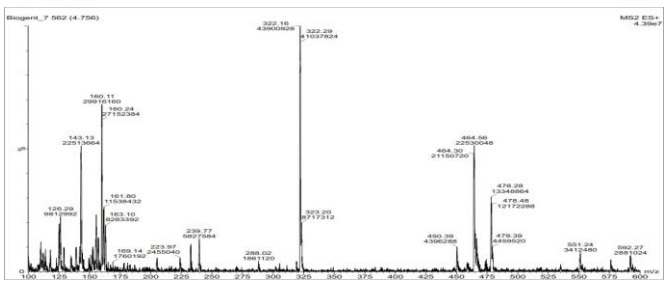
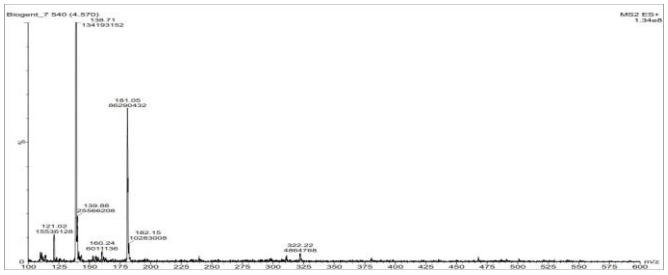
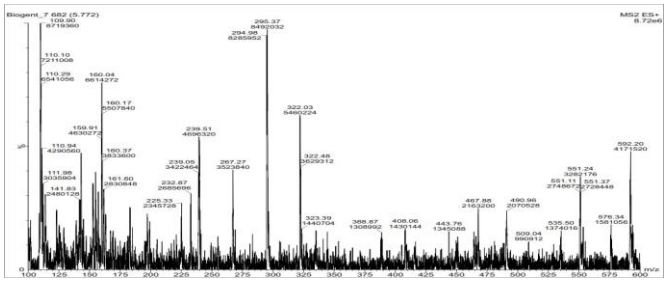


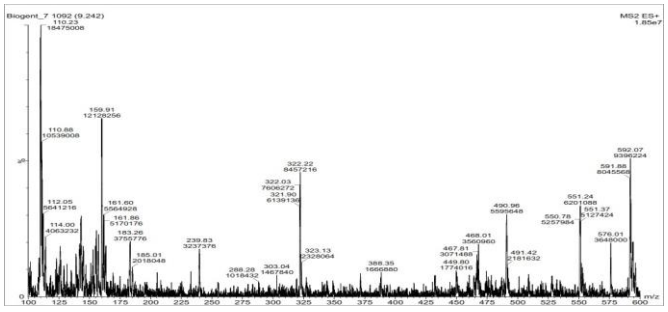
(c)



(d)



(e)



(f)

Figure 10. LC-MS spectrums of components in Inj-lll sample (a) 0.16; (b) 0.26;(c) 4.76; (d) 4.57;(e) 5.77; (f) 9.24 min.

3.2.4. Interpretation of the compound present in the Inj-lV sample.

The HPLC chromatogram of the Inj-IV sample is shown in Figure 11 and TIC in Figure 12, and the ions *m/z* 322, *m/z* 205, *m/z* 160, and *m/z* 163 in Figure 13 (a) for a peak at the time (0.16 min) indicates the presence of garamine in one of these components. The impurity 2-deoxystreptamine in *m/z* 163, impurities Y-02077H-δ, VII-2, XK-62-5 and GEN C_{1a} in *m/z* 450, impurities XK-62-3, Y- 02077H-γ,VII-1, GENs C_2, C_{2a} and C_{2b} in *m/z* 464, and GEN C_1 in *m/z* 478. As Shown in Figure 13 (b) and (c) for a peak at the time (0.27 min) and (4.86 min) respectively same impurities, which in (a) except *m/z* 319 in Figure 13 (b) and (c) indicates the presence of gentamine C_1. In addition, the impurity *m/z* 482 in Figure 13 (d) at the time (4.27 min) indicates the presence of JI-20A. The impurities XK-62-7, XK-62-8, and Y-02077H-β in *m/z* 492 in Figure 13 (e) for a peak at the time (8.26 min). Moreover protonated molecule *m/z* 449 indicated the presence of impurity sisomicin in Figure 13 (f) for a peak at the time (8.93 min). The same result was found in a study carried out by N. Al- Jammal. and M., Al-Mardini which proved the presence of some impurities such as garamine, sisomicin, gentamine $C_1$and JI-20A [13].

The total number of impurities in Inj-IV sample nineteen, garamine, deoxystreptamine, Y-02077H-δ, Y-02077H-γ,Y-02077H-β, Vll-2, XK-62-5, $GENC_{1a}$,XK-62-3,Vll-1,$GENC_2$,GEN C_{2a}, GEN C_{2b}, GEN C_1, gentamineC_1, JI-20A,XK-62-7,XK-62-8 and sisomicin. As well as, two unknown impurities in 490 and 110.

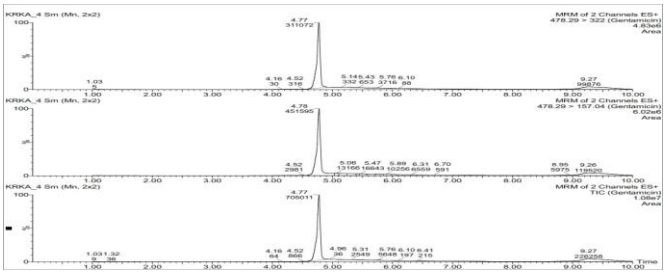


Figure11. HPLC chromatogram of Inj-lV sample.

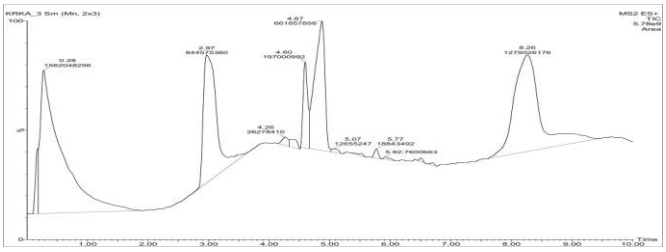
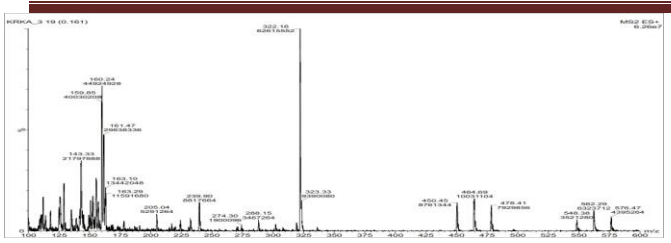
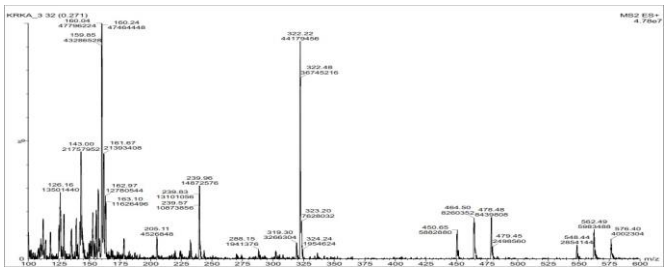


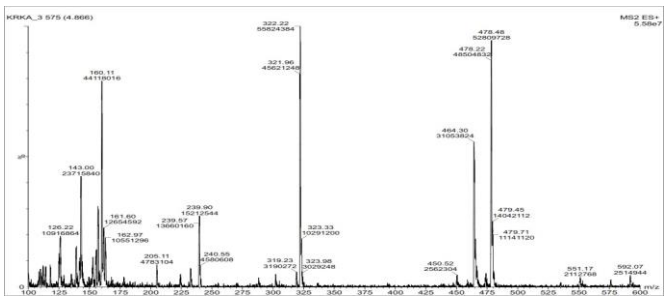
Figure 12. TIC of Inj-lVsample.



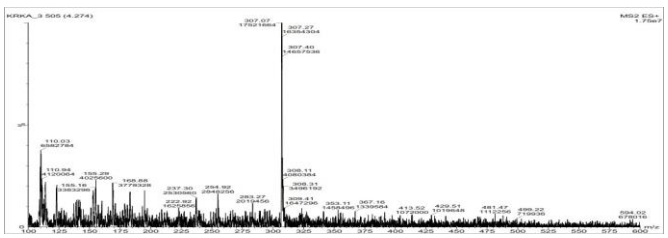
(a)



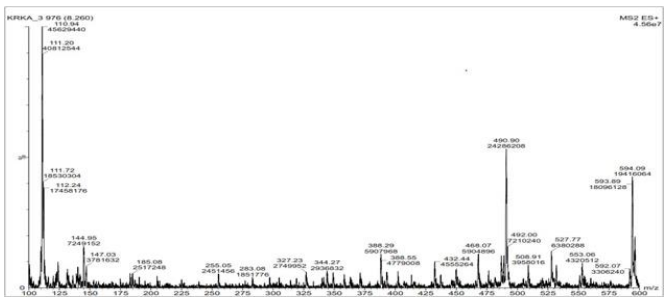
(b)



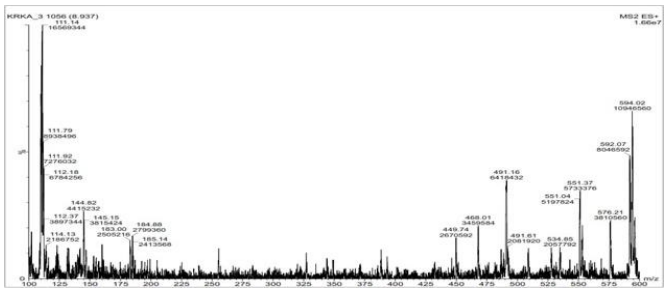
(c)



(d)



(e)



(f)

Figure 13. LC-MS spectrums of components in Inj-lV sample (a) 0.16;(b) 0.27; (c)4.86; (d) 4.27; (e) 8.26; (f) 8.93min.

3.2.5. Interpretation of the compound present in Inj-V

The HPLC chromatogram and TIC of the Inj –V sample are represented in Figures 14 and 15 respectively, the fragmentation behavior of GEN and the LC-MS spectrum is shown in Figure 16 (a) for a peak at the time (0.16 min), *m/z* 322 is fragmented into the product ions *m/z* 205, *m/z* 163, which indicates the presence of impurity garamine and impurity deoxystreptamine in *m/z* 163. Moreover, the *m/z* 319 indicates the presence of impurity gentamine C_1.The impurities Y-02077H-δ,Vll-2,XK-62-5, and GEN C_{1a} in *m/z* 450, and impurities XK-62-3, Y-02077H-γ, Vll-1, and GENs C_2, C_{2a}, and C_{2b} in *m/z* 464 and GEN C_1 in *m/z* 478 were identified. Figures 16 (b) and (c) were for a peak at the time (0.27 min) and (4.76 min) respectively, showing the same impurities as in Figure 16 (a). Protonated molecule *m/z* 449 indicated the impurity sisomicin and impurities XK-62-7, XK-62-8, and Y-02077H-β in *m/z* 492 in Figure 16 (d) for a peak at the time (8.27 min). The results indicated the same result as the study of R. Grahek, and L. Zupancic-Kralj except with a difference in GENA, A_1, A_3 in *m/z* 469 **[16]**.

The total number of impurities in Inj -V sample eighteen, garamine, deoxystreptamine, gentamine C_1, Y-02077H-δ,Y-02077H-γ, Y-02077H-β, Vll-2, XK-62-5, GENsC_1, XK-62-3, Vll-1,GENsC_2, C_{2a} and C_{2b}, sisomicin, XK-62-7, and XK-62-8 . As well as , two unknown impurities 490 and 110.

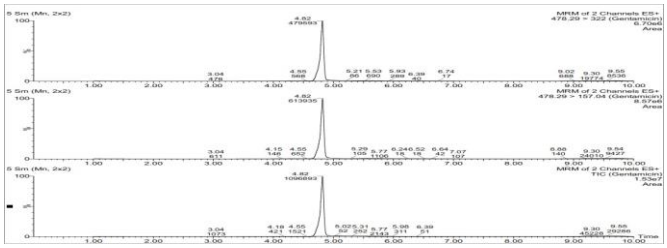


Figure14. HPLC chromatogram of sample.

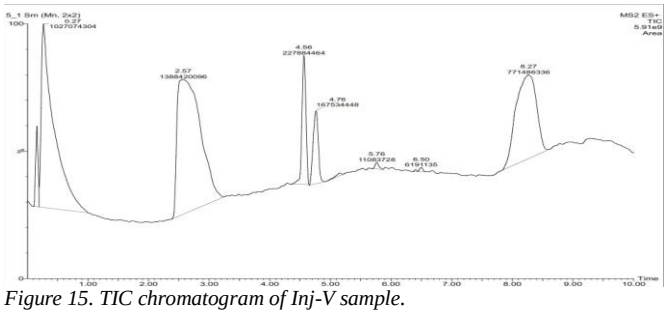
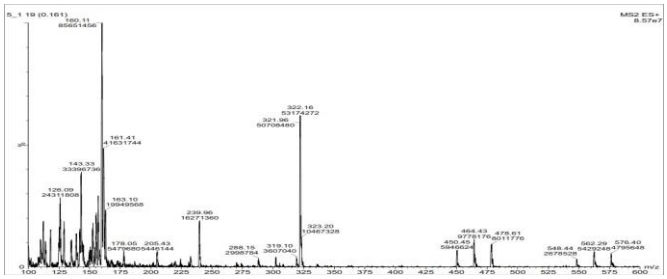
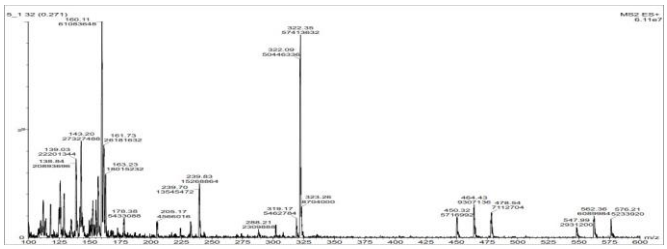


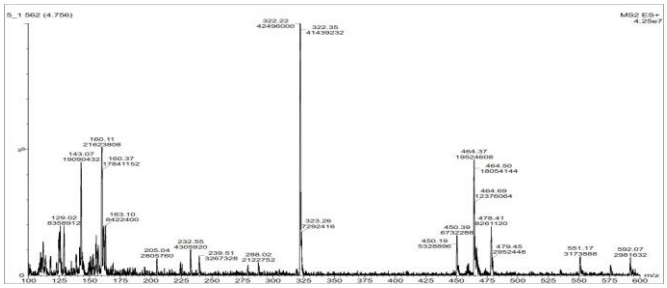
Figure 15. TIC chromatogram of Inj-V sample.



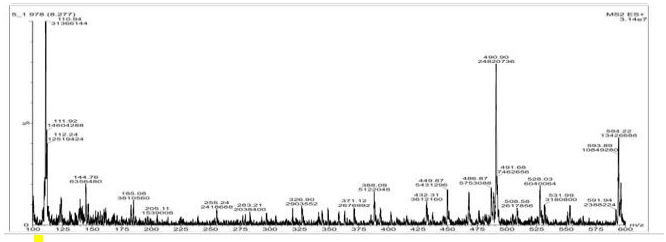
(a)



(b)



(c)



(d)

Figure 16. LC-MS spectrums of components in Inj-V(a) 0.16; (b)0.27; (c)4.76;(d)8.27 min.

Impurity	Samples				
	Inj-l	Inj-ll	Inj-lll	Inj-lV	Inj-V
Garamine	+	+	+	+	+
Deoxystreptamine		-	+	+	+
GEN C1	+	+	+	+	+
VII-2	+	+	+	+	+
XK-62-5	+	+	+	+	+
Y-02077H-δ	+	+	+	+	+
Y-02077H-γ	+	+	+	+	+
Y-02077H-β	+	-	-	+	+
VII-1	+	+	+	+	+
XK-62-3	+	+	+	+	+
XK-62-7	+	-	-	+	+
XK-62-8	+	-	-	+	+
Sisomicin	+	+	+	-	+
Garosamine	+	-	-	+	-
GEN C1	+	+	+	+	+
GENC1a	+	+	+	+	+
GENC2	+	+	+	+	+
GENC2a	+	+	+	+	+
GENC2b	+	+	+	+	+
JI-20A	+	+	+	+	+
*490	+	-	+	+	+
*110	+	-	+	+	+

490, 110* impurities unknown.(+) existence (-) not existence.*

4.Conclusion

The objective of this study was the detection of the most presence impurities in the pharmaceutical formulation from the results obtained, the number of impurities present in Inj-I was nineteen whilein Inj-II was fourteen and in Inj-III was fifteen and in Inj-IV nineteen and Inj-V was eighteen and unknown impurities in m/z 490, 110 were a presence in all samples except Inj-II. The study recommends that the Yemeni authorities for specification, standardization, and quality control put in priorities on its competence in the control of drugs and supervision of theprocess of exporting and importing all kinds of drugs. A study recommends intensifying and supporting and encouraging similar research to its association with the health and safety of the user.

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