



May 24, 2006

SUBJECT: Presence of Azithromycin Sesquihydrate (Form G) in Azithromycin 250 mg and 500 mg Tablets Manufactured by PLIVA Hrvatska d.o.o., Croatia

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SUMMARY

Commercial samples of azithromycin 250 mg and 500 mg tablets manufactured by Pliva Hrvatska d.o.o. were purchased in the United States and forwarded to the Special Testing & Analytical Development Lab at Pfizer, Groton, CT for analysis to determine the form of azithromycin in the product. A combination of ^{13}C Solid State NMR (ssNMR), Fourier Transform Infrared Spectroscopy (FTIR), Powder X-Ray Diffraction (PXRD), and headspace gas chromatography (GC) analyses were performed on the samples. Results from the spectroscopic tests were compared to reference spectra of azithromycin Form G (azithromycin sesquihydrate), Form A (azithromycin dihydrate) and the other forms recorded in US Patent No. US 6,977,243. The PXRD results indicated that the samples contained azithromycin in a crystalline form within Family I, which is comprised of Forms F, G, H, J, M, N, O and P. The PXRD results also provided evidence for absence of Form Q and those in Family II, which is comprised of Forms C, D, E, and R.

Further analysis by ssNMR and headspace GC provided for differentiation between the Family I isomorphs. The ssNMR results obtained for each of the two tablet strengths demonstrated excellent agreement (46 of 49 peaks matched) with the ssNMR spectrum of our Form G reference material. The ssNMR results for the 250 mg tablet showed a trace (~1%) of Form A in the sample. Form A was not detected in the 500 mg strength. The ssNMR spectra for the samples also showed absences of diagnostic signals that indicated absence of Forms F, H, J, M, N (from Family I isomorphs). Headspace GC analysis found no detectable n-butanol and n-propanol in the tablet samples and supported absence of Forms O and P in the samples. The headspace GC analysis also found absence of detectable levels of solvents that are components of azithromycin Forms D, E, J, M, N, and R. The headspace GC analysis found trace of ethanol (0.04% by weight relative to total azithromycin) in the 250 mg tablet. If all of the ethanol was assumed to be present as azithromycin monohydrate hemi-ethanolate (Form F), the contribution of Form F to total azithromycin content would be less than 1.5%. Based on the collective results from headspace GC, FT-IR, PXRD, and ssNMR analyses, the Pliva tablets are concluded to contain primarily azithromycin in the sesquihydrate form (Form G).

OBJECTIVES

Testing was performed on Pliva azithromycin 250 mg and 500 mg tablets to determine the form of azithromycin present in the sample. A combination of ssNMR, FT-IR and PXRD spectroscopic techniques were used for the analysis. Additional testing by

headspace gas chromatography was used to verify presence or absence of solvents associated with various known crystal forms of azithromycin.

SAMPLE DESCRIPTION

The 250 mg and 500 mg tablets used in these analyses were obtained by Pfizer from the distributor (AmerisourceBergen) and forwarded to the Special Testing & Analytical Development Laboratory at Pfizer GQAR, Groton, CT for testing. Samples were stored at all times at controlled room temperature. Photographs and other details for the 250 mg and 500 mg tablet samples are presented in **Figures 1 and 2**, respectively.

ANALYTICAL RESULTS

1. Fourier Transform Infrared Spectroscopy (FTIR)

A Nicolet model Magna-IR 550 Fourier Infrared (FT-IR) spectrometer was used to analyze the Azithromycin tablet samples using method described in Pfizer Standard Test Procedure (STP) I 3.94. Each sample was analyzed as a potassium bromide pellet preparation. Resulting spectra for the 250 and 500 mg samples along with overlays with azithromycin dihydrate reference, are shown in **Figures 3 and 4**, respectively.

Diagnostic IR bands unique for azithromycin dehydrate in the regions of $3560\pm 3\text{ cm}^{-1}$, $3491\pm 5\text{ cm}^{-1}$, $1344\pm 3\text{ cm}^{-1}$, $1282\pm 3\text{ cm}^{-1}/1270\pm 3\text{ cm}^{-1}$ (doublet) and $1084\pm 3\text{ cm}^{-1}$ were not found in either of the two tablet strengths. These data indicate absence of azithromycin dihydrate in the samples (within estimated detection limit of 25% by weight relative to total azithromycin content).

Further analysis was conducted to identify other ingredients using a series of extractions of the tablet samples to separate the individual components. Isolated components were analyzed by FT-IR to determine identity. The tablet core was found to be comprised primarily of azithromycin (estimated 65% w/w), calcium phosphate (estimated 14% w/w) and microcrystalline cellulose (estimated 16% w/w). Lesser amounts of a starch and magnesium stearate were also identified in the core. These results are consistent with components identified in the package insert (see **Figures 1 and 2**). Majority of the other ingredients listed in the package insert are components of the tablet coatings.

2. Analysis by Powder X-Ray Diffraction (PXRD)

PXRD diffractograms were collected for the Pliva 250 and 500 mg azithromycin tablets using a Bruker D4 X-Ray Diffractometer. A portion of each tablet was gently ground to a fine powder in a mortar and pestle for the analysis. Resulting diffractograms were compared to those obtained previously for azithromycin dihydrate (Form A) and azithromycin Form G (azithromycin sesquihydrate, lot 51047-21-4H) reference samples.

Comparisons of the diffractogram for azithromycin dihydrate (Form A) with those obtained for the Pliva 250 and 500 mg tablets are shown in **Figures 5 and 6**, respectively. The most diagnostic peaks for azithromycin dihydrate in the region from 7 to 22 degrees in 2-theta were not present in a pattern indicative of Form A. These data provide evidence for the absence of detectable azithromycin dihydrate in the tablets. Estimated detection limit for azithromycin dihydrate by the PXRD technique is 5% by weight relative to total azithromycin content.

The PXRD results for the Pliva samples also provided evidence that Family II forms of azithromycin are not present in the sample. Family II includes Form D (monohydrate/monocyclohexane solvate), Form E (azithromycin monohydrate/mono-

tetrahydrofuran solvate), Form C (azithromycin monohydrate, as described in US 6,977,243), and Form R (azithromycin hydrate/methyl tert-butyl ether solvate). The most diagnostic PXRD signals for the isomorphs in this family occur at 3.9, 10.1, 10.6 and 21.4 2-theta. All spectra in **Figures 5 and 6** were found to be missing the most easily discernible signals (i.e., those with highest intensity) at 3.9, 10.1 and 10.6 2-theta. One additional form, Form Q (azithromycin hydrate/hemi-tetrahydrofuran solvate) was also found to be absent in the Pliva tablets. This result was demonstrated by absence of diagnostic signals for Form Q at 6.8 and 8.4 2-theta in the sample spectra shown in **Figures 5 and 6**.

Diffraction patterns of the 250 mg and 500 mg tablets are shown with overlays of the Form G diffraction pattern in **Figures 7 and 8**, respectively. Each of the sample spectra are found to contain peaks that match both position and relative intensity of those found in the reference spectrum of Form G. Form G is one form in a family of eight azithromycin isomorphs (Family I) that have similar x-ray diffraction characteristics. In addition to Form G, the other isomorphs in this family are Form F (azithromycin monohydrate/hemi-ethanol solvate), Form H (azithromycin monohydrate/hemi-propylene glycol solvate), Form J (azithromycin monohydrate/hemi-n-propanol solvate), Form M (azithromycin monohydrate/hemi-isopropanol solvate), Form N (azithromycin water/ethanol/isopropanol solvate), Form O (azithromycin hemi-hydrate/hemi-n-butanol solvate), and Form P (azithromycin hemi-hydrate/hemi-n-pentanol solvate). Because the PXRD spectra are essentially identical for each of the forms in this family, additional analysis (e.g., ssNMR) was needed to distinguish which is present in the samples.

3. Analysis by ^{13}C Solid State NMR (ssNMR)

Under direction of our laboratory, the ^{13}C -ssNMR spectral analyses were conducted at the Pfizer Global Research and Development NMR Laboratory in Groton, CT, USA. Results of these experiments are summarized below. For the analysis, an individual tablet was ground gently to a powder and a portion of the powder was packed into an NMR tube. A one-dimensional ^{13}C -ssNMR spectrum was collected for each of the samples using a ^1H - ^{13}C carbon cross-polarization magic angle spinning (CPMAS) technique. Full details of the NMR analyses are reported in research reports CP62993_IP06022_27Mar2006 and CP62993_IP06024.27Mar2006.

The resulting ^{13}C CPMAS spectra (ssNMR) of each sample were compared to the spectra of azithromycin Form G and Form A that had been previously documented (see PharmSci NMR report CP62993.061401, prepared by A. Medek and L. Lohr on May 28, 2002). **Figures 9 and 10** show ssNMR results for the 250 mg and 500 mg tablets, respectively. Results supported presence of azithromycin in both tablet strengths as primarily Form G. The 250 mg tablet showed evidence of a trace amount of Form A (**Figure 9**). The trace of Form A was indicated by presence of the characteristic peaks for Form A at 39.1 ppm, 52.2 ppm and 178.1 ppm. The level of the Form A in the 250 mg tablet was slightly above the estimated detection limit (0.8%, w/w) for this sample and was too low to be accurately quantified.

The ssNMR results presented in **Figures 9 and 10** demonstrate that the azithromycin in Pliva 250 mg and 500 mg tablets is present as the sesquihydrate Form G. Within the Family I isomorphs, each of the other Forms F, H, J, M, N, O, and P may be eliminated by absence of ssNMR signals corresponding to the crystalline solvent components in each form. Form F is excluded by absence of the signal for crystal-bound ethanol at 58.0 ppm. Form J is excluded by absence of detectable signals in the sample for crystal-bound n-propanol at 11.5 ppm and 25.2 ppm. Forms M and N are excluded by absence

of detectable signals for crystal-bound isopropanol at 26.0 ppm. Form H is not present since its characteristic peaks at 103.2, 82.7, 66.9, 46.8, 33.3, 15.4 and 7.0 ppm are missing. Headspace GC analysis (discussed in Section 4) demonstrated absence of n-butanol and n-pentanol and provides evidence for excluding the remaining two forms (Forms O and P) in Family I.

Table 1 shows the comparison of carbon chemical shifts observed on the sample with those of azithromycin Form G disclosed in the example section of US 6,977,243 patent. Of 49 peaks listed in the patent, 46 were identified (within the ± 0.2 accuracy limits) in each of the tablet samples. Exceptions were noted for peaks at 30.4 ppm (a low intensity and broad peak in Form G standard; most likely interfered with excipients signals and fell just outside the ± 0.2 accuracy limits), at 65.2 ppm (peak exhibited as a shoulder with no defined maximum), and at 75.7 ppm (low intensity peak in Form G standard, most likely overlapped with excipients signals). These variations from the Form G reference spectra are to be expected when the material is formulated into a dosage form with other excipients. Signal interferences from crystalline excipients and solid-solid interactions between the azithromycin and excipient materials leading to line width broadening can each contribute to these variations. Overall, the variations are minor and do not preclude a positive identification of Form G in the samples.

4. Analysis by Headspace Gas Chromatography (GC).

Headspace GC analyses were performed using a Tekmar 7000 Headspace Autosampler and Agilent 6890 Gas Chromatograph with flame ionization detection. Each tablet was dissolved in water (250 mg into 50 mL, 500 mg into 100 mL) and then 5 mL aliquots were placed into a 20 mL headspace vial containing 1 g of anhydrous sodium sulfate. Sealed vials were incubated at 85 C for 10 min and then 2 mL of headspace was injected into the chromatograph. Separation was performed using a 30 m x 0.32 mm i.d. RTX-624 (1.8 μ m film) capillary column. Oven temperature program was 40 C (5 min hold) – ramp 2 C/min to 90 C (0 min hold) – ramp 30 C/min to 225 C (2 min hold).

Retention times for various solvents on the chromatographic system were established by analyzing various aqueous solutions containing solvent reference materials. A summary of solvents and retention times is presented in the table below.

Solvent	Retention time
Ethanol	3.54
Isopropanol	4.33
Methyl tert-butyl ether	5.25
n-Propanol	6.52
Tetrahydrofuran	8.18
Cyclohexane	8.72
n-Butanol	12.21
n-Pentanol	19.80

Headspace GC profiles obtained for the 250 mg and 500 mg Pliva Azithromycin tablets are presented in **Figure 11**. A small response for ethanol was detected in the 250 mg tablet sample only. None of the other seven solvents was detected in the samples. Based on a signal to noise analysis of responses from an external standard solution, limits of detection for n-propanol, isopropanol, 1-butanol, 1-pentanol, and tetrahydrofuran were each found to be 10 ppm (0.001% w/w) or less. The limits of detection for cyclohexane and methyl tert-butyl ether were not specifically measured in this analysis,

but would have lower detection limits as a result of relatively lower solubility in water (hence greater concentration in headspace) than the other solvents.

The quantity of ethanol detected in the 250 mg sample was estimated by comparing response from the sample to that from an external standard solution of ethanol. The amount of ethanol in the Pliva 250 mg sample was 0.04% (relative to azithromycin content). No ethanol was detected in the 500 mg sample. Azithromycin Form F (monohydrate hemi-ethanolate) contains a theoretical 2.9% ethanol by weight. Even if the 0.04% ethanol in the Pliva 250 mg tablet was present as Form F (rather than as free solvent), this would constitute less than 1.5% Form F relative to total azithromycin content. The absence of detectable responses for other solvents provides evidence that the Pliva Azithromycin tablets do not contain significant amounts of Forms D, E, J, M, N, O, P, and R.

CONCLUSIONS

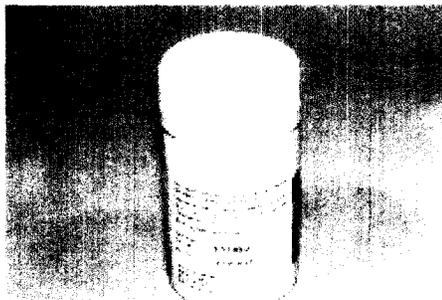
Results from these analyses provide conclusive evidence that the Pliva Azithromycin 250 mg and 500 mg tablets tested in this study contained azithromycin as azithromycin sesquihydrate (Form G).

REFERENCES

1. Notebook 108526 pp. 16-24
2. Notebook 1943 pp. 12-14
3. Notebook 1961 p. 15
4. Pfizer Standard Test Procedure I 3.94 (4/22/98) – Identification of azithromycin dihydrate by Infrared spectroscopy
5. PGRD Report CP62993_IP06022_27Mar2006, prepared by Tim Hanser
6. PGRD Report: CP62993_IP06024_27Mar2006, prepared by Tim Hanser
7. PGRD Report CP62993.061401, prepared by A. Medek and L. Lohr on May 28, 2002
6. United States Patent No. 6,977,243 (issued Dec. 20, 2005, Certificate of Correction issued Feb. 7, 2006)



A – bottle (front)



B- bottle (back)



C- tablets

Manufactured by: PLIVA Hrvatska d.o.o., Zagreb, Croatia for PLIVA®, Inc., East Hanover, NJ 07936

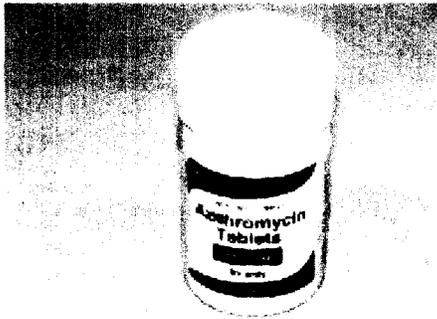
Claimed active ingredient and strength (from package label): Azithromycin monohydrate equivalent to 250 mg azithromycin

Inactive Ingredients (as listed in package insert): croscarmellose sodium, dibasic calcium phosphate anhydrous, hypromellose, lactose monohydrate, polyethylene glycol, magnesium stearate, microcrystalline cellulose, partially pregelatinized starch, sodium citrate, sodium lauryl sulfate, titanium dioxide, FD&C Blue #2 (500 mg only).

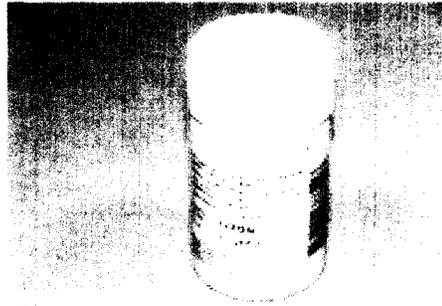
Test sample details: 250 mg tablets in bottle, Lot No. 337115A, expiration date 11/2007. Oval, white tablets debossed with "PLIVA" on one side and "787" on opposite side. Weight of one representative tablet recorded in laboratory as 382.12 mg.

Chain of custody: The samples were purchased from AmerisourceBergen, 101 Norfolk Street, Mansfield, MA 02048, USA and sent directly to Pfizer GQAR, Eastern Point Road, Groton, CT 06340, USA for testing. The 250 mg bottle was received in the laboratory with the safety seal intact.

Figure 1. Pliva Azithromycin (azithromycin) 250 mg tablets – Photographs and details of samples received at Pfizer GQAR laboratory in Groton.



A – bottle (front)



B- bottle (back)



C- tablets

Manufactured by: PLIVA Hrvatska d.o.o., Zagreb, Croatia for PLIVA®, Inc., East Hanover, NJ 07936

Claimed active ingredient and strength (from package label): Azithromycin monohydrate equivalent to 500 mg azithromycin

Inactive Ingredients (as listed in package insert): croscarmellose sodium, dibasic calcium phosphate anhydrous, hypromellose, lactose monohydrate, polyethylene glycol, magnesium stearate, microcrystalline cellulose, partially pregelatinized starch, sodium citrate, sodium lauryl sulfate, titanium dioxide, FD&C Blue #2 (500 mg only).

Test sample details: 500 mg tablets in bottle, Lot No. 323125B, expiration date 12/2007. Oval, blue-coated tablets debossed with "PLIVA" on one side and "788" on opposite side. Weight of one representative tablet recorded in laboratory as 762.93 mg.

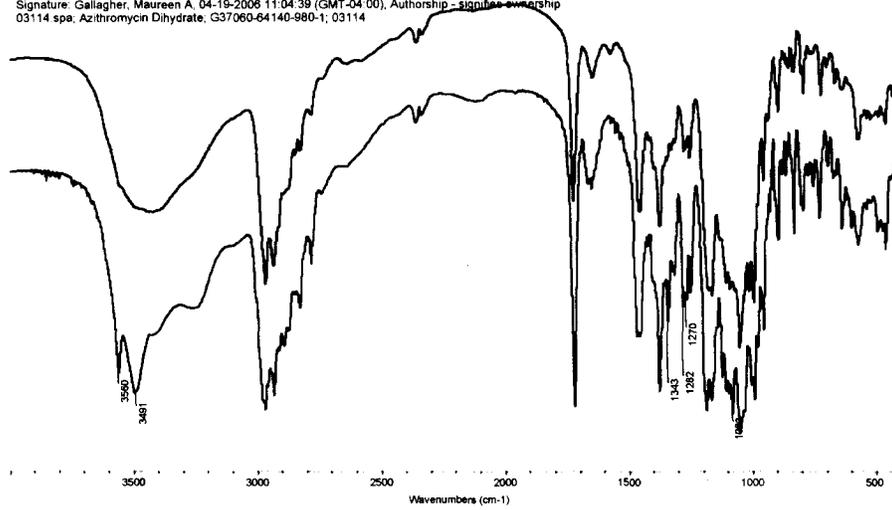
Chain of custody: The samples were purchased from AmerisourceBergen, 101 Norfolk Street, Mansfield, MA 02048, USA and sent directly to Pfizer GQAR, Eastern Point Road, Groton, CT 06340, USA for testing. The 500 mg bottle was received in the laboratory with the safety seal intact.

Figure 2. Pliva Azithromycin (azithromycin) 500 mg tablets – Photographs and details of samples received at Pfizer GQAR laboratory in Groton.

A

Azithromycin 250mg IP06022 Lot #337115A by KBR Mon Apr 03 09:45:16 2006 (GMT-04:00)
03114 spa: Azithromycin Dihydrate, G37060-64140-980-1, 03114

Signature: Gallagher, Maureen A, 04-19-2006 11:04:39 (GMT-04:00), Authorship - signifies ownership
03114 spa: Azithromycin Dihydrate, G37060-64140-980-1, 03114



B

Azithromycin 250mg IP06022 Lot #337115A by KBR Mon Apr 03 09:45:16 2006 (GMT-04:00)
03114 spa: Azithromycin Dihydrate, G37060-64140-980-1, 03114

Signature: Gallagher, Maureen A, 04-19-2006 11:04:39 (GMT-04:00), Authorship - signifies ownership
03114 spa: Azithromycin Dihydrate, G37060-64140-980-1, 03114

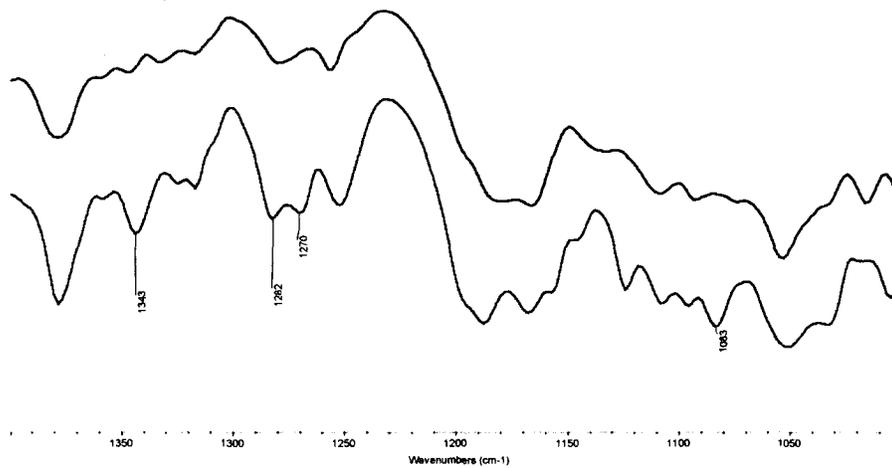
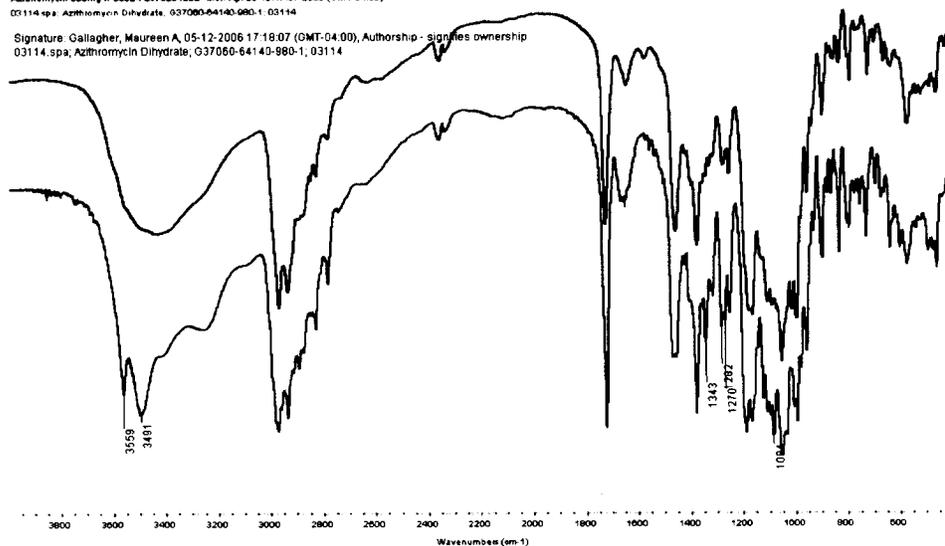


Figure 3. FTIR spectra of Pliva azithromycin 250 mg tablet (upper trace, blue) and azithromycin dihydrate lot G37060-64140-980-1 (lower trace, red) shown: **(A)** full scale from 4000 cm^{-1} – 400 cm^{-1} and **(B)** expanded scale from 1400 cm^{-1} – 1000 cm^{-1} range. The analysis indicated that azithromycin dihydrate was not detected in the sample.

A

Azithromycin 500mg IP06024 Lot 3231258 Mon Apr 03 10:17:07 2006 (GMT-04:00)
03114.spe; Azithromycin Dihydrate; G37060-64140-980-1; 03114

Signature: Gallagher, Maureen A, 05-12-2006 17:18:07 (GMT-04:00), Authorship - signifies ownership
03114.spe; Azithromycin Dihydrate; G37060-64140-980-1; 03114



B

Azithromycin 500mg IP06024 Lot 3231258 Mon Apr 03 10:17:07 2006 (GMT-04:00)
03114.spe; Azithromycin Dihydrate; G37060-64140-980-1; 03114

Signature: Gallagher, Maureen A, 05-12-2006 17:18:07 (GMT-04:00), Authorship - signifies ownership
03114.spe; Azithromycin Dihydrate; G37060-64140-980-1; 03114

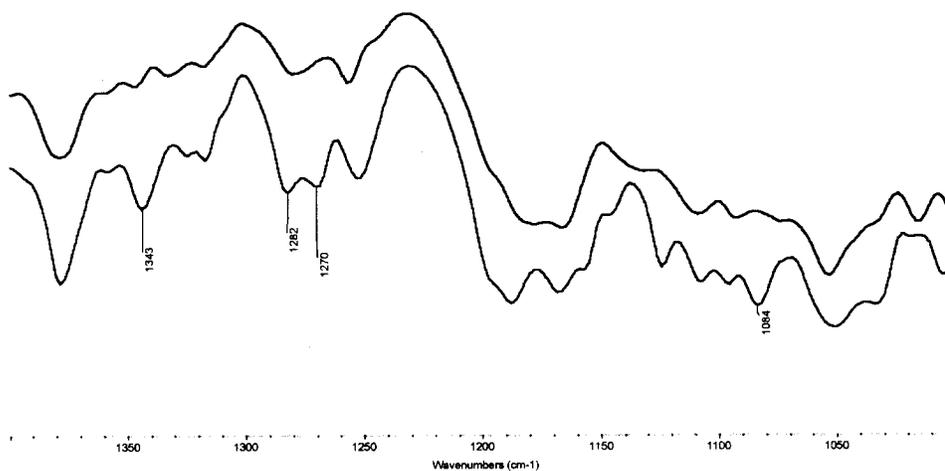


Figure 4. FTIR spectra of Pliva azithromycin 500 mg tablet (upper trace, blue) and azithromycin dihydrate lot G37060-64140-980-1 (lower trace, red) shown: (A) full scale from 4000 cm^{-1} – 400 cm^{-1} and (B) expanded scale from 1400 cm^{-1} – 1000 cm^{-1} range. The analysis indicated that azithromycin dihydrate was not detected in the sample.

IP06022 vs. AZITHROMYCIN DIHYDRATE QCRS

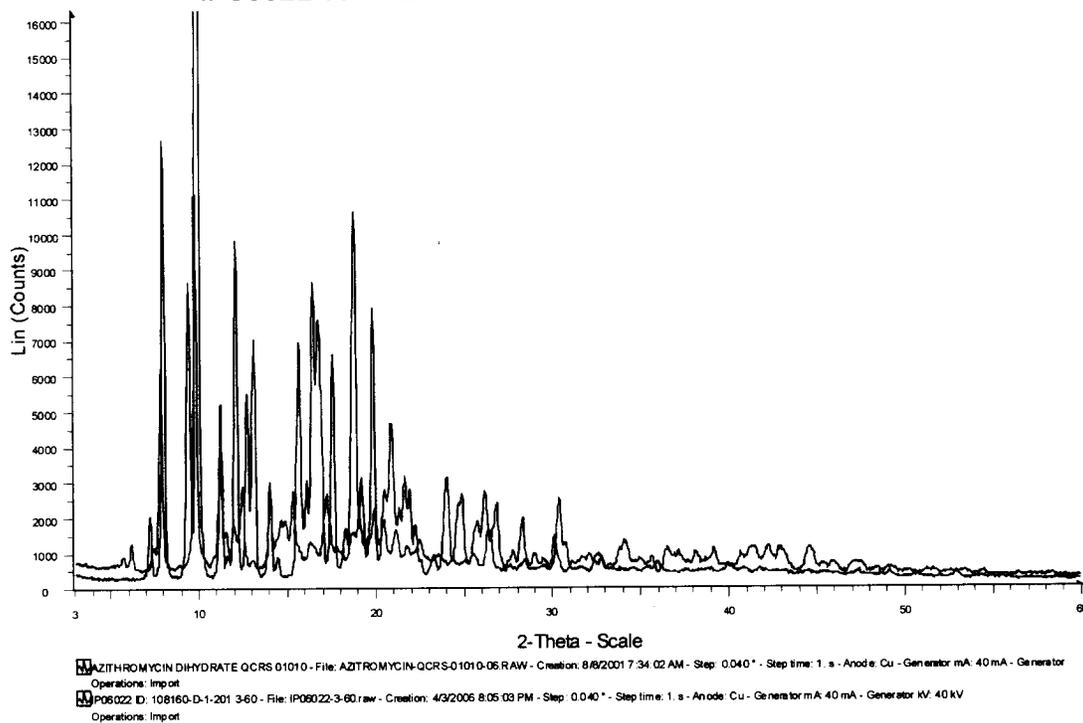


Figure 5. Overlay of diffractograms for Pliva azithromycin 250 mg tablet and azithromycin dihydrate (QCRS lot 01010QCS06). The absence of several diagnostic peaks for azithromycin dihydrate in the sample over range of 7 to 22 degrees in 2-theta indicated that azithromycin dihydrate was not detected.

IP06024 vs. AZITHROMYCIN DIHYDRATE QCRS

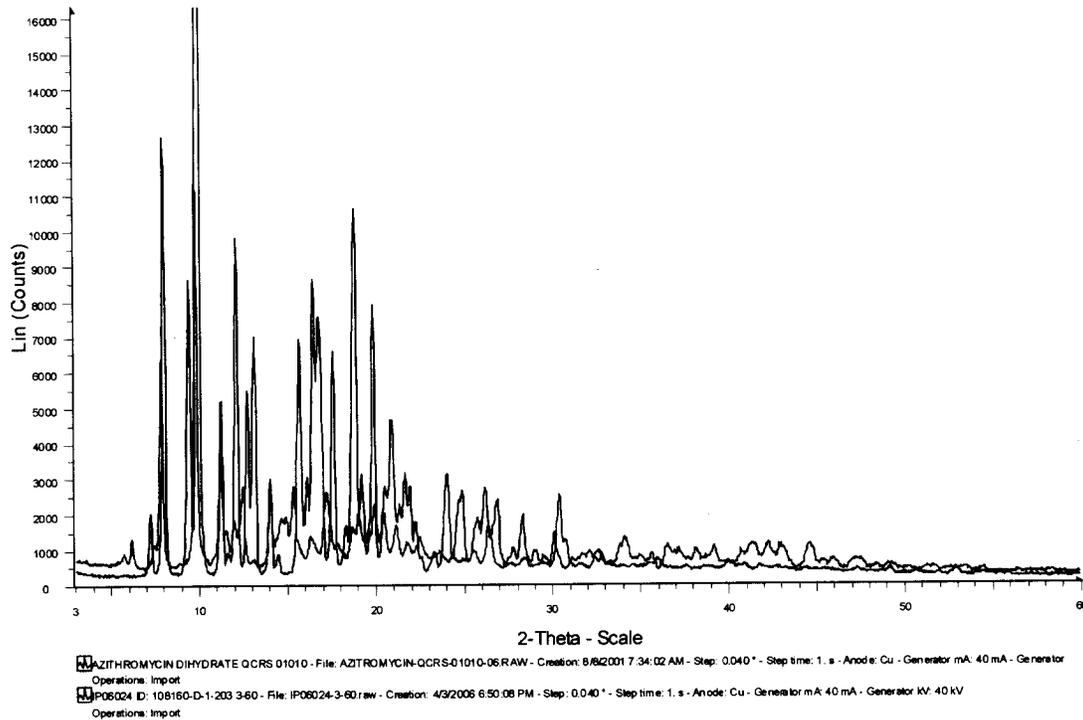


Figure 6. Overlay of diffractograms for Pliva azithromycin 500 mg tablet and azithromycin dihydrate (QCRS lot 01010-QCS06). The absence of several diagnostic peaks for azithromycin dihydrate in the sample over range of 7 to 22 degrees in 2-theta indicated that azithromycin dihydrate was not detected.

IP06022 vs. AZITHROMYCIN FORM G

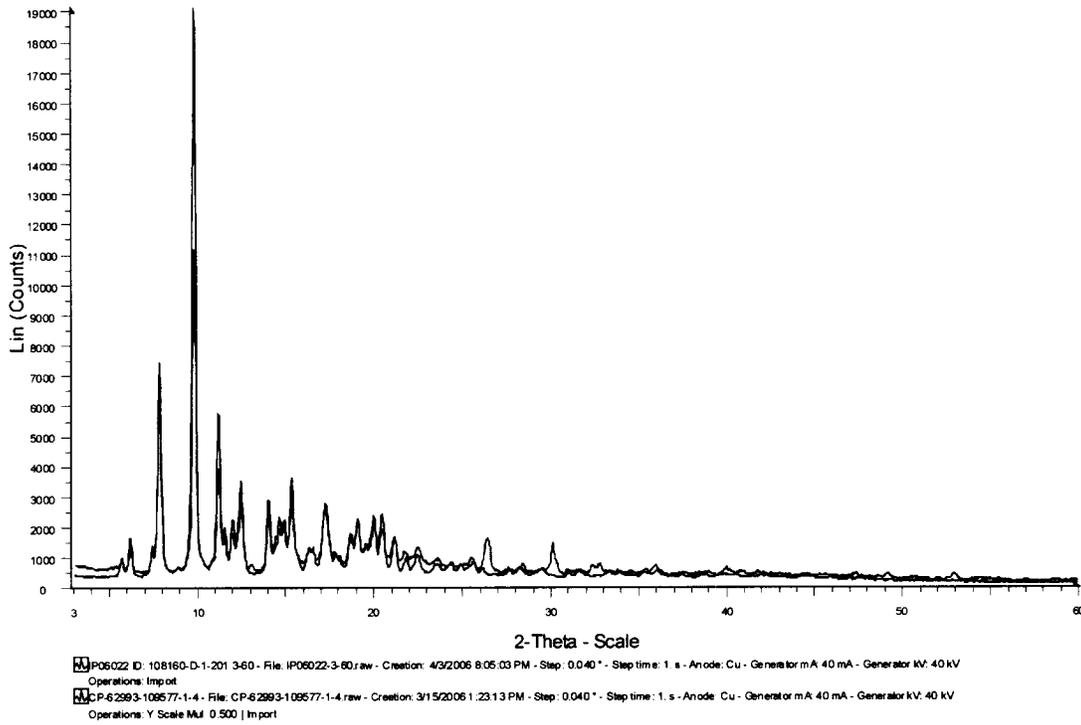


Figure 7. Overlay of diffractograms for Pliva azithromycin 250 mg tablet and azithromycin Form G reference material.

IP06024 vs. AZITHROMYCIN FORM G

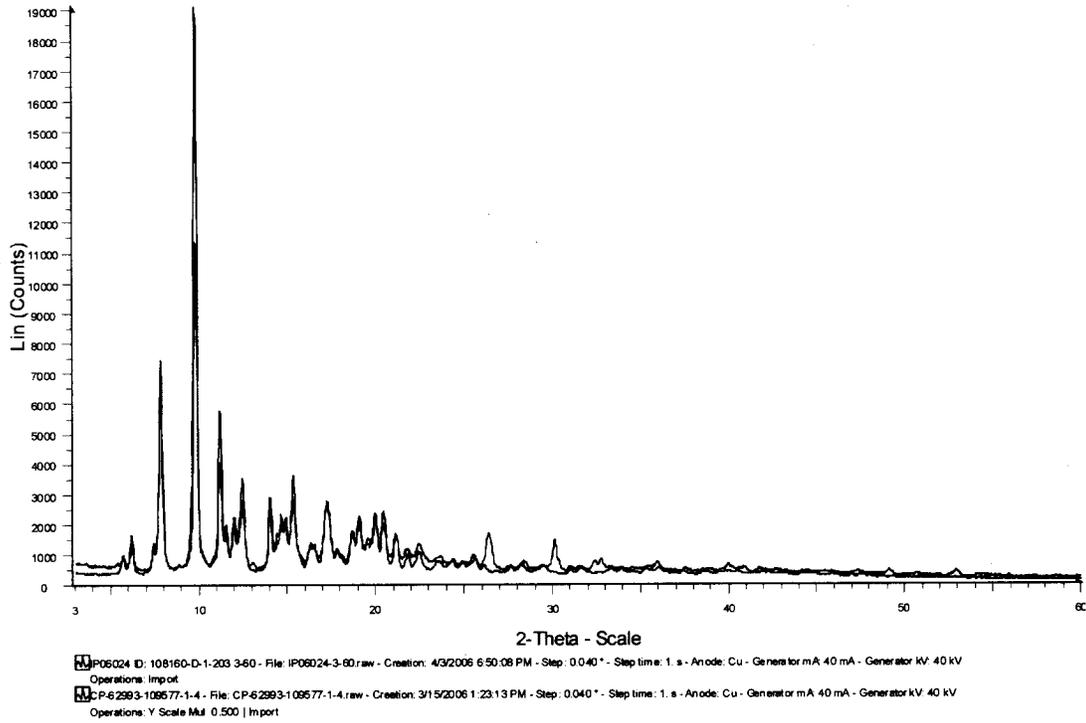


Figure 8. Overlay of diffractograms for Pliva azithromycin 500 mg tablet and azithromycin Form G reference material

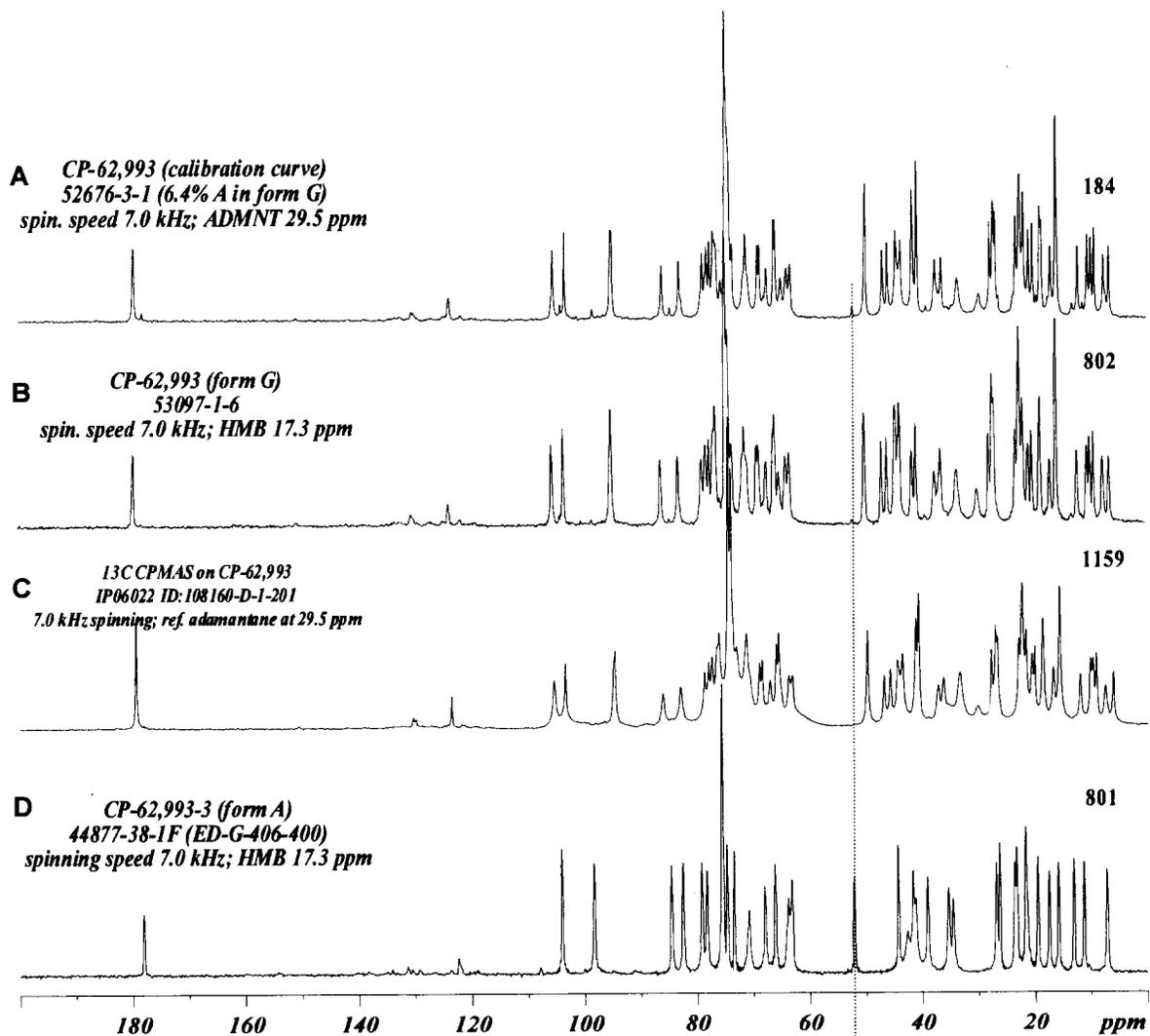


Figure 9. Comparison of ¹³C CPMAS ssNMR spectra of (A) mixed azithromycin standards containing 6.4% of Form A in otherwise pure Form G, (B) azithromycin Form G reference, (C) Pliva 250 mg tablet, and (D) azithromycin Form A reference. The Pliva 250 mg tablet ssNMR spectrum showed trace signals at 39.1 ppm, 52.2 ppm and 178.1 ppm, indicating presence of a trace amount of Form A. A detailed comparison of the carbon chemical shifts in ppm units for azithromycin Form G (from United States Patent No. 6,977,243) and corresponding azithromycin shifts for the 250 mg tablet is shown in Table 1.

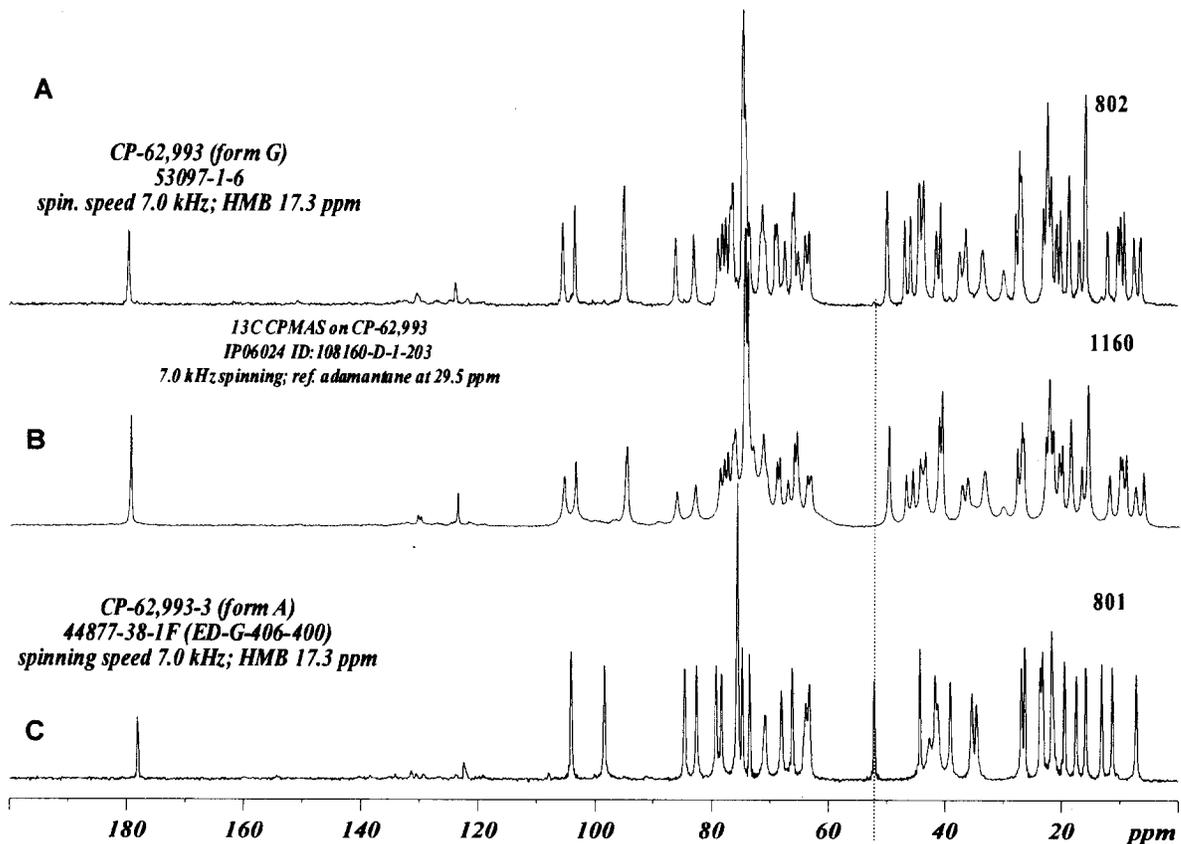
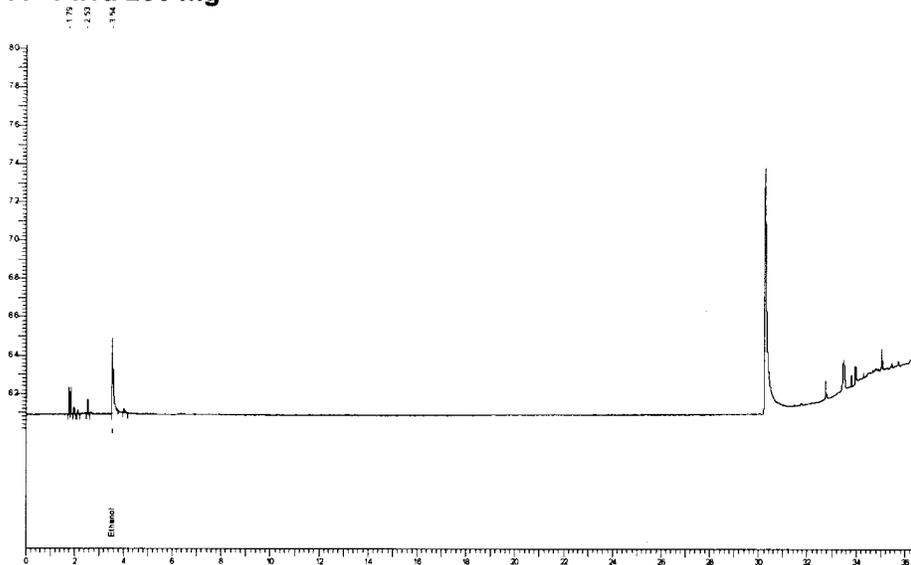


Figure 10. Comparison of ¹³C CPMAS ssNMR spectra of (A) azithromycin Form G reference, (B) Pliva 500 mg tablet, and (C) azithromycin Form A reference. No Form A signal was detected in the Pliva 500 mg tablet. A detailed comparison of the carbon chemical shifts in ppm units for azithromycin Form G (from United States Patent No. 6,977,243) and corresponding azithromycin shifts for the 500 mg tablet is shown in Table 1.

A - Pliva 250 mg



B - Pliva 500 mg

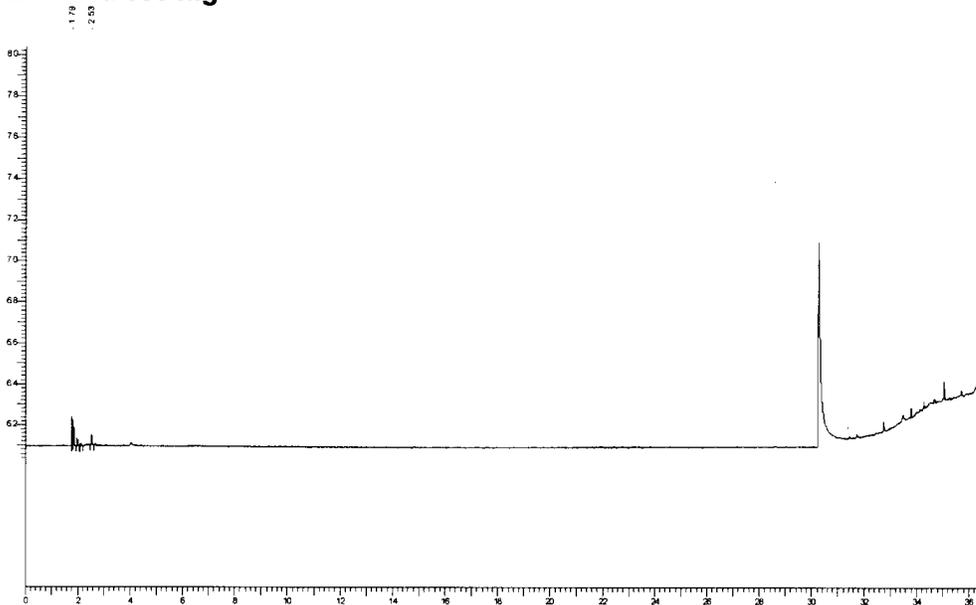


Figure 11. Headspace GC profiles for Pliva Azithromycin tablets: (A) 250 mg tablet and (B) 500 mg tablet. Only 250 mg tablet GC chromatogram (A) showed a ethanol peak at retention time of 3.54 min. System artifact peaks eluting after 30 minutes are from high boiling solvent contamination from previous (unrelated) testing. Overall, the system artifact peaks are minor and did not impact the conclusions from the headspace GC analyses.

Table 1. ¹³Carbon ssNMR shifts of azithromycin as listed for Form G in US 6,977,243 and shifts observed in spectra of the Pliva azithromycin samples shown in Figures 9 and 10. Of 49 peaks listed in the patent, 46 were identified (within the ± 0.2 accuracy limits) in each of the tablet samples. Exceptions (noted in footnotes below) were minor and do not preclude a positive identification of Form G in the samples.

250 mg tablet (ppm)	500 mg tablet (ppm)	Form G from Patent (accurate within ± 0.2 ppm)
179.5	179.5	179.5
105.6	105.6	105.5
103.6	103.6	103.5
94.8	94.8	95.0
86.3	86.3	86.2
83.1	83.1	83.1
78.9	78.9	78.9
78.2	78.2	78.2
77.6	77.6	77.6
76.4	76.4	76.4
(a)	(a)	75.7
74.7	74.7	74.7
74.3	74.3	74.3
73.3	73.3	73.5
71.5	71.5	71.3
69.2	69.2	69.1
68.7	68.7	68.8
67.3	67.3	67.4
65.8	65.8	65.9
(b)	(b)	65.2
64.0	64.0	64.0
63.4	63.4	63.3
50.0	50.0	50.0
47.1	47.1	46.9
46.0	46.0	46.0
44.7	44.7	44.5
43.8	43.8	43.7
41.5	41.5	41.5
41.0	40.9	40.8
37.5	37.5	37.5
36.5	36.5	36.5
33.7	33.6	33.6
30.4 (c)	30.4 (c)	30.0
28.0	28.0	27.9
27.3	27.3	27.3
23.2	23.2	23.1
22.6	22.6	22.5
21.9	21.9	21.9
20.8	20.8	20.9
20.3	20.3	20.2
18.9	18.9	18.8
17.0	17.0	17.0
15.9	15.9	16.0
12.2	12.2	12.2
10.4	10.4	10.4
10.0	10.0	9.9
9.4	9.4	9.3
7.8	7.8	7.6
6.4	6.4	6.5

- (a) Low intensity peak in the standard of Form G. Most likely overlapped with excipient signals in the sample.
 (b) Peak detected as a shoulder with no defined maximum.
 (c) Peak detected but outside ± 0.2 ppm window.