3.2.S.3.1 Elucidation of the Structure and Other Characteristics

This section consists of two parts: *Elucidation of the Structure of Irbesartan* includes data obtained from spectroscopic studies and their interpretation in support of the proposed chemical structure; and *Physicochemical Characterization* provides informations on the morphology, hygroscopicity, solubility, particle size distribution and other physical characteristics.

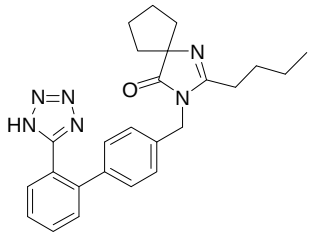
1. Elucidation of the Structure of Irbesartan

1.1 General information

The chemical structure of Irbesartan, manufactured at the facilities of Changjiang Pharm was well characterized by HEC Pharm R&D Center. The elemental analysis of C, H, N was conducted by the Instrumental Analysis & Research Center of Sun Yat-Sen University, Guangzhou.

Information on the Irbesartan sample and USP Reference Standard (RS) used in the chemical structure elucidation are presented below:

Table 3.2.S.3.1-1 Information on the Irbesartan Sample and USP RS

In-house Sample	
Batch Number	IRB-1208001
Chemical Structure	
Molecular Formula	$C_{25}H_{28}N_6O$
Molecular Weight	428.5g/moL
USP Reference Standard	
Batch Number	G0H216

The in-house sample of Irbesartan was produced using the current manufacturing process in Changjiang Pharm. Detailed information regarding the manufacturing process and its control is presented in section *3.2.S.2.2 Description of Manufacturing Process and Process Controls*.

The chemical structure of Irbesartan was elucidated by elemental analysis, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS).The detailed structure analysis is presented in the following pages.

1.2 Elemental Analysis

Instrument: Elementary Vario EL

Results: Elemental analysis results are shown in Table 3.2.S.3.1-2.

Table 3.2.S.3.1-2 Elemental Analysis Results of Irbesartan

Name of Sample	Determination	Mass Percentage (%)		
		C	H	N
In house sample (IRB-1208001)	1st	69.97	6.60	19.60
	2nd	69.95	6.57	19.58
Theoretical value	-	70.07	6.59	19.61

Analysis: The results show that the mass percentages of the elements C, H, N in the sample are basically consistent with their theoretical values calculated based on molecular formula of $C_{25}H_{28}N_6O$.

1.3 Ultraviolet Spectroscopy

Instrument: Varian (Agilent) Carry 50 UV spectrophotometer

Solution: Separately dissolve samples of Irbesartan and USP Irbesartan RS in methanol, 0.1 mol/L hydrochloric acid - methanol solution and 0.1 mol/L sodium hydroxide - methanol solution.

Analysis: The maximum absorption wavelengths of the solutions are listed in the following table:

Table 3.2.S.3.1-3 UV Analysis Results of Irbesartan

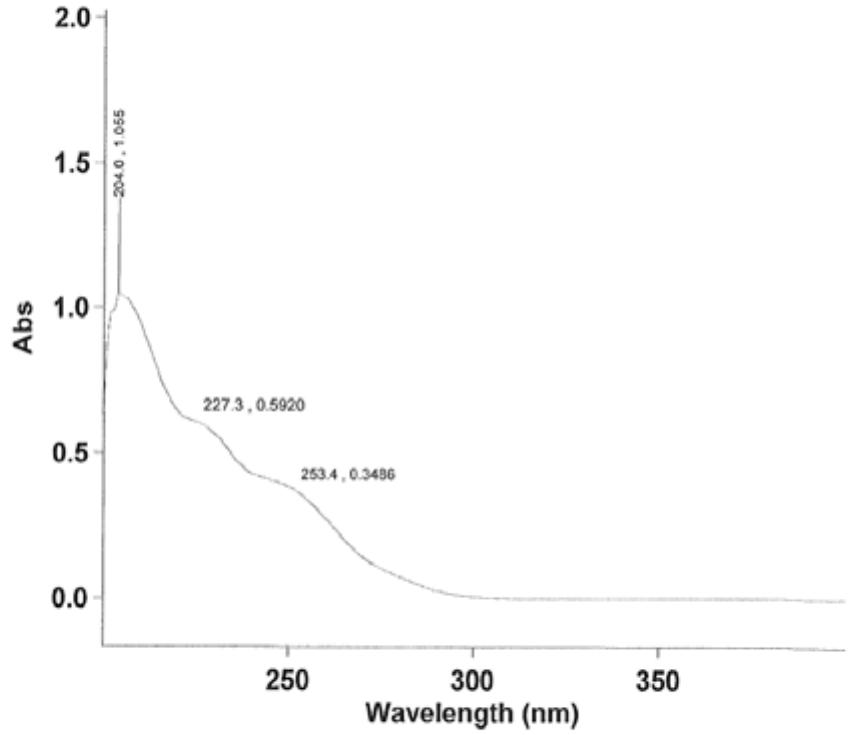
Solution		λ_{max1} (nm)	λ_{max2} (nm)	λ_{max3} (nm)
Methanol	Sample	204.0	227.3	253.4
	USP RS	204.0	227.8	252.1
0.1 mol/L Hydrochloric acid - methanol solution	Sample	204.0	226.0	249.0
	USP RS	205.0	226.4	247.4
0.1 mol/L Sodium hydroxide - methanol solution	Sample	-	216.0	251.4
	USP RS	-	217.1	251.7

Conclusion: The UV spectra produced by the sample of Irbesartan agree with those of the USP Irbesartan RS.

Spectra: The spectra obtained with the sample and USP Irbesartan RS are presented below under the following titles:

Abs

2012-9-26 21:48:24 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 09:47:13 PM 2012
Method:
Batch: E:\JGQZ\20120926\IRB-1208001-MeOH.DSW
Software version: 3.00(339)
Operator:

Sample Name: IRB-1208001

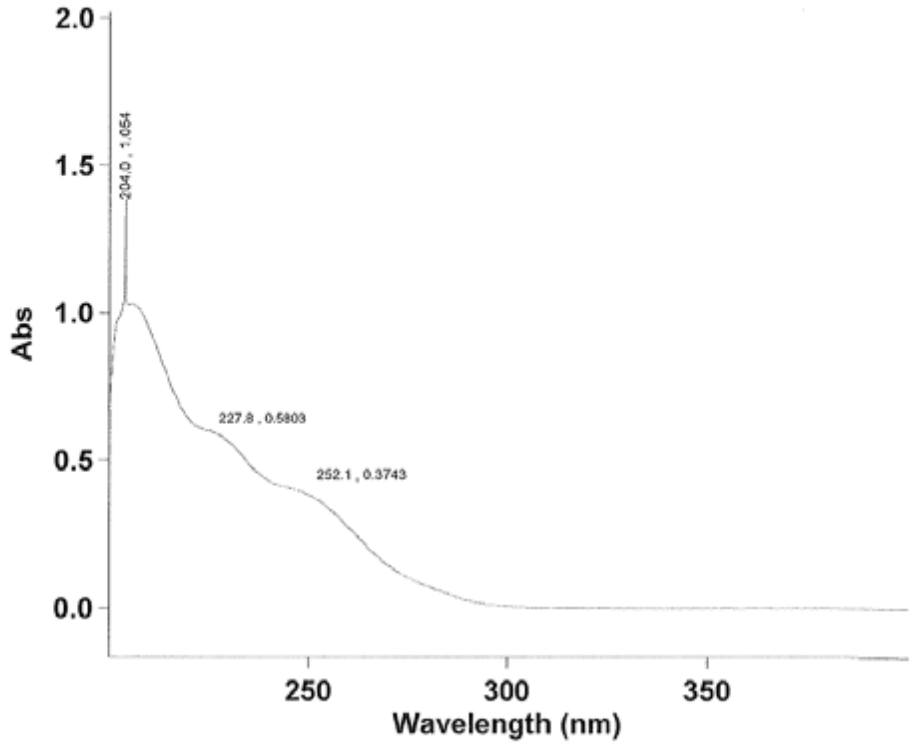
Collection Time	2012-9-26 21:47:17
Peak Table	
Peak Style	Peaks
Peak Threshold	0.0100
Range	399.9nm to 200.1nm

Wavelength (nm)	Abs
204.0	1.055

Fig 3.2.S.3.1-1 UV Spectrum of Irbesartan in methanol

A005

2012-9-26 21:51:10 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 09:50:08 PM 2012
Method:
Batch: E:\JGQZ\20120926\G0H216-MeOH.DSW
Software version: 3.00(339)
Operator:

Sample Name: G0H216

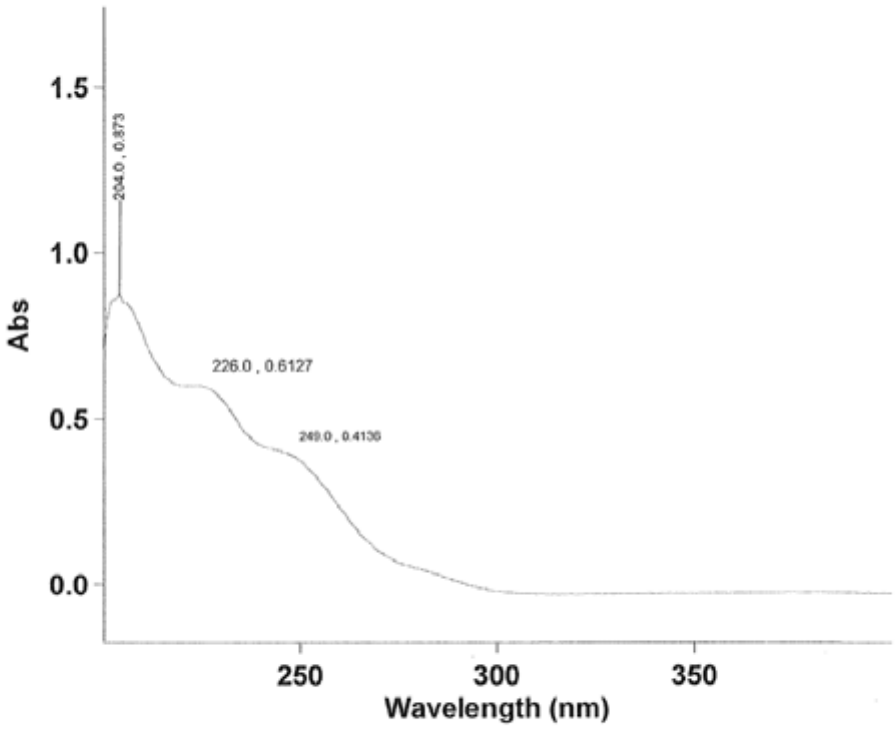
Collection Time	2012-9-26 21:50:11
Peak Table	
Peak Style	Peaks
Peak Threshold	0.0100
Range	399.9nm to 200.1nm

Wavelength (nm)	Abs
204.0	1.054

Fig 3.2.S.3.1-2 UV Spectrum of USP Irbesartan RS in methanol

A003

2012-9-26 20:53:40 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 08:50:01 PM 2012
Method:
Batch: E:\JCQZ\20120926\IRB-1208001-HCL.DSW
Software version: 3.00(339)
Operator:

Sample Name: IRB-1208001

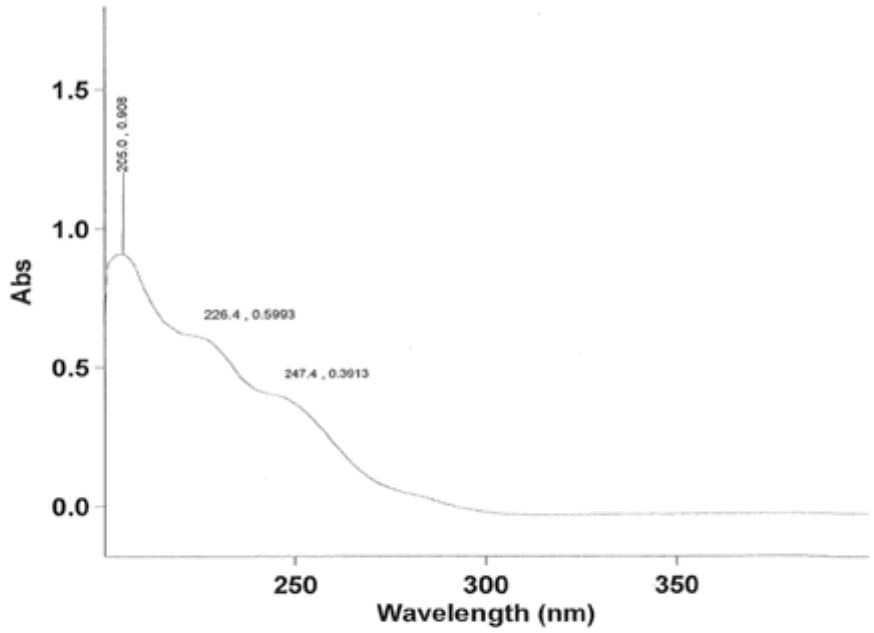
Collection Time	2012-9-26 20:50:06
Peak Table	
Peak Style	Peaks
Peak Threshold	0.0100
Range	399.9nm to 200.1nm

Wavelength (nm)	Abs
204.0	0.873

Fig 3.2.S.3.1-3 UV Spectrum of Irbesartan in 0.1 mol/L hydrochloric acid - methanol solution

A006

2012-9-26 20:39:48 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 08:38:22 PM 2012
Method:
Batch: E:\JGQZ\20120926\G0H216-HCL.DSW
Software version: 3.00(339)
Operator:

Sample Name: G0H216

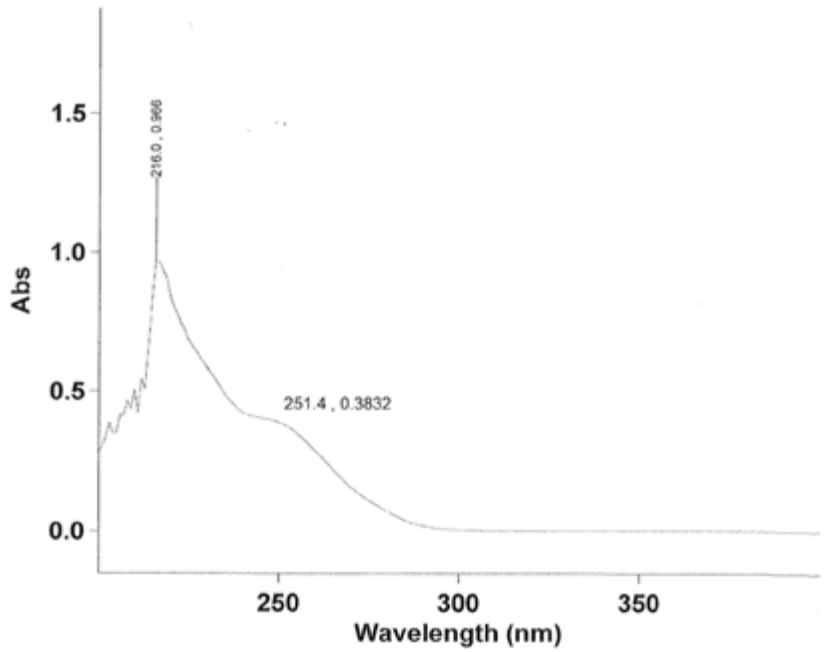
Collection Time	2012-9-26 20:38:26
Peak Table	
Peak Style	Peaks
Peak Threshold	0.0100
Range	399.9nm to 200.1nm

Wavelength (nm)	Abs
205.0	0.908

Fig 3.2.S.3.1-4 UV Spectrum of USP Irbesartan RS in 0.1 mol/L hydrochloric acid - methanol solution

A004

2012-9-26 21:29:58 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 09:28:18 PM 2012
Method:
Batch: E:\JGQZ\20120926\IRB-1208001-NaOH.DSW
Software version: 3.00(339)
Operator:

Sample Name: IRB-1208001
Collection Time 2012-9-26 21:28:23

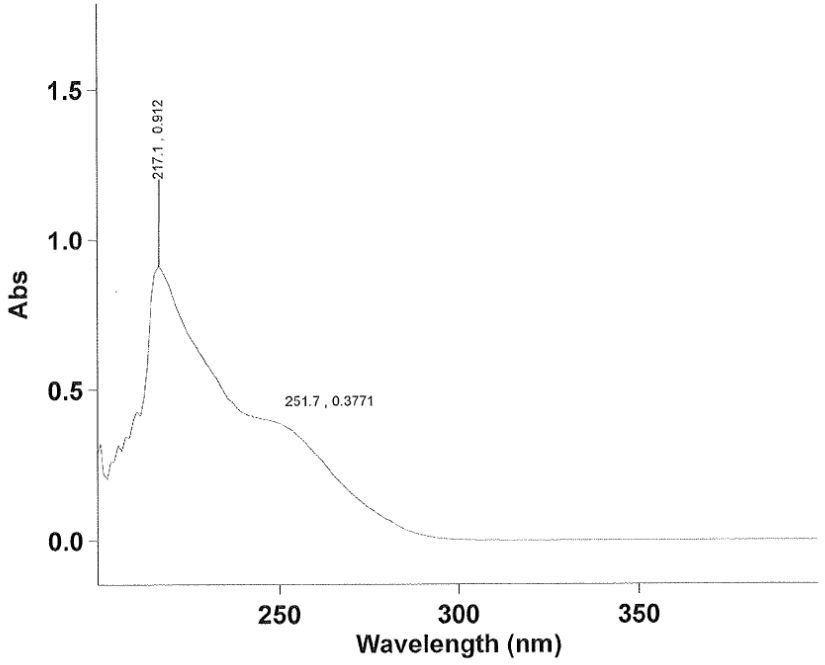
Peak Table
Peak Style Peaks
Peak Threshold 0.0100
Range 399.9nm to 200.1nm

Wavelength (nm)	Abs
216.0	0.966
212.0	0.545
210.0	0.505
207.9	0.468
203.1	0.386

Fig 3.2.S.3.1-5 UV Spectrum of Irbesartan in 0.1 M sodium hydroxide - methanol solution

A007

2012-9-26 21:22:36 Page 1 of 1



Scan Analysis Report

Report Time : 星期三 26 九月 09:21:25 PM 2012
Method:
Batch: E:\JGQZ\20120926\G0H216-NaOH.DSW
Software version: 3.00(339)
Operator:

Sample Name: G0H216

Collection Time	2012-9-26 21:21:29
Peak Table	
Peak Style	Peaks
Peak Threshold	0.0100
Range	399.9nm to 200.1nm

Wavelength (nm)	Abs
217.1	0.912
210.9	0.429
206.1	0.317
201.0	0.321

Fig 3.2.S.3.1-6 UV Spectrum of USP Irbesartan RS in 0.1 mol/L sodium hydroxide - methanol solution

1.4 Infrared Spectroscopy

Instrument: NICOLET IS10 Fourier Transform Infrared Spectrometer

Procedure: Grind 1 - 2 mg of the sample and 300 - 400 mg of potassium bromide matrix. Press the mixture to form a transparent disc. Test the sample at 400 - 4000 cm^{-1} and record the IR spectrum. Repeat the procedure with USP Irbesartan RS.

Result: The main absorption peaks and other relevant spectral information from the sample and USP Irbesartan RS are listed in Table 3.2.S.3.1-4.

Table 3.2.S.3.1-4 Comparative Data of the IR Spectra of Irbesartan

Absorption peak/cm^{-1}		Strength	Vibration type	Function Group
Sample	USP RS			
3438	3436	Weak	ν_{N-H}	-N-H
3061, 3031	3061, 3034	Weak	ν_{C-H}	Aromatic ring
2960, 2932, 2873	2960, 2932, 2873	Strong	ν_{C-H}	$-CH_2-$, $-CH_3$
1733	1733	Strong	$\nu_{C=O}$	-C=O
1618	1617	Strong	δ_{N-H}	-N-H
1435, 1408	1436, 1409	Middle -Strong	$\nu_{C=C}$	Aromatic ring
1337	1337	Middle -Strong	δ_{C-H}	$-CH_3$
758	758	Strong	δ_{C-H}	Aromatic ring

Conclusion: All the main vibration bands observed in IR spectrum from the sample are consistent with the structural moieties of Irbesartan. The IR spectrum of the sample is also concordant with that of the USP Irbesartan RS. Therefore, the IR spectrum strongly supports the molecular structure assigned to Irbesartan.

Spectra: The spectra obtained with the sample and USP Irbesartan RS are presented in the following pages with the title below.

Fig 3.2.S.3.1-7 IR Spectrum Obtained with the Sample

Fig 3.2.S.3.1-8 IR Spectrum Obtained with the USP Irbesartan RS

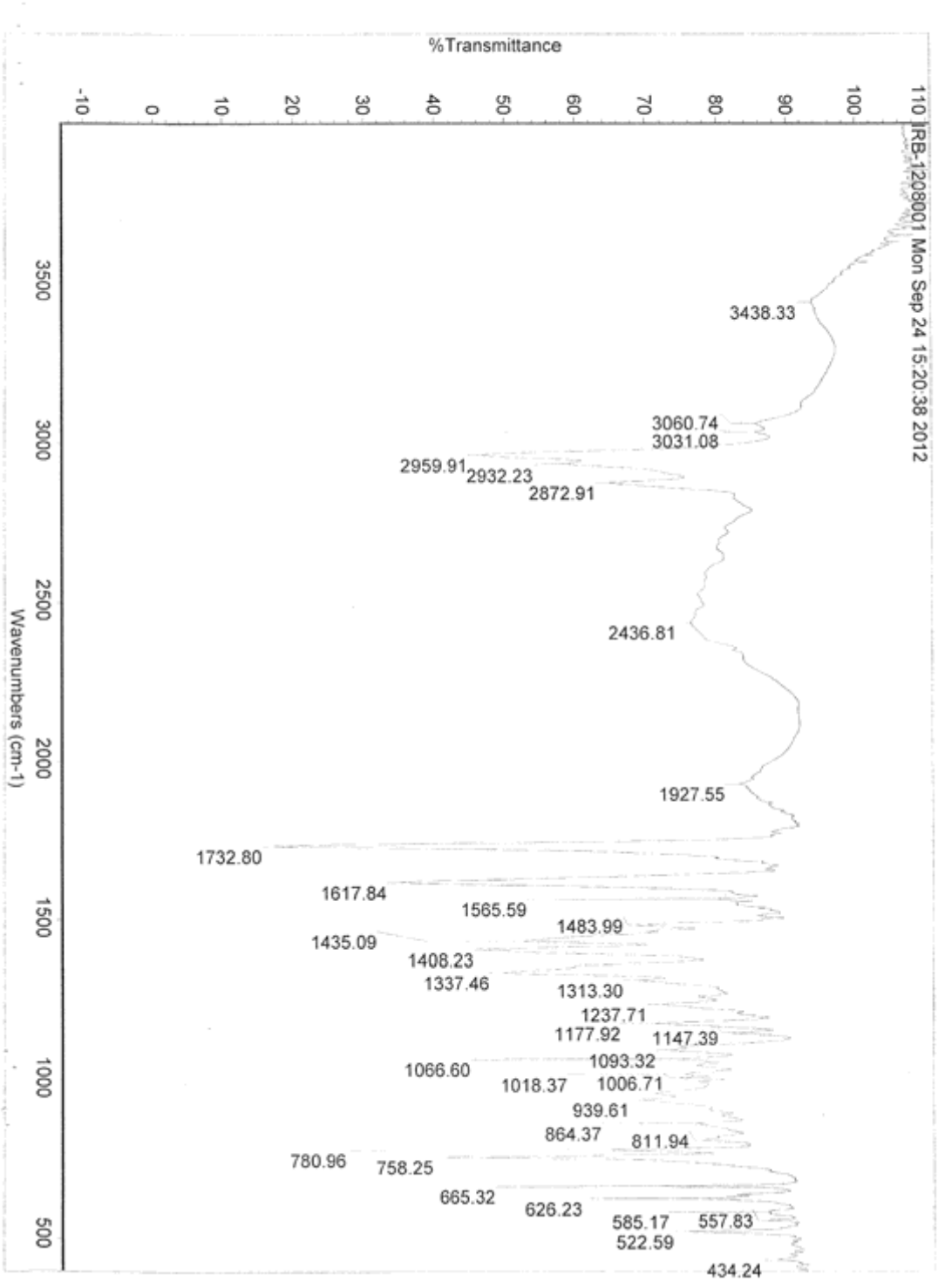


Fig 3.2.S.3.1-7 IR Spectrum Obtained with the Sample

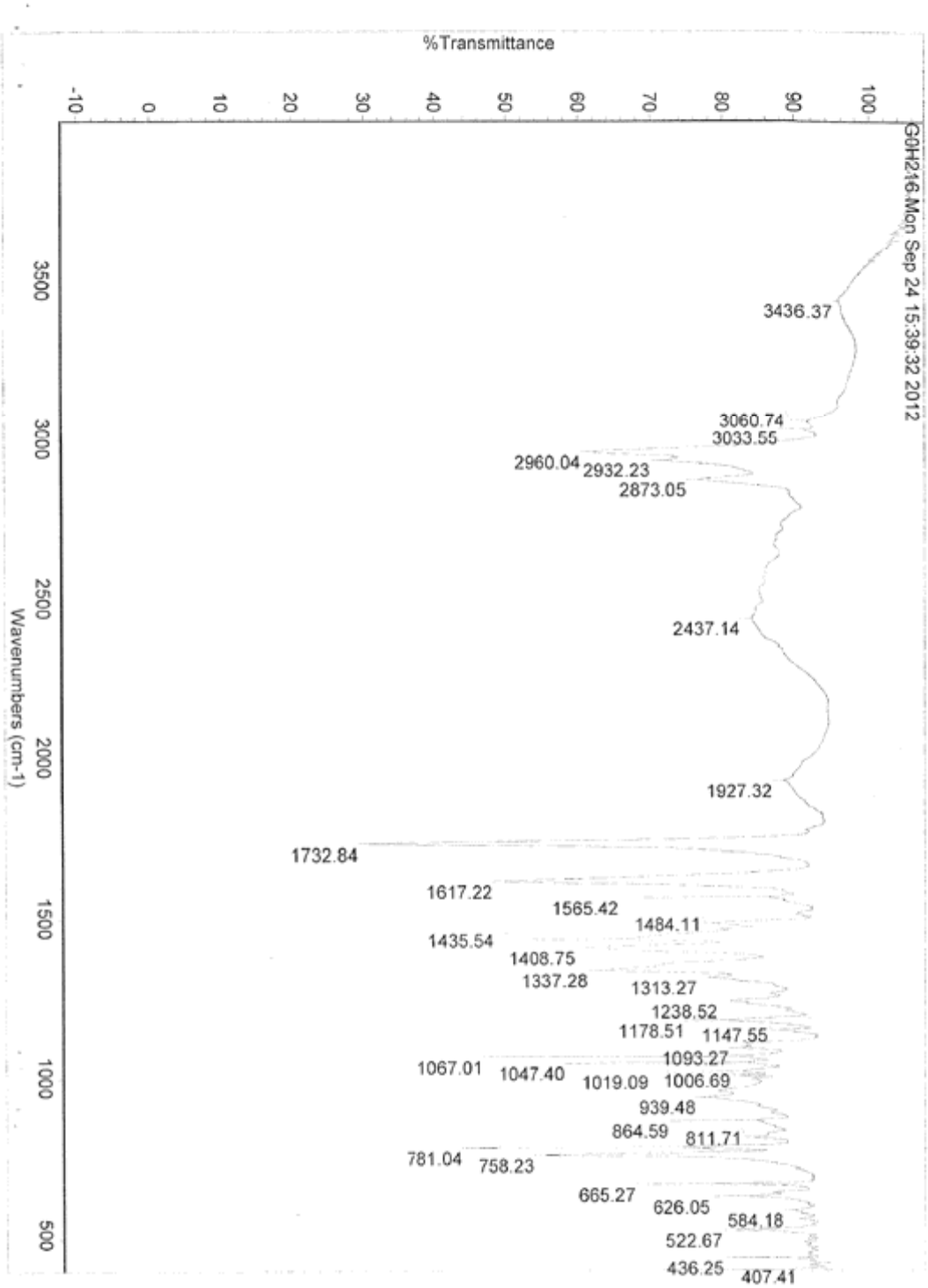


Fig 3.2.S.3.1-8 IR Spectrum Obtained with the USP Irbesartan RS

1.5 Nuclear Magnetic Resonance (NMR) Spectroscopy

Instrument: Superconducting Fourier Transform Nuclear Magnetic Resonance Spectrometry (Bruker AVANCE AV 400)

Condition: DMSO-d_6

Results: The data from the NMR spectra of the sample and USP Irbesartan RS are listed in the following tables.

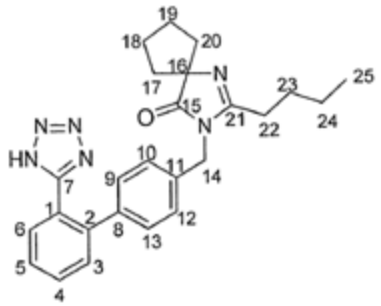


Table 3.2.S.3.1-5 ^{1}H- and ^{13}C-NMR Spectral Data

Serial No.	Chemical Shift δ_H (ppm)		Chemical Shift δ_C (ppm)	
	IRB-1208001	G0H216	IRB-1208001	G0H216
1	-	-	123.5	123.5
2	-	-	141.0	141.0
3	7.54	7.54	130.5	130.5
4	7.68	7.68	131.0	131.0
5	7.66	7.66	130.5	130.5
6	7.57	7.57	127.7	127.8
7	-	-	155.0	155.0
8	-	-	138.3	138.4
9	7.09	7.09	129.2	129.2
10	7.09	7.09	126.2	126.2
11	-	-	136.2	136.2
12	7.09	7.09	129.2	129.2
13	7.09	7.09	126.2	126.2
14	4.68	4.68	42.2	42.2
15	-	-	185.6	185.6
16	-	-	75.7	75.8
17	1.66	1.65	36.7	36.8
18	1.83	1.83	25.4	25.4

Serial No.	Chemical Shift δ_H (ppm)		Chemical Shift δ_C (ppm)	
	IRB-1208001	G0H216	IRB-1208001	G0H216
19	1.83	1.83	25.4	25.4
20	1.83	1.83	36.7	36.7
21	-	-	161.1	161.1
22	2.29	2.29	27.4	27.5
23	1.47	1.47	26.5	26.6
24	1.26	1.26	21.4	21.5
25	0.79	0.79	13.5	13.6

Conclusion: ^{1}H, ^{13}C spectra show that the number of proton, carbon in both the Irbesartan sample and USP Irbesartan RS are the same. The spectra are concordant.

Spectra: The spectra obtained with the in-house sample and USP Irbesartan RS are presented in the following pages with the titles below.

Fig 3.2.S.3.1-9 ^{1}H Spectrum of the In-house Irbesartan Sample

Fig 3.2.S.3.1-10 ^{1}H Spectrum of the USP Irbesartan RS

Fig 3.2.S.3.1-11 ^{13}C Spectrum of the In-house Irbesartan Sample

Fig 3.2.S.3.1-12 ^{13}C Spectrum of the USP Irbesartan RS

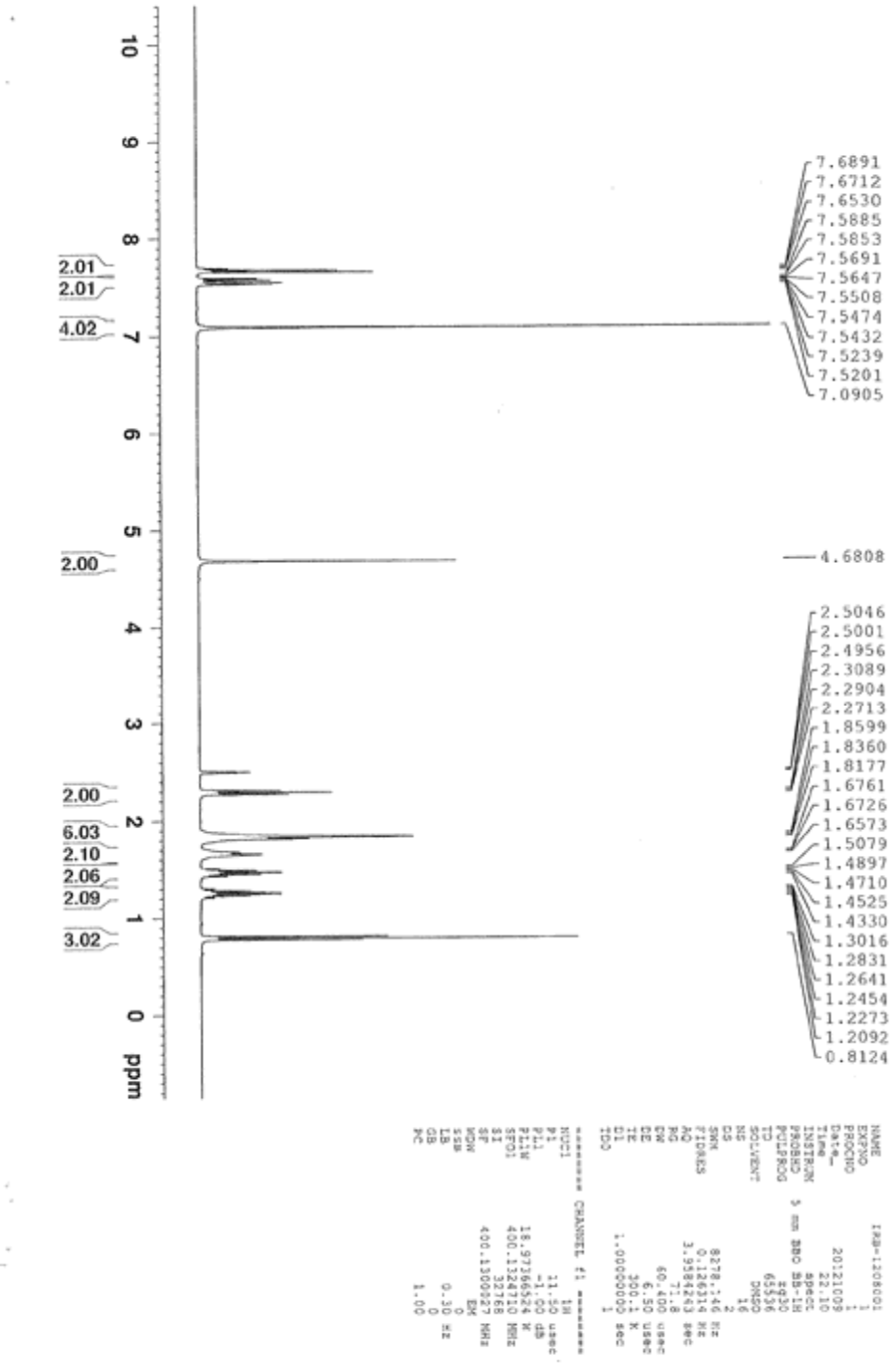


Fig 3.2.S.3.1-9 ^{1}H Spectrum of the In-house Irbesartan Sample

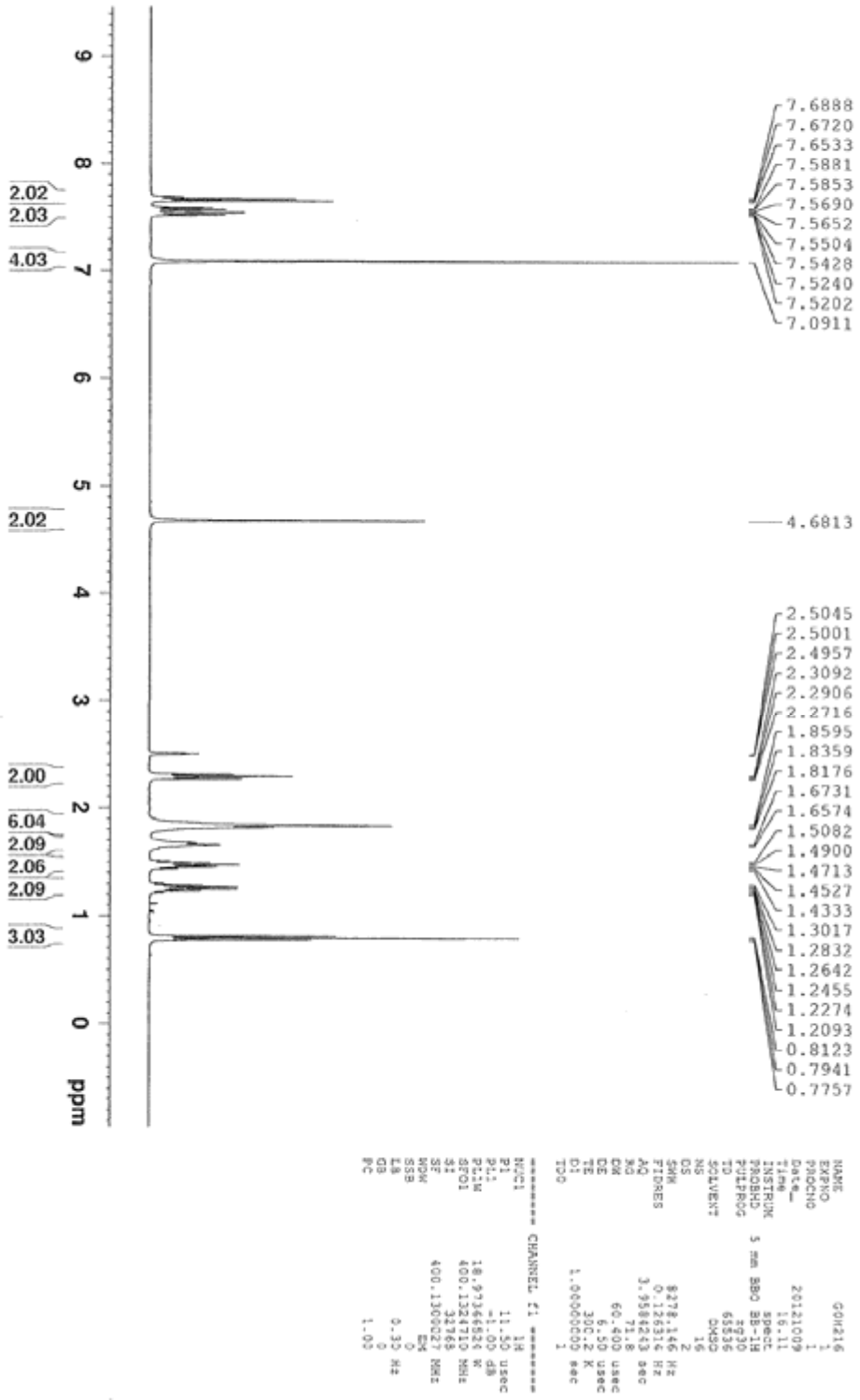


Fig 3.2.S.3.1-10 ^{1}H Spectrum of the USP Irbesartan RS

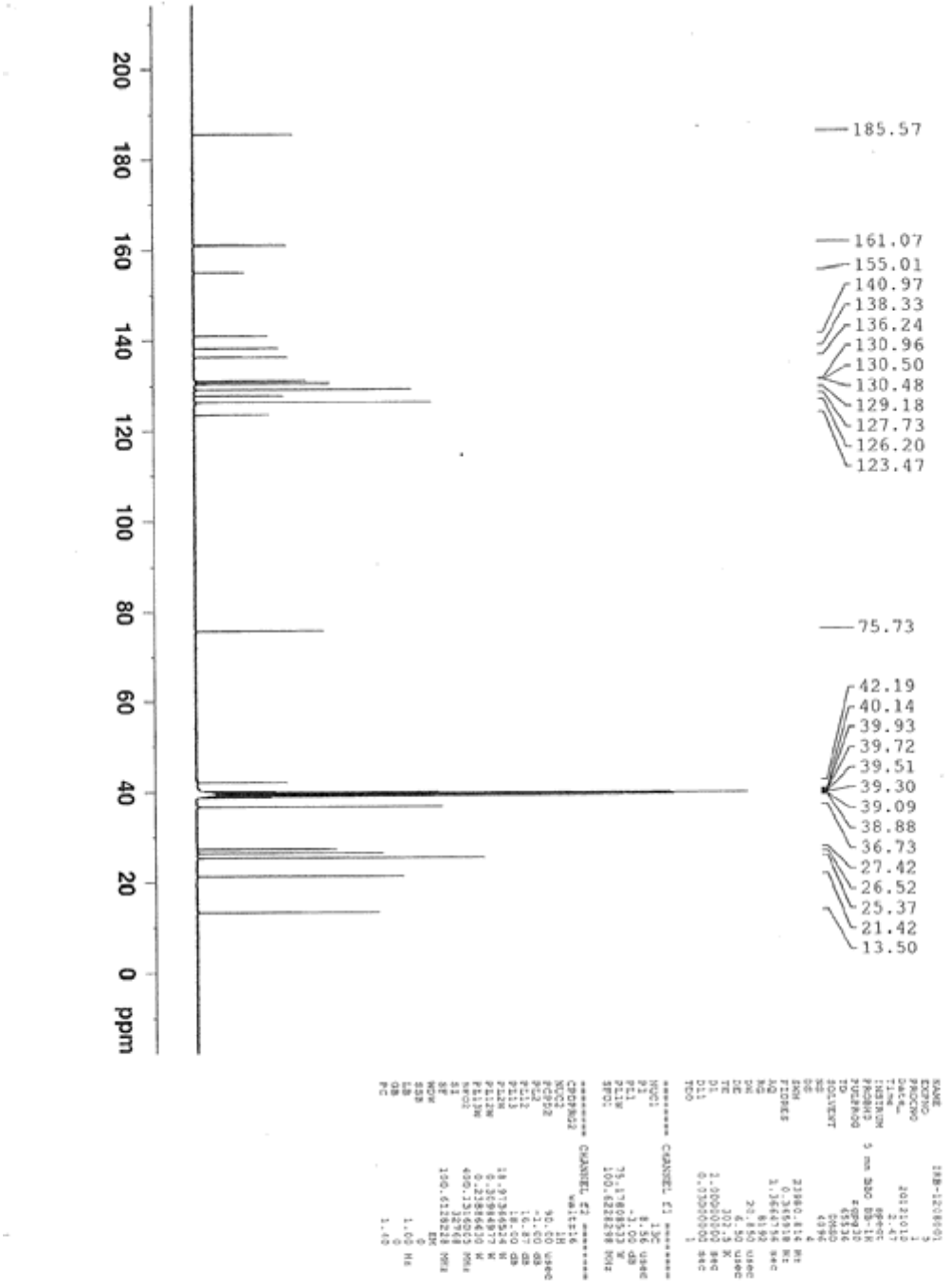


Fig 3.2.S.3.1-11 ^{13}C Spectrum of the In-house Irbesartan Sample

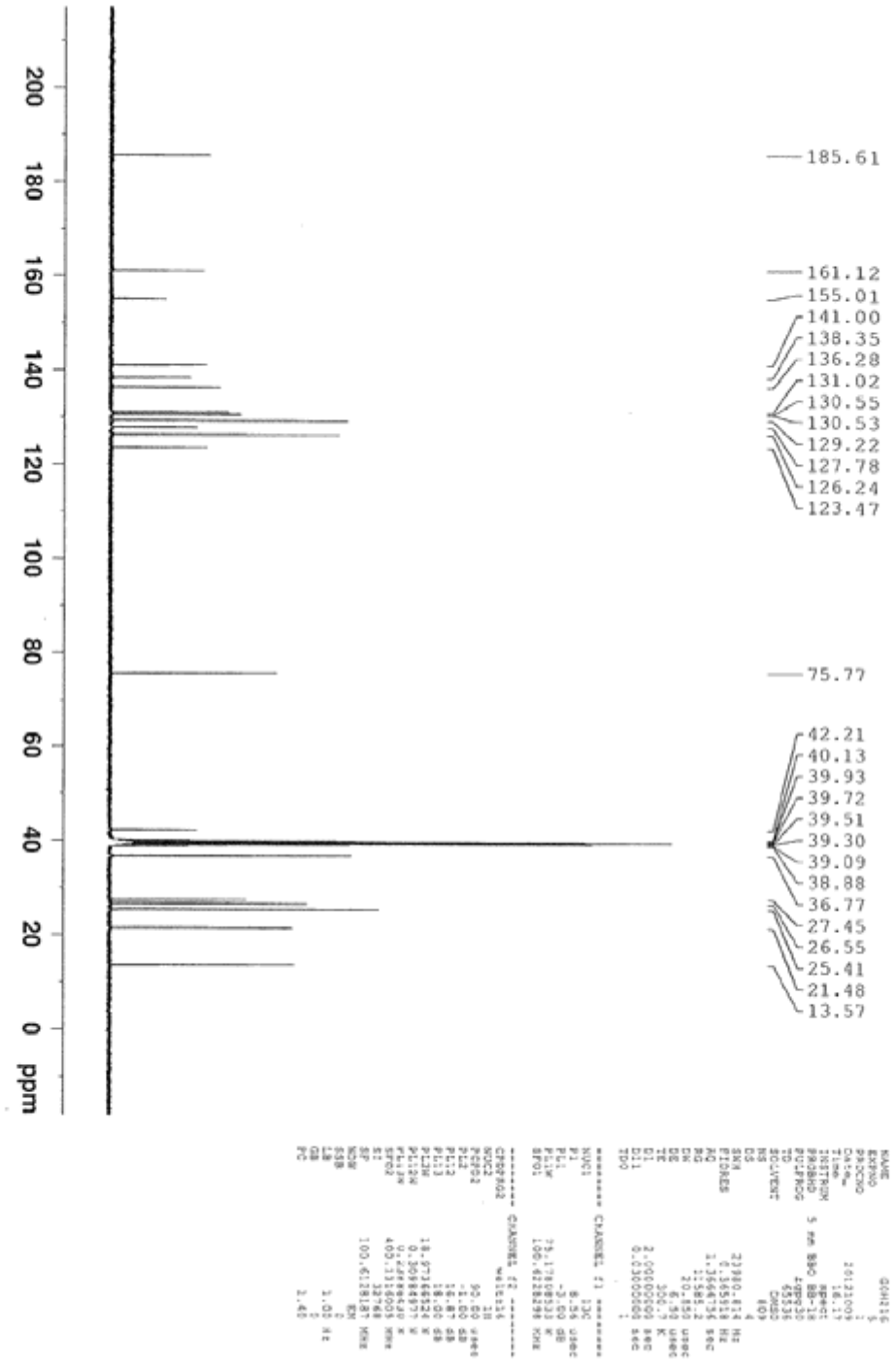


Fig 3.2.S.3.1-12 ^{13}C Spectrum of the USP Irbesartan RS

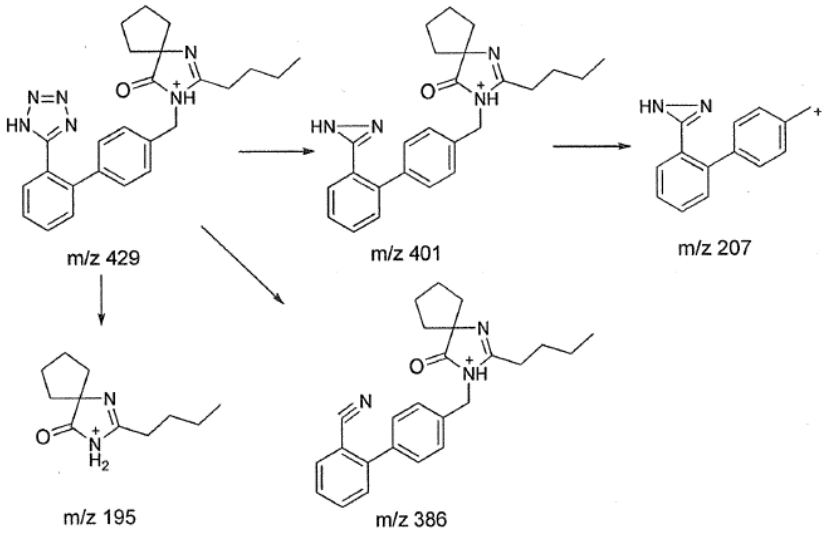
1.6 Mass Spectrometry

Instrument: Agilent 1200 HPLC, Agilent 6320 Iron Trap MS

Experimental condition: ESI Positive, AUTOMS (2) Mode

Results: Refer to the spectra presented in the following pages.

Analysis: The $[M + H]^+$ ion at m/z 429 obtained with ESI full scan mode suggests a molecular weight 428 which corresponds to the chemical structure proposed. With the AUTOMS (2) mode, the ion at m/z 429 produces 4 significant ions at m/z 401, 386, 207 and 195, respectively. The molecular fragments corresponding to these 4 ions and the MS fragmentation mechanism are shown below:



Spectra: The spectra obtained with in-house sample and USP Irbesartan RS are presented below with the following titles:

Fig 3.2.S.3.1-13MS Spectrum of the In-house Irbesartan Sample

Fig 3.2.S.3.1-14MS Spectrum of the USP Irbesartan RS

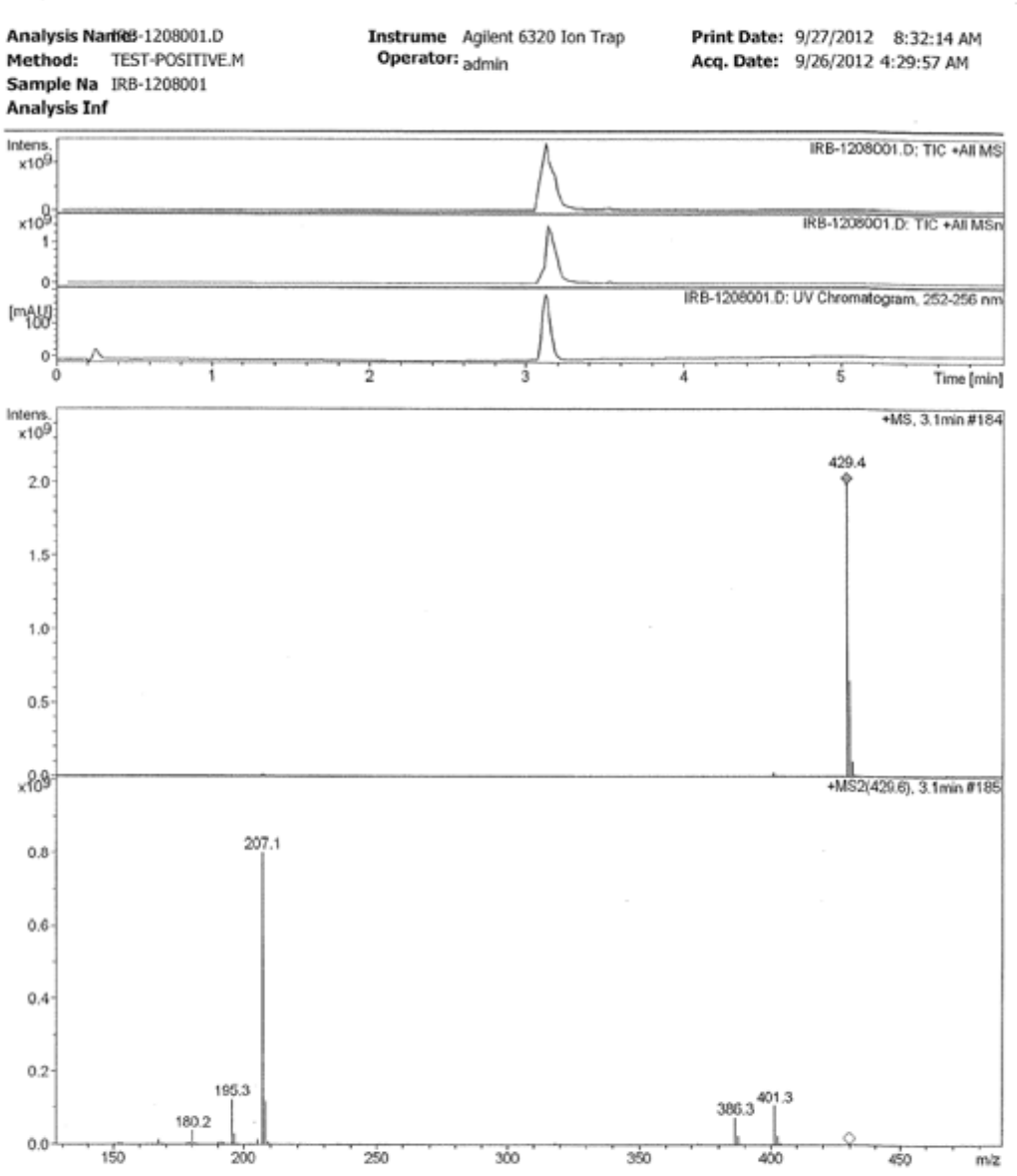


Fig 3.2.S.3.1-13MS Spectrum of the In-house Irbesartan Sample

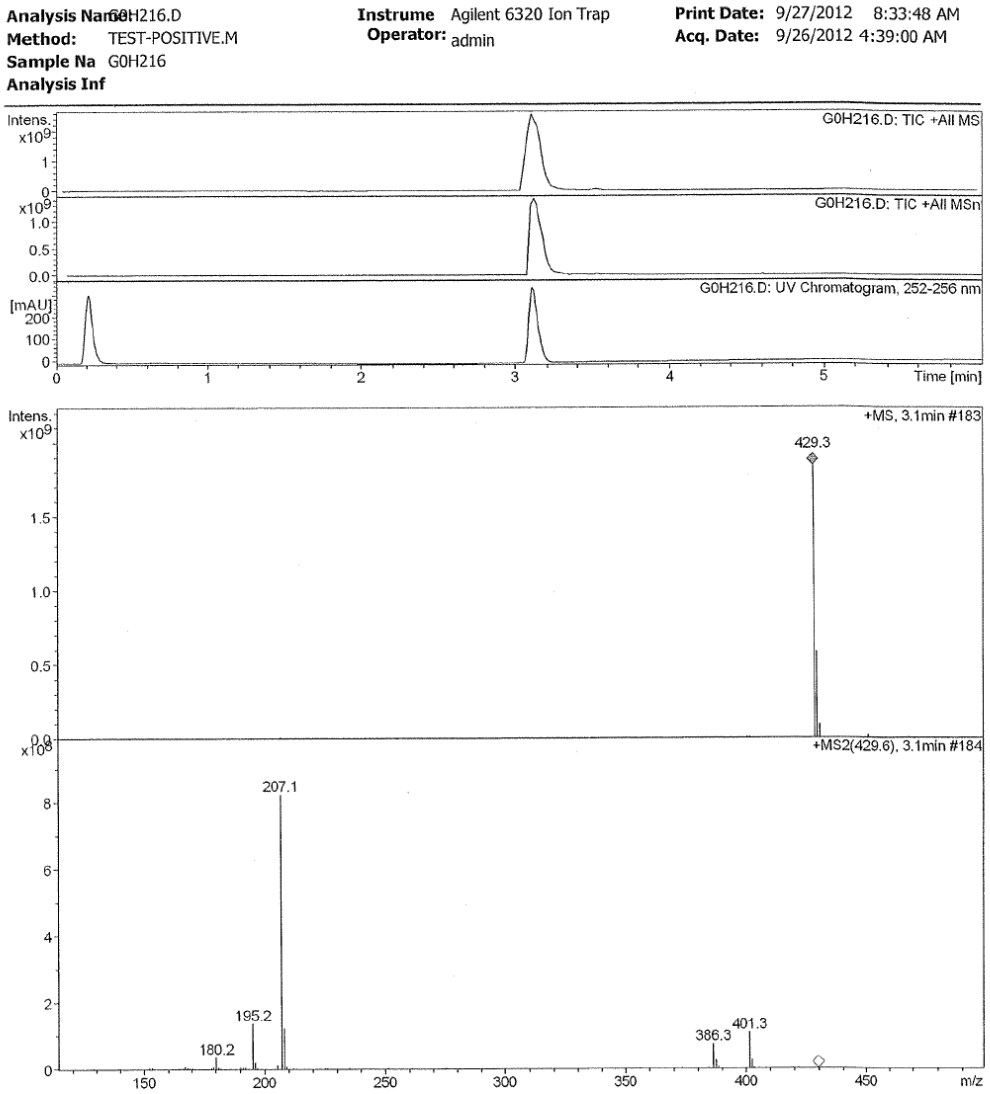


Fig 3.2.S.3.1-14MS Spectrum of the USP Irbesartan RS

1.7 Summary of the Structure Characterization Results

The elemental analysis results demonstrate that the content of C, H, N in the sample are basically consistent with the theoretical value and that of the USP Irbesartan RS.

The UV spectra obtained with the sample show the same maximum absorption wavelengths as those of the USP Irbesartan RS.

The IR spectrum of the sample is concordant with that of the USP Irbesartan RS, which indicates that the function groups of the in-house sample are consistent with those of the USP Irbesartan RS.

^{1}H NMR and ^{13}C NMR spectra show that the characteristics of the in-house sample are consistent with those of USP Irbesartan RS. The NMR spectra indicate that the structure of the in-house sample is consistent with the assigned Irbesartan structure.

The molecular formula of Irbesartan is $C_{25}H_{28}N_6O$. The $[M + H]^+$ ion at m/z 429 matches the molecular weight of Irbesartan, which is 428 theoretically. It is same as that obtained with USP Irbesartan RS.

2. Physicochemical Characterization

2.1 Physical Form

Lrbesartan manufactured at Changjiang Pharm is a white or almost white crystals or crystalline powder.

2.2 Odour

Lrbesartan is an odourless synthetic product.

2.3 Morphology

The crystalline form of Irbesartan manufactured at Changjiang Pharm is the form A with a lath shape, as determined by X-ray powder diffraction (XRD), thermal analysis (DSC and TGA) and polarizing microscope (PLM). The XRD, DSC, TGA and PLM results are described in the following section.

2.3.1Thermogravimetric Analysis (TGA)

Instrument: TA Q500 Thermo Gravimetric Analyzer

Experimental Conditions: TG heat increased from room temp to 350 °C at a rate of 10 °C per minute.

Results: The TGA results indicate that Irbesartan is stable before the fusion at about 184°C. The results of three submission batches are summarized in the table below.

Table 3.2.S.3.1-6 Thermo Gravimetric Analysis Results

IRB-1208001		**IRB-1208002**		**IRB-1208003**	
Temp.(^{o}C)	Weight loss (%)	Temp. (^{o}C)	Weight loss (%)	Temp. (^{o}C)	Weight loss(%)
28.4-150.3	0.046	28.1-150.3	0.132	25.9-150.3	0.128
> 184.8	decomposition	> 184.4	decomposition	> 184.4	decomposition

Spectra: The TGA spectra are presented below under the following titles:

Fig. 3.2.S.3.1-15a TGA Spectrum of the In-house Sample IRB-1208001

Fig. 3.2.S.3.1-15b TGA Spectrum of the In-house Sample IRB-1208002

Fig. 3.2.S.3.1-15c TGA Spectrum of the In-house Sample IRB-1208003

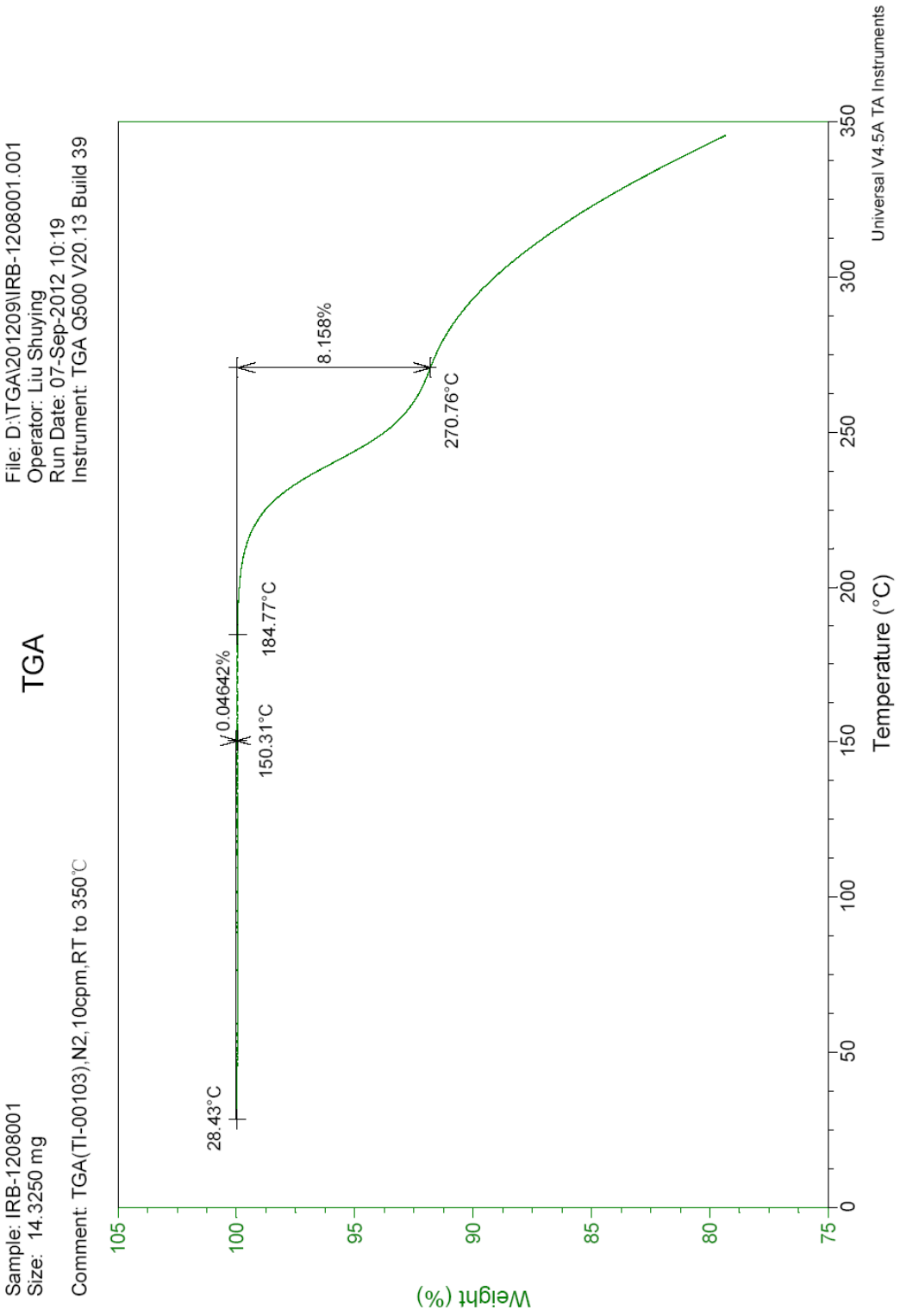


Fig. 3.2.S.3.1-15a TGA Spectrum of the In-house Sample IRB-1208001

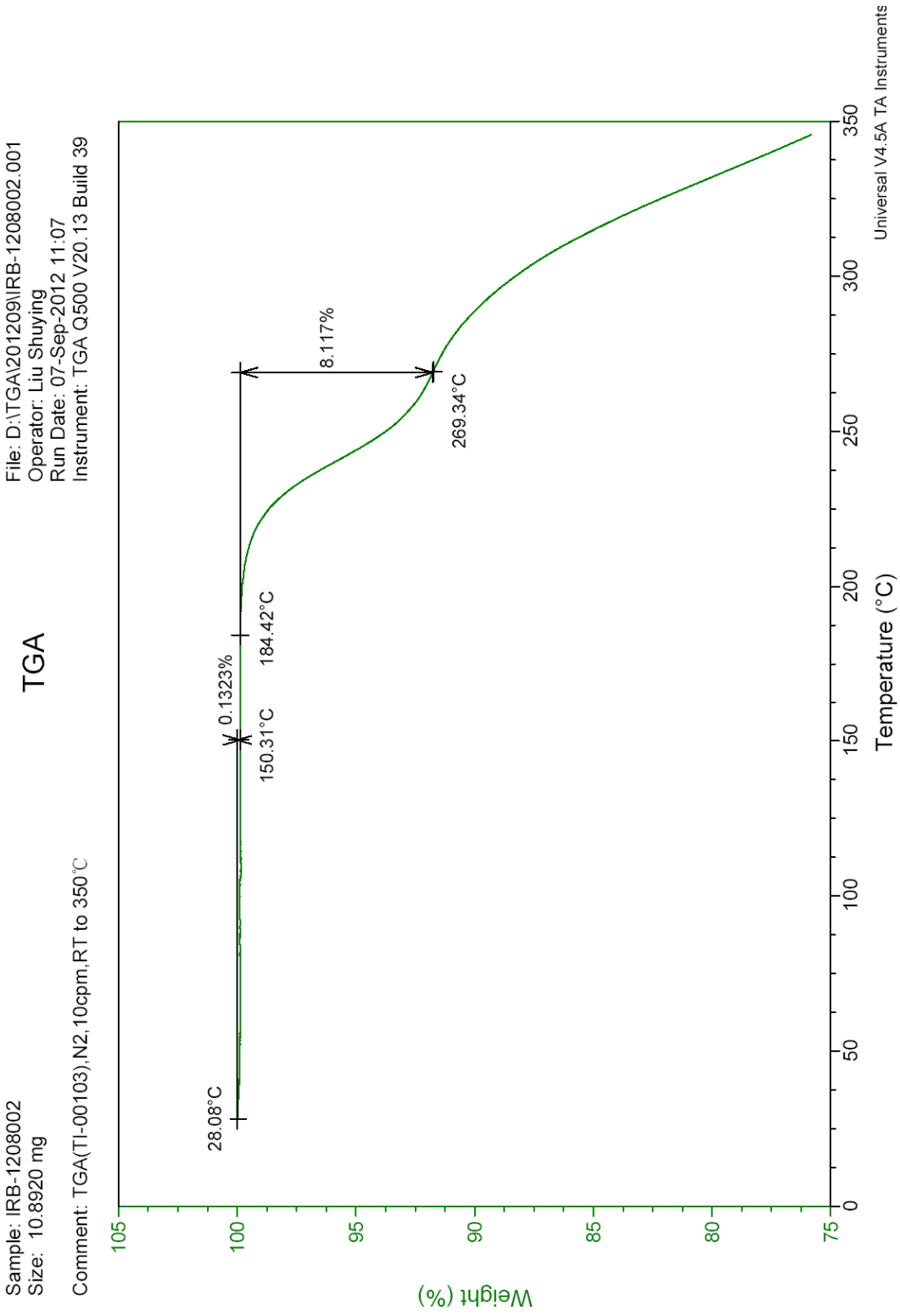


Fig. 3.2.S.3.1-15b TGA Spectrum of the In-house Sample IRB-1208002

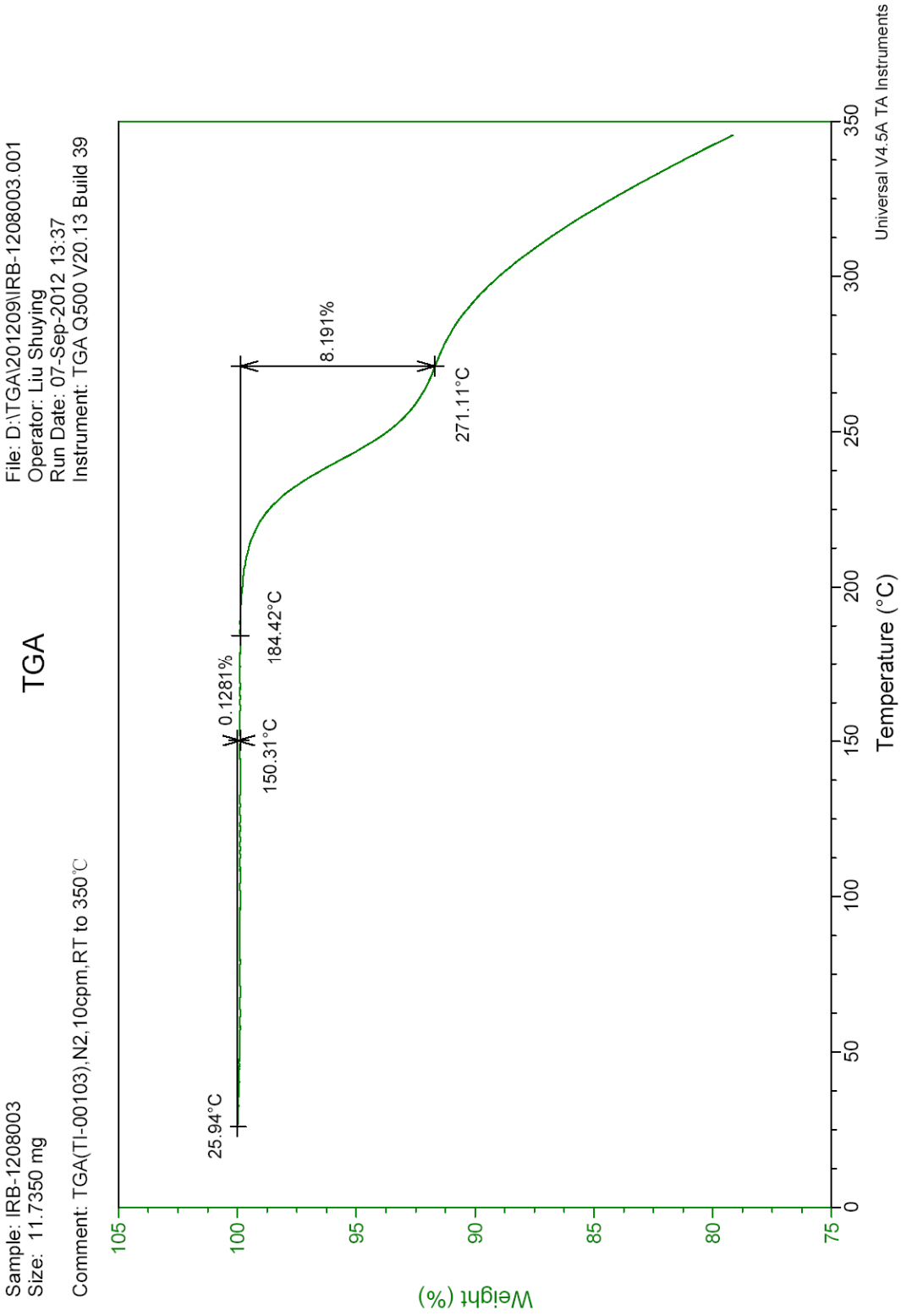


Fig. 3.2.S.3.1-15c TGA Spectrum of the In-house Sample IRB-1208003

2.3.2 Differential Scanning Calorimetry (DSC)

Instrument: TA Q2000 Differential Scanning calorimeter

Experimental conditions: DSC heat increased from 40 ^{o}C to 350 ^{o}C at a rate of 10 ^{o}C per minute. Atmosphere: N_2 at a rate of 20 mL/min.

Results: Refer to the spectra presented below. The test data are summarized in Table 3.2.S.3.1-7.

Table3.2.S.3.1-7 Differential Scanning Calorimetry Results

Sample	Patent [1]	IRB-1208001	IRB-1208002	IRB-1208003
onset temp.(^{o}C)	182.8	182.52	182.32	182.82

Conclusion: The fusion temperatures for the three submission batches are consistent with that for Irbesartan form A crystal prescribed in the CN patent 95118711.2 [1].

Spectra: The DSC spectra are presented below under the following titles:

Fig. 3.2.S.3.1-16a DSC Spectrum of the In-house Irbesartan Sample IRB-1208001

Fig. 3.2.S.3.1-16b DSC Spectrum of the In-house Irbesartan Sample IRB-1208002

Fig. 3.2.S.3.1-16c DSC Spectrum of the In-house Irbesartan Sample IRB-1208003

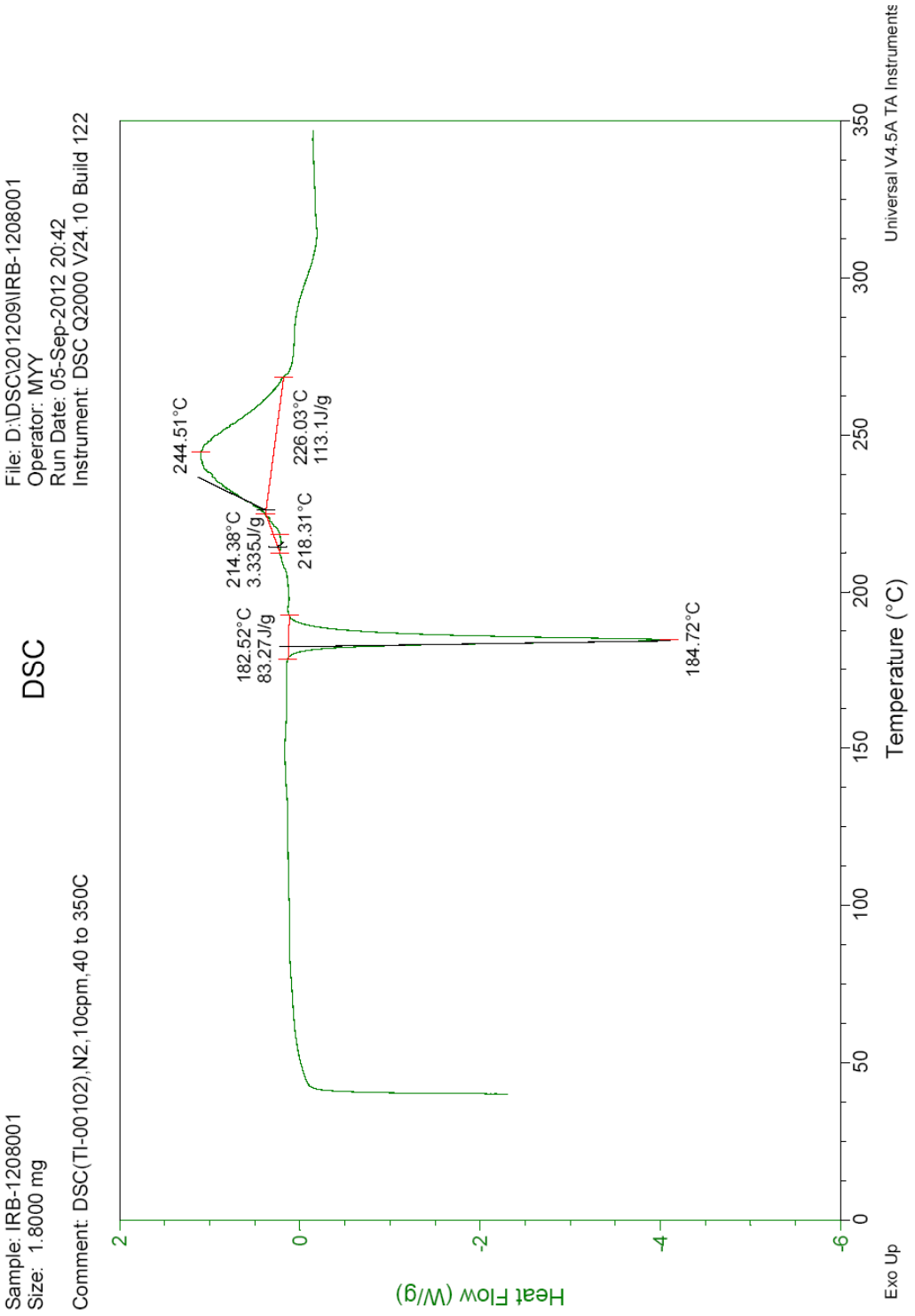


Fig. 3.2.S.3.1-16a DSC Spectrum of the In-house Irbesartan Sample IRB-1208001

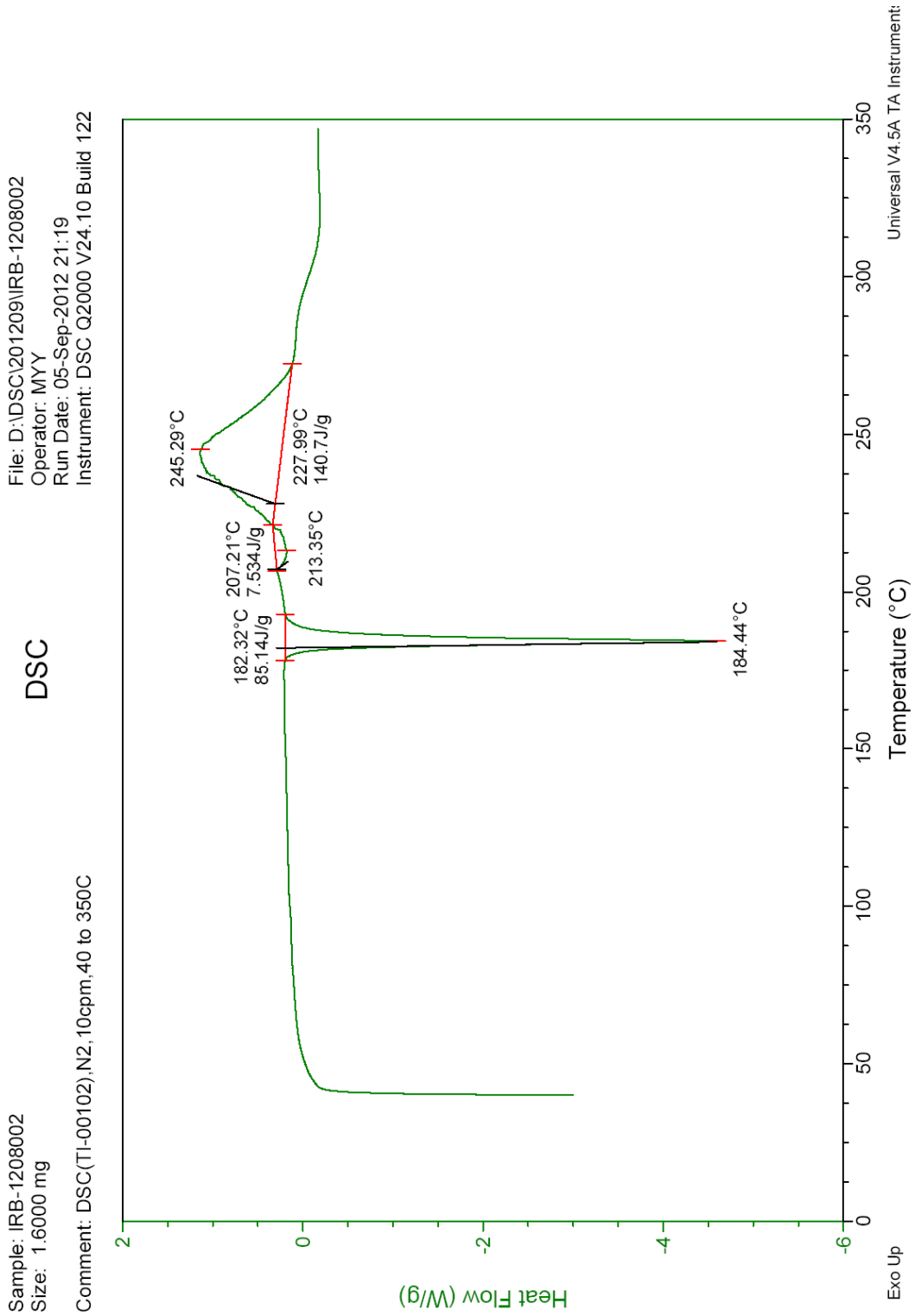


Fig. 3.2.S.3.1-16b DSC Spectrum of the In-house Irbesartan Sample IRB-1208002

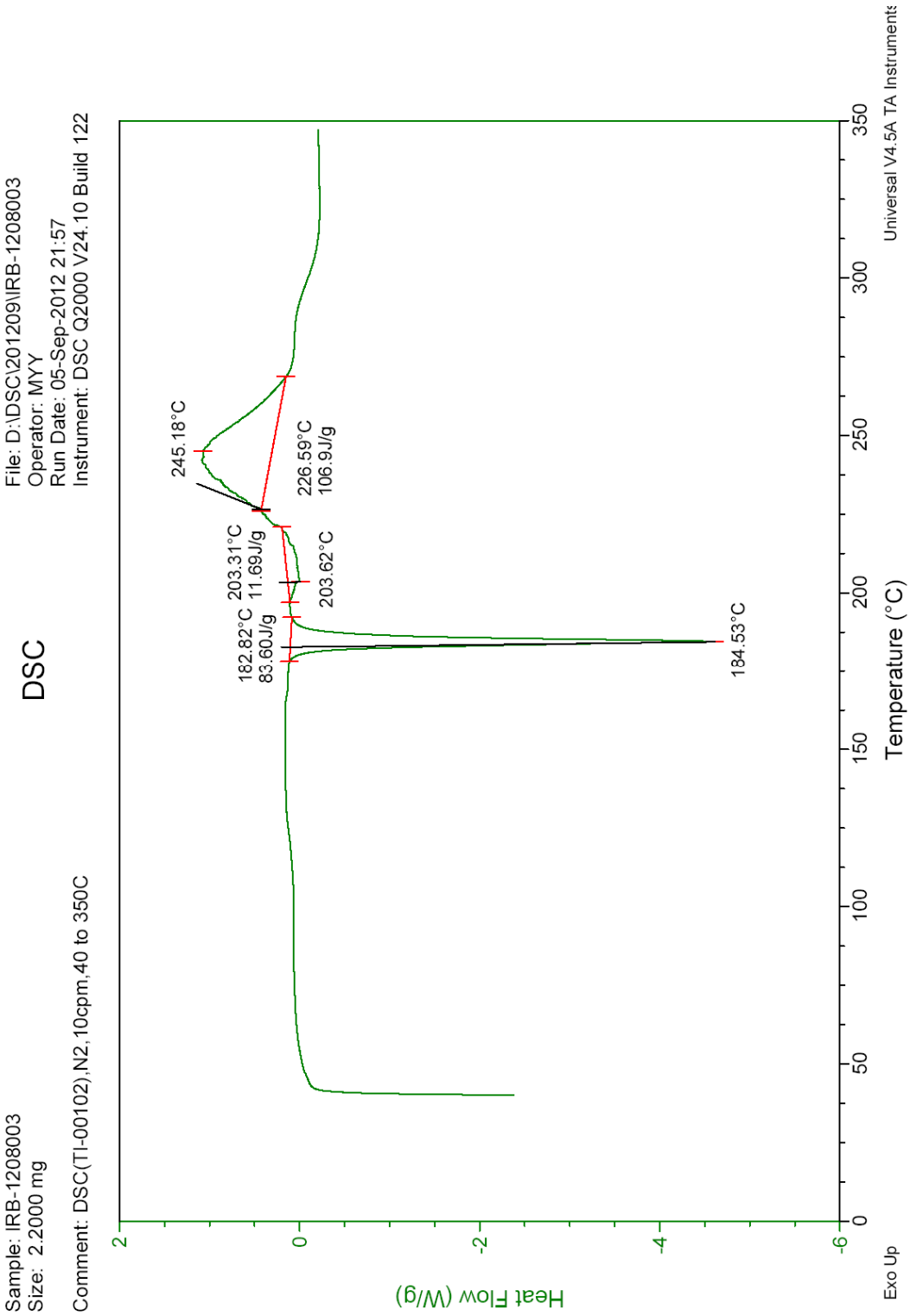


Fig. 3.2.S.3.1-16c DSC Spectrum of the In-house Irbesartan Sample IRB-1208003

2.3.3 X-ray Powder Diffraction Analysis (XRPD)

Instrument: PANalytical Empyrean X-ray Diffraction Analyzer

Results: Refer to the spectra presented below and in the patent[1]. The test data are summarized in the following table:

Table3.2.S.3.1-8 X-ray Powder Diffraction Analysis Results

Peak No.	Patent [1]		IRB-1208001		IRB-1208002		IRB-1208003	
	d	I/I_0	d	I/I_0	d	I/I_0	d	I/I_0
1	18.98	100.00	18.73	100.00	18.64	100.00	18.79	100.00
2	10.89	5.81	10.84	4.69	10.81	2.67	10.85	4.25
3	9.49	7.43	9.41	3.15	9.39	2.69	9.43	5.01
4	8.48	6.60	8.43	1.40	8.41	1.93	8.44	4.42
5	7.13	46.23	7.10	66.63	7.09	47.05	7.11	91.47
6	6.68	11.25	6.66	5.16	6.65	5.70	6.66	11.72
7	6.30	7.45	6.27	2.84	6.26	2.74	6.27	5.36
8	5.45	8.85	5.43	2.66	5.42	2.65	5.43	4.85
9	5.22	16.82	5.21	17.47	5.20	13.25	5.21	23.35
10	5.03	11.81	5.02	5.77	5.02	5.12	5.02	9.85
11	4.71	15.91	4.70	6.13	4.69	5.86	4.70	11.40
12	4.58	45.40	4.57	20.01	4.57	25.05	4.57	59.32
13	4.44	26.12	4.43	17.05	4.43	16.89	4.43	30.44
14	4.32	25.44	4.31	11.61	4.31	12.31	4.32	23.63
15	4.22	25.86	4.21	11.98	4.20	13.34	4.20	25.68
16	4.11	21.72	4.10	14.25	4.10	12.80	4.10	22.93
17	3.93	25.46	3.93	9.88	3.92	11.83	3.92	25.96
18	3.85	33.89	3.84	21.19	3.83	22.44	3.84	40.93
19	3.77	27.76	3.76	15.89	3.76	16.64	3.76	30.14
20	3.38	9.09	3.38	2.24	3.37	2.54	3.38	4.41
21	3.33	11.75	3.32	4.40	3.32	4.98	3.33	9.47
22	3.23	13.68	3.22	9.88	3.22	9.13	3.22	15.85
23	3.14	11.99	3.13	5.68	3.13	6.08	3.13	10.70
24	2.80	8.97	2.80	4.88	2.80	4.35	2.77	1.78
25	2.71	9.50	2.71	5.05	2.71	4.99	2.71	8.12

Conclusion: By comparing the X-ray powder diffraction spectra obtained from the in-house samples with that presented in CN patent 95118711.2 [1], it can be deduced that the sample is form A crystal.

Spectra: The XRPD spectra obtained with the in-house samples and that provided in CN patent 95118711.2 **[1]** are presented below under the following title:

Fig. 3.2.S.3.1-17a X-ray Spectrum of the In-house Irbesartan Sample IRB-1208001

Fig. 3.2.S.3.1-17b X-ray Spectrum of the In-house Irbesartan Sample IRB-1208002

Fig. 3.2.S.3.1-17c X-ray Spectrum of the In-house Irbesartan Sample IRB-1208003

Fig. 3.2.S.3.1-17d X-ray Spectrum of the Irbesartan in the Patent [1]

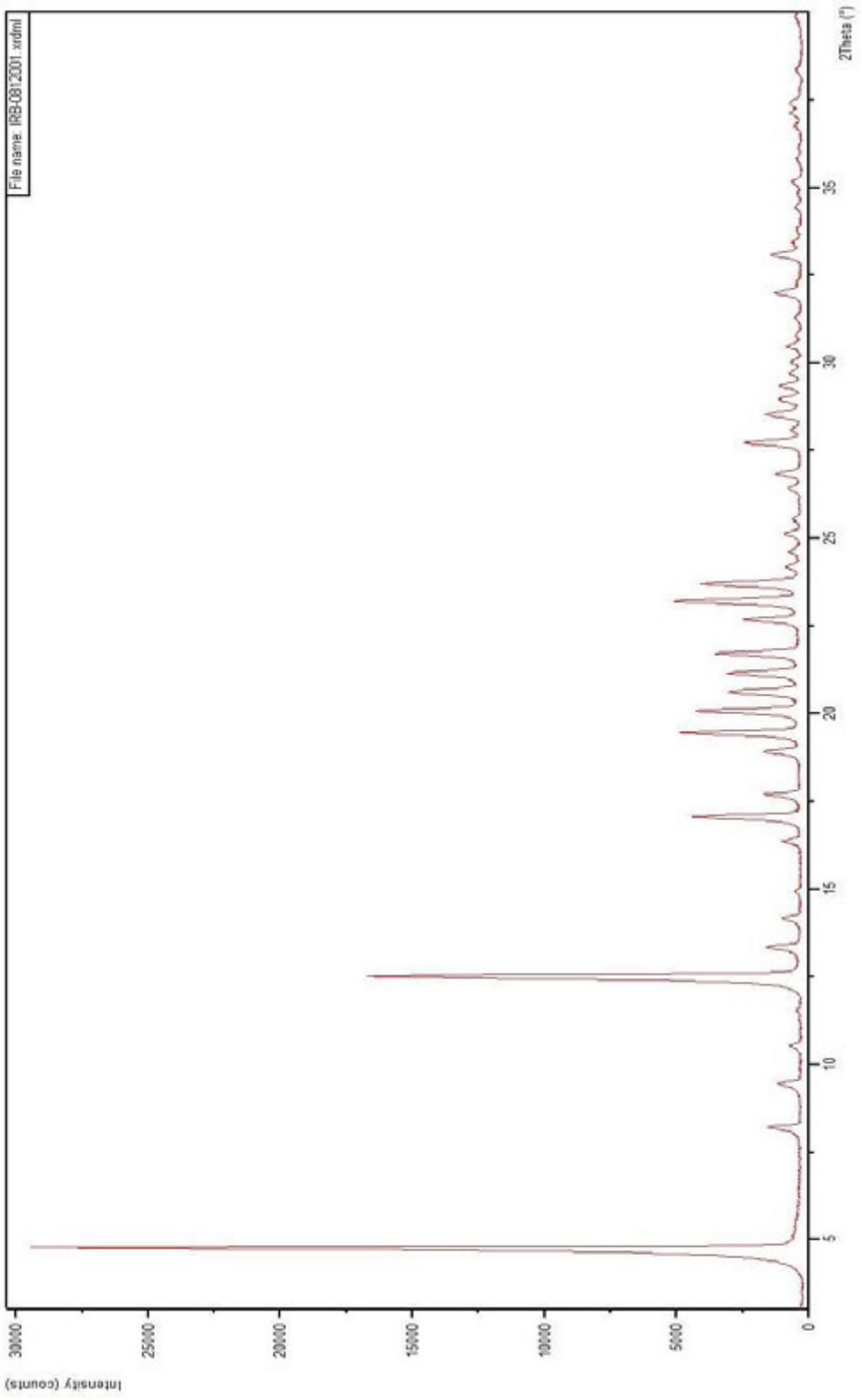


Fig. 3.2.S.3.1-17a X-ray Spectrum of the In-house Irbesartan Sample IRB-1208001

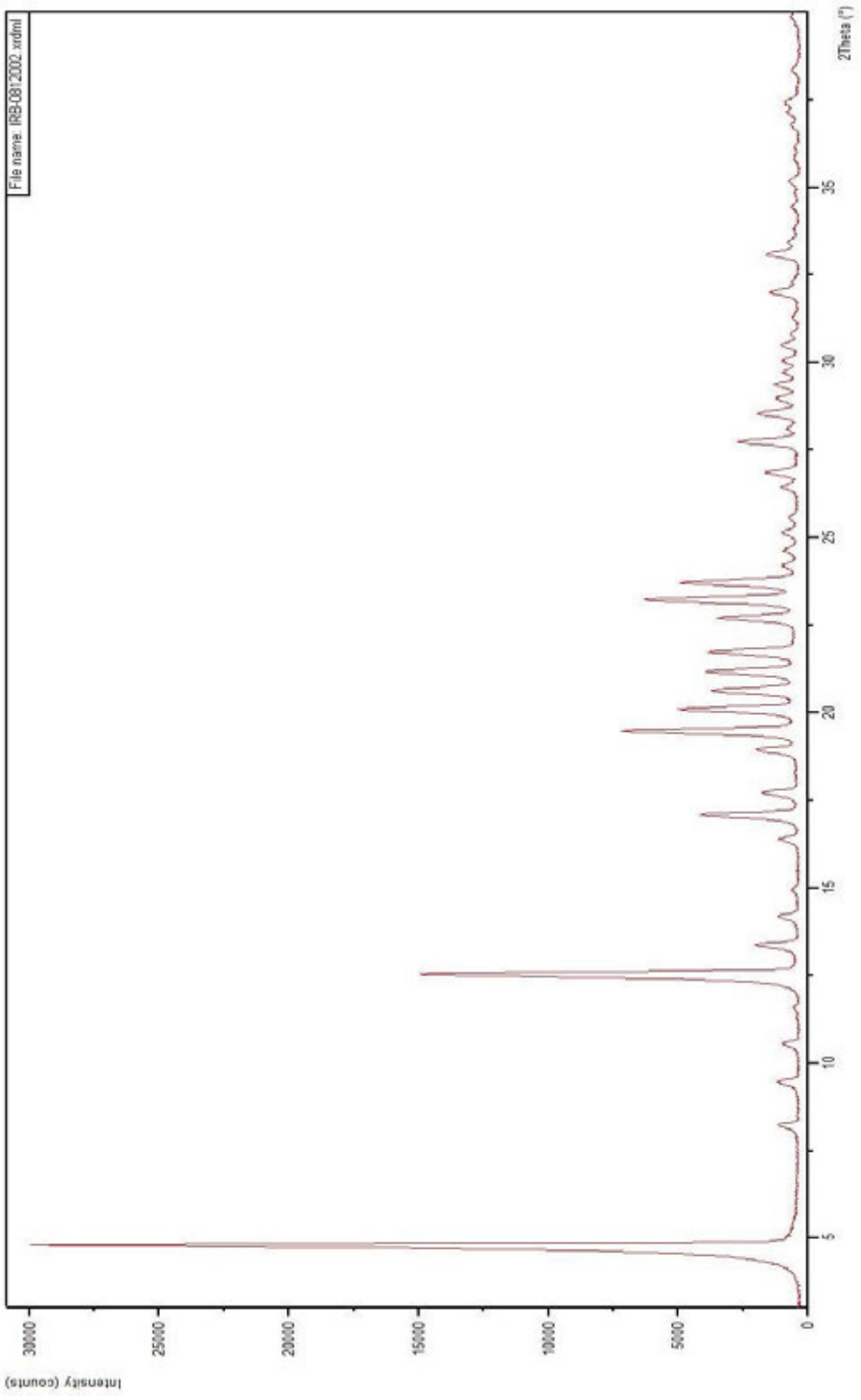


Fig. 3.2.S.3.1-17b X-ray Spectrum of the In-house Irbesartan Sample IRB-1208002

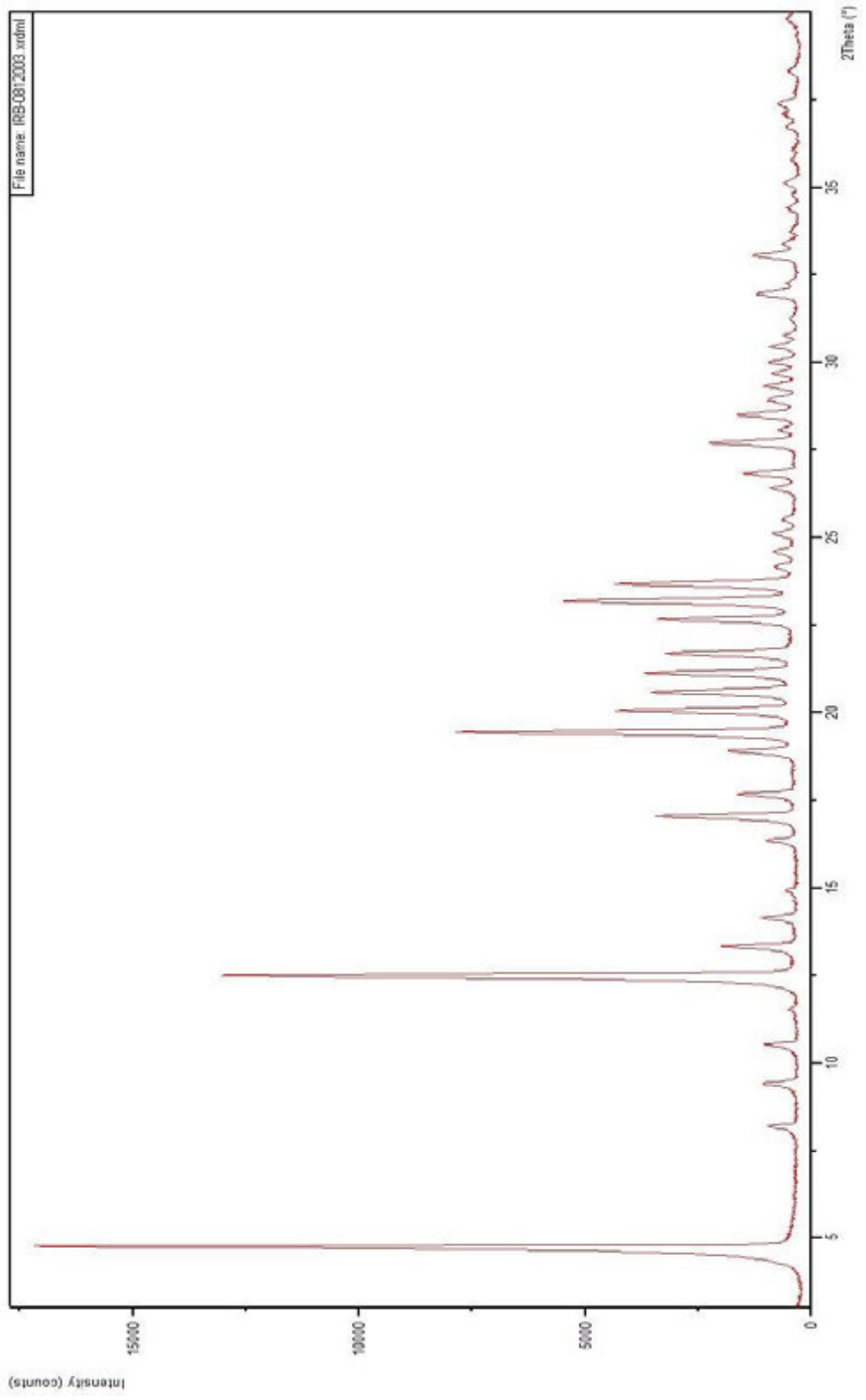


Fig. 3.2.S.3.1-17c X-ray Spectrum of the In-house Irbesartan Sample IRB-1208003

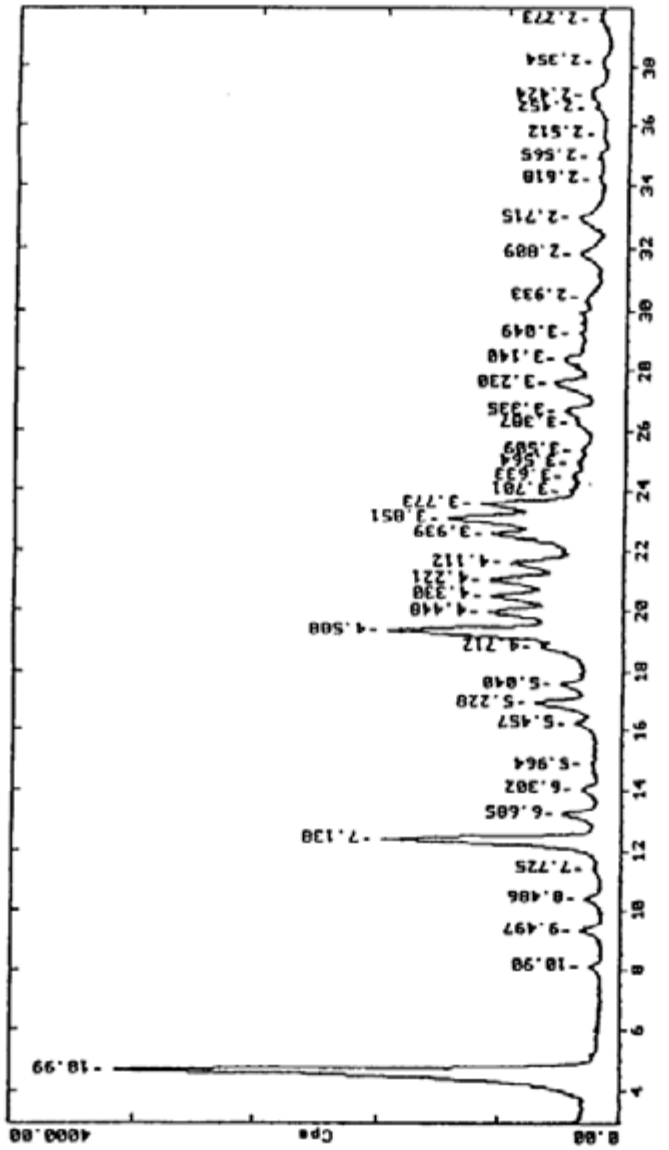


Fig. 3.2.S.3.1-17d X-ray Spectrum of the Irbesartan in the Patent [1]

2.3.4 Polarizing Microscope (PLM) Observation

Instrument: Polarizing microscope (TI-00131)

Procedure: Observe the shape and dimensions of the in-house samples with polarizing microscope. The shape of the crystal can be defined basing on the length-to-width ratio, which corresponds to a lath shape when less than 10.

Results: The length-to-width ratios of the three submission batches are provided in Table3.2.S.3.1-9.

Table3.2.S.3.1-9 Polarizing Microscope Observation Results

Length/width		**Sample**		
		IRB-1208001	**IRB-1208002**	**IRB-1208003**
Position	1	2.24	2.55	2.00
	2	3.11	4.71	2.70
	3	2.49	0.93	2.19

Conclusion: The in-house Irbesartan sample is crystalline powder with lath shape.

Photographs: The photographs are presented below under the following titles.

Fig. 3.2.S.3.1-18a PLM Photograph of the In-house Irbesartan Sample IRB-1208001

Fig. 3.2.S.3.1-18b PLM Photograph of the In-house Irbesartan Sample IRB-1208002

Fig. 3.2.S.3.1-18c PLM Photograph of the In-house Irbesartan Sample IRB-1208003

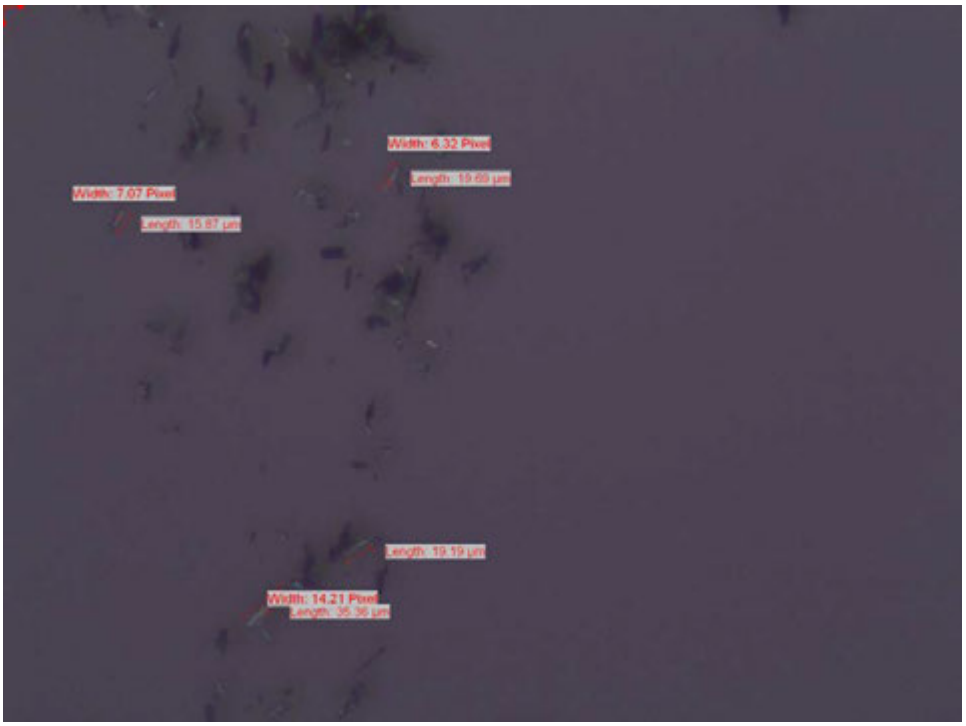


Fig. 3.2.S.3.1-18a PLM Photograph of the In-house Irbesartan Sample IRB-1208001

Fig. 3.2.S.3.1-18b PLM Photograph of the In-house Irbesartan Sample IRB-1208002

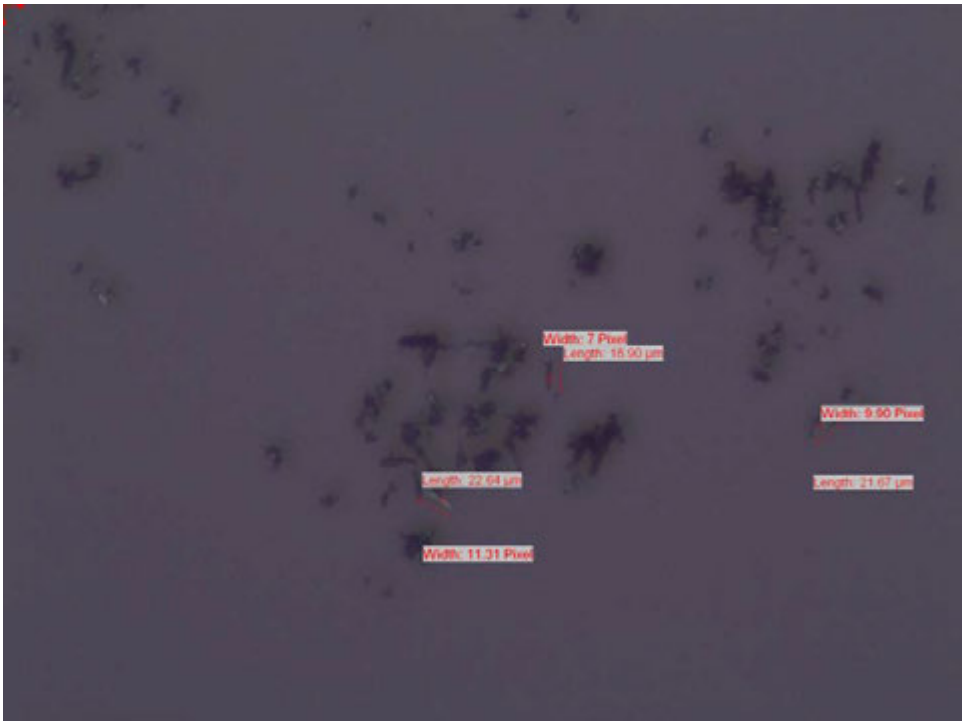


Fig. 3.2.S.3.1-18c PLM Photograph of the In-house Irbesartan Sample IRB-1208003

2.4 Hygroscopicity

The hygroscopicity of Irbesartan was tested using the method described in Ph. Eur. 5.11. Weigh a glass weighing bottle 50 mm in external diameter and 15 mm high together with its stopper (m_1). Place a suitable amount of Irbesartan in the bottle and weigh again (m_2). Place the unstoppered weighing bottle in a desiccator containing a saturated solution of ammonium chloride, at 25 ^{o}C. Allow to stand for 24 h. Stopper the weighing bottle and weigh (m_3). Calculate the percentage increase in mass using the formula below:

$$\frac{m_3 - m_2}{m_2 - m_1} \times 100\%$$

The result is interpreted as follows:

- *Deliquescent*: sufficient water is absorbed to form a liquid;
- *Very hygroscopic*: increase in mass is equal to or greater than 15 percent;
- *Hygroscopic*: increase in mass is less than 15 percent and equal to or greater than 2 percent;
- *Slightly hygroscopic*: increase in mass is less than 2 percent and equal to or greater than 0.2 percent.

The results are presented in Table3.2.S.3.1-10.

Table3.2.S.3.1-10 Hygroscopicity Results of Irbesartan

Batch Number	m_1 (g)	m_2 (g)	m_3 (g)	Weight Increase (%)	Conclusion
IRB-1208001	31878.88	32728.52	32729.20	0.08	Not hygroscopic
IRB-1208002	27560.18	28398.60	28398.98	0.04	
IRB-1208003	29488.95	30479.79	30480.39	0.06	

2.5 Solubility

Procedure: Dissolve Irbesartan in a suitable amount of solvent. Place in room temperature (23-25°C). Shake vigorously for 30 s every 5 min. Observe the solubilisation in 30 min. The substance is completely dissolved if there are no visible particles. The solubility of a substance is expressed according to the following table:

Table 3.2.S.3.1-11 Descriptive Terms of Solubility

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble or Insoluble	10,000 and over

Result: Results are presented in the table below.

Table 3.2.S.3.1-12 Solubility Results of Irbesartan

Solvent	Batch Number	Sample (mg)	Volume (mL)		Conclusion
			Incompletely Dissolved	Completely Dissolved	
Methanol	IRB-1208001	100	3	10	Sparingly Soluble
	IRB-1208002	100	3	10	
	IRB-1208003	100	3	10	
Ethanol	IRB-1208001	100	10	N/A	Slightly Soluble
		10	N/A	10	
	IRB-1208002	100	10	N/A	
		10	N/A	10	
	IRB-1208003	100	10	N/A	
		10	N/A	10	
Dichloro-methine	IRB-1208001	100	10	N/A	Slightly Soluble
		10	N/A	10	
	IRB-1208002	100	10	N/A	
		10	N/A	10	
	IRB-1208003	100	10	N/A	
		10	N/A	10	
Water	IRB-1208001	10	10	N/A	Practically insoluble
		1	10	N/A	
	IRB-1208002	10	10	N/A	
		1	10	N/A	
	IRB-1208003	10	10	N/A	
		1	10	N/A	

2.6 Melting Point

The melting point was tested using the method described in Ph.Eur.2.2.16. The initial temperature was 180^{o}C, which was raised to 186 ^{o}C at a rate of 1^{o}C/min. The test results are shown in Table 3.2.S.3.1-13.

Table 3.2.S.3.1-13 Melting Point Results of Irbesartan

Determination	Sample		
	IRB-1208001	IRB-1208002	IRB-1208003
Melting point (^{o}C)	184	184	185

2.7 Particle Size Distribution

Instrument：Malvern MS2000 Laser Particle Size Distribution Analyzer

Results：The relative volume is the ratio of the volume of particles in a designated size range to the volume of total measured particles. The results are listed in the table below.

Table 3.2.S.3.1-14 Particle Size Distribution in Irbesartan

Sample	(0.1) Diameter/μm	(0.5) Diameter/μm	(0.9) Diameter/μm
IRB-1208001	1.025	2.935	6.556
IRB-1208002	0.979	2.898	6.228
IRB-1208003	0.968	3.027	7.740

The copies of original records are presented below under the following titles:

Fig. 3.2.S.3.1-19 Copy of the Record of Particle Size Distribution of IRB-1208001

Fig. 3.2.S.3.1-20 Copy of the Record of Particle Size Distribution of IRB-1208002

Fig. 3.2.S.3.1-21 Copy of the Record of Particle Size Distribution of IRB-1208003

MASTERSIZER 2000

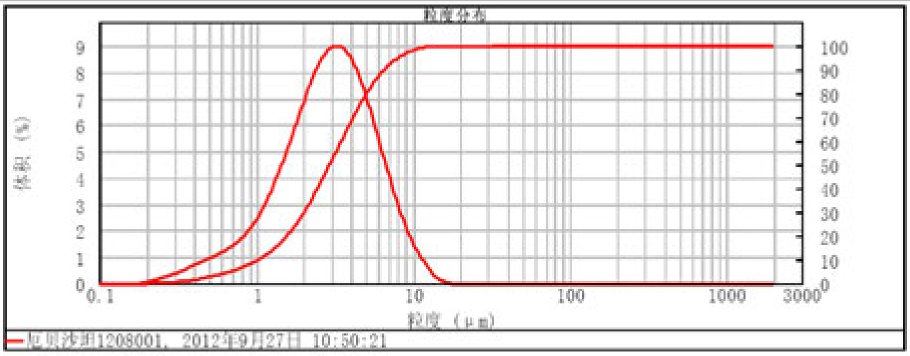
东阳光药业 - 粒度分析报告

样品名称: 厄贝沙坦1208001	SOP名称: 厄贝沙坦1207001	测量时间: 2012年9月27日 10:50:21
样品来源及类型: Factory = Paris	操作者: 固体三组	分析时间: 2012年9月27日 10:50:22
样品参考批号: 123-ABC	结果来源: 测量	

颗粒名称: Default	进样器名: Scirocco 2000 (A)	分析模式: 通用	灵敏度: 增强
颗粒折射率: 1.520	颗粒吸收率: 0.1	粒径范围: 0.020 to 2000.000 um	遮光度: 0.36 %
分散剂名称:	分散剂折射率: 1.000	残差: 1.292 %	结果模拟: 关

浓度: 0.0000 %Vol	径距: 1.884	一致性: 0.587	结果类别: 大于 150.00 μm 的百分数: 0.00%
比表面积: 3.03 m^2/g	表面积平均粒径D[3,2]: 1.980 um	体积平均粒径D[4,3]: 3.454 um	大于 75.00 μm 的百分数: 0.00%

d(0.1): 1.025 um d(0.5): 2.935 um d(0.9): 6.556 um



粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %
0.010	0.00	0.105	0.00	1.096	11.18	11.482	99.18	120.226	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	14.08	13.183	99.78	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	17.72	15.136	99.97	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	22.23	17.378	100.00	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	27.57	19.953	100.00	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.01	2.188	34.03	22.909	100.00	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.14	2.512	41.20	26.303	100.00	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.35	2.884	48.98	30.200	100.00	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.67	3.311	57.08	34.674	100.00	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	1.11	3.802	65.13	39.811	100.00	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	1.70	4.365	72.75	45.709	100.00	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	2.45	5.012	79.63	52.481	100.00	549.541	100.00	5754.399	100.00
0.052	0.00	0.550	3.34	5.754	85.50	60.256	100.00	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	4.38	6.607	90.23	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	5.61	7.586	93.84	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	7.08	8.710	96.40	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	8.90	10.000	98.12	104.713	100.00	1096.478	100.00		

操作说明:

alvern Instruments Ltd.
alvern, UK
Mastersizer 2000 版. 5.12C
序列号: MAL1051136
文件名: 厄贝沙坦.mea
记录编号: 10
27 九月 2012 11:10:0

Fig. 3.2.S.3.1-19 Copy of the Record of Particle Size Distribution of IRB-1208001

MASTERSIZER 2000

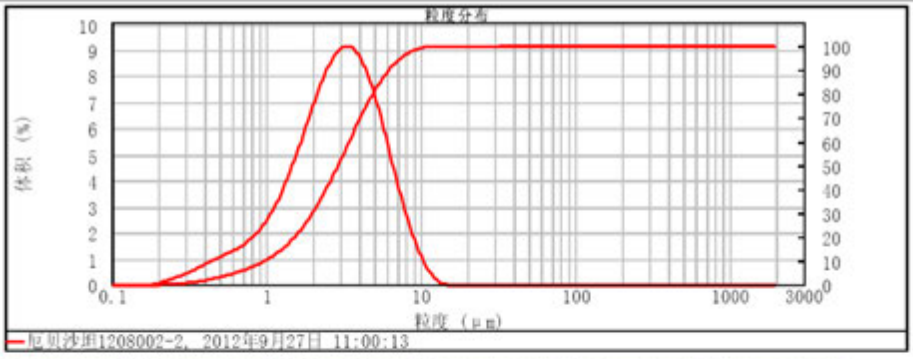
东阳光药业 - 粒度分析报告

样品名称: 厄贝沙坦1208002-2	SOP名称: 厄贝沙坦1207001	测量时间: 2012年9月27日 11:00:13
样品来源及类型: Factory = Paris	操作者: 固体三组	分析时间: 2012年9月27日 11:00:14
样品参考批号: 123-ABC	结果来源: 测量	

颗粒名称: Default	进样器名: Scirocco 2000 (A)	分析模式: 通用	灵敏度: 增强
颗粒折射率: 1.520	颗粒吸收率: 0.1	粒径范围: 0.020 to 2000.000 um	遮光度: 1.57 %
分散剂名称:	分散剂折射率: 1.000	残差: 0.926 %	结果模拟: 关

浓度: 0.0001 %Vol	径距: 1.811	一致性: 0.56	结果类别: 大于 150.00 μm 的百分数: 0.00%
比表面积: 3.13 m^2/g	表面积平均粒径D[3,2]: 1.915 um	体积平均粒径D[4,3]: 3.322 um	大于 75.00 μm 的百分数: 0.00%

d(0.1): 0.979 um d(0.5): 2.898 um d(0.9): 6.228 um



粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %
0.010	0.00	0.105	0.00	1.096	11.93	11.482	99.76	120.226	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	14.82	13.183	99.99	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	18.44	15.136	100.00	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	22.91	17.378	100.00	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	28.32	19.953	100.00	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.02	2.188	34.66	22.909	100.00	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.16	2.512	41.86	26.303	100.00	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.40	2.884	49.72	30.200	100.00	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.76	3.311	57.95	34.674	100.00	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	1.26	3.802	66.18	39.811	100.00	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	1.93	4.365	74.03	45.709	100.00	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	2.77	5.012	81.10	52.481	100.00	549.541	100.00	5754.399	100.00
0.052	0.00	0.550	3.76	5.754	87.11	60.256	100.00	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	4.90	6.607	91.88	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	6.22	7.586	95.39	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	7.76	8.710	97.72	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	9.62	10.000	99.09	104.713	100.00	1096.478	100.00		

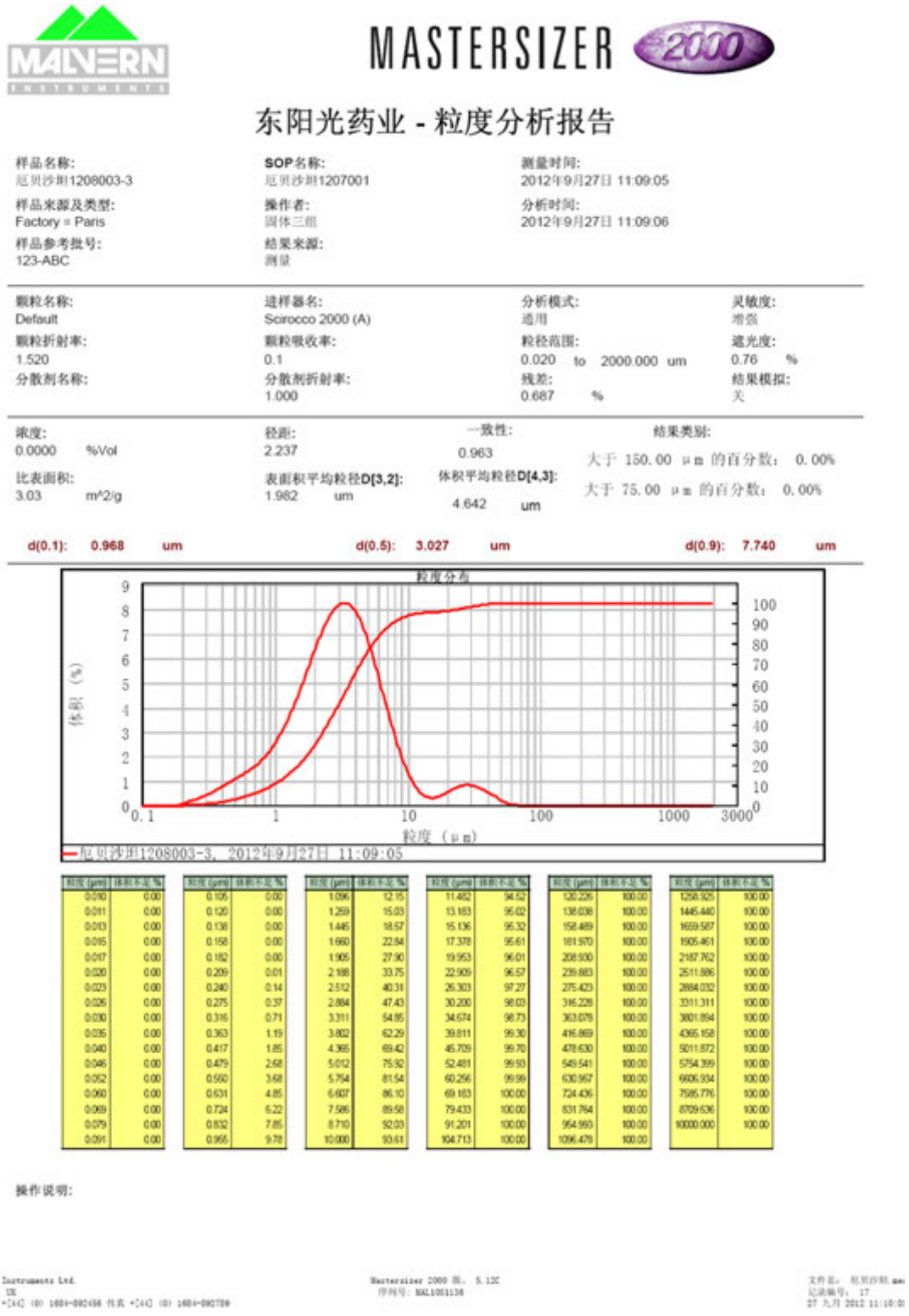
操作说明:

Malvern Instruments Ltd. Malvern, UK

Mastersizer 2000 版, 5.12C 序列号: MAL1051136

文件名: 厄贝沙坦.mea 记录编号: 14 27 九月 2012 11:10:02

Fig. 3.2.S.3.1-20 Copy of the Record of Particle Size Distribution of IRB-1208002



MASTERSIZER 2000

东阳光药业 - 粒度分析报告

样品名称: 厄贝沙坦1208003-3	SOP名称: 厄贝沙坦1207001	测量时间: 2012年9月27日 11:09:05	
样品来源及类型: Factory = Paris	操作者: 固体三组	分析时间: 2012年9月27日 11:09:06	
样品参考批号: 123-ABC	结果来源: 测量		
颗粒名称: Default	进样器名: Scirocco 2000 (A)	分析模式: 通用	灵敏度: 增强
颗粒折射率: 1.520	颗粒吸收率: 0.1	粒径范围: 0.020 to 2000.000 um	遮光度: 0.76 %
分散剂名称:	分散剂折射率: 1.000	残差: 0.687 %	结果模拟: 关
浓度: 0.0000 %Vol	径距: 2.237	一致性: 0.963	结果类别: 大于 150.00 μm 的百分数: 0.00%
比表面积: 3.03 m^2/g	表面积平均粒径D[3,2]: 1.982 um	体积平均粒径D[4,3]: 4.642 um	大于 75.00 μm 的百分数: 0.00%

d(0.1): 0.968 um d(0.5): 3.027 um d(0.9): 7.740 um

粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %	粒度 (μm)	体积不足 %
0.010	0.00	0.105	0.00	1.096	12.15	11.482	94.52	120.226	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	15.03	13.183	95.02	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	18.57	15.136	95.32	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	22.84	17.378	95.61	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	27.90	19.953	96.01	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.01	2.188	33.75	22.909	96.57	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.14	2.512	40.31	26.303	97.27	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.37	2.884	47.43	30.200	98.03	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.71	3.311	54.85	34.674	98.73	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	1.19	3.802	62.29	39.811	99.30	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	1.85	4.365	69.42	45.709	99.70	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	2.68	5.012	75.92	52.481	99.93	549.541	100.00	5754.399	100.00
0.052	0.00	0.550	3.68	5.754	81.54	60.256	99.99	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	4.85	6.607	86.10	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	6.22	7.585	89.58	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	7.85	8.710	92.03	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	9.78	10.000	93.61	104.713	100.00	1096.478	100.00		

操作说明:

Malvern Instruments Ltd. Malvern, UK 电话: + [44] (0) 1684-892456 传真 +[44] (0) 1684-892789

Mastersizer 2000 版, S.12C 序列号: MAL1051136

文件名: 厄贝沙坦.mea 记录编号: 17 27 九月 2012 11:10:0

Fig. 3.2.S.3.1-21 Copy of the Record of Particle Size Distribution of IRB-1208003