



CONFIDENTIAL REPORT

Sterner, Kessler, Goldstein, Fox LLC

Prepared By:
Avomeen Analytical Services
4840 Venture Dr.
Ann Arbor, MI 48108
Issued Date: June 30, 2016



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CIP2028
Argentum Pharmaceuticals LLC v. Cipla Ltd.
IPR2017-00807

PTX0129-00001

To: Josephine Kim
Sterne, Kessler, Goldstein & Fox PLLC
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Testing of Fluticasone and Azelastine Nasal Spray

Thank you for contacting Avomeen Analytical Services for testing of Fluticasone and Azelastine Nasal Spray. Following are the results, methodology, and data associated with our analysis.

Table 1: Sample description

	Avomeen ID	Batch Number	Sample Description	Expire Day
Sample 1	053116ST1395	A16009SV	Boxes of AZEFLO N/S drug product, LUPIN	01/2018
Sample 2	053116ST1396	DND0214	Boxes of NASOMAC –AF drug product, MACLEODS	10/20/2017
Sample 3	053116ST1398	MS1476	Boxes of COMBINASE AQ drug product, CADILA	12/2017
Sample 4	053116ST1399	ASA16002	Boxes of FLORESP AZ Drug product, EMCURE	01/2018
Sample 5	053116ST1400	1601009	Boxes of EZICAS AZ Drug Product , INTAS	12/2017
Sample 6	053116ST1401	END0237	Boxes of NASOCOM AZ drug product, DR REDDY	11/2017

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Figure 1: Samples as received

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Executive Summary

The testing results of Fluticasone and Azelastine Nasal Spray for particle size, pH Value, EDTA, Glycerin, Polysorbate 80, and MCC are shown in Table 2. The accuracy of each measurement will be within five relative percent per excipient. The information of APIs and the preservatives on the label is also included in Table 3.

Table 2: Testing results for particle size, PH Value, EDTA, Glycerin, Polysorbate 80, and MCC

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
Ethylenediaminetetraacetic Acid (EDTA) (wt %)	<0.0001	<0.0001	0.02	<0.0001	<0.0001	<0.0001
Glycerin (wt %)	2.1	2.4	2.0	3.0	2.4	2.5
Polysorbate 80 (wt %)	Detected	Detected	Detected	Detected	Detected	Detected
Micro Crystalline Cellulose with carboxymethyl cellulose (wt %)	2.8	2.7	2.9	2.9	2.9	2.9
Particle Size Mean Diameter(nm) by ZetaPALS	460.4	309.8	442.9	460.9	452.2	391.7
Particle Size Mean Diameter(μm) by light microscopy	1.14 ±0.32	0.84±0.38	0.98±0.40	0.98±0.42	1.02±0.41	0.84±0.28
pH Value	6.21	6.32	5.75	6.27	6.33	6.33

Table 3: Information on the label for APIs and preservatives

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
Azelastine Hydrochloride IP (W/v)	0.14	0.14	0.14	0.14	0.14	0.14
Fluticasone Propionate IP (W/v)	0.05	0.05	0.05	0.05	0.05	0.05
Benzalkonium Chloride Solution IP (W/v)	0.02	0.01	0.01	0.02	0.01	0.01
Phenylethyl Alcohol IP (W/v)	0.25	0.25	0.25	0.25	0.25	0.25

Quality Statement

The work reported herein was conducted non- GMP and was not reviewed by Quality Assurance. All data in this report accurately reflects the raw data stored in the archives of Avomeen Analytical Services.

Analytical Testing

High Performance Liquid Chromatography (HPLC) Analysis for Ethylenediaminetetraacetic Acid (EDTA)

Instrument: Agilent 1100

Column: Supelco Lichrosphere RPC18, 250 mm × 4.6 mm, 5 μm

Column Temperature: 30°C

Flow rate: 1 mL/min

Injection Volume: 10 μL

Mobile phase: 25 mM sodium acetate buffer with 1 mM tetrabutylammonium bromide in 950 mL deionized water and 50 mL Methanol, pH 4.0, isocratic 20 min

Detector wavelength: 265 nm

EDTA standard preparation: EDTA standard was derivatized with a ferric chloride solution and analyzed by HPLC-UV. An EDTA standard (EDTA content 1.002 mg/mL) stock solution was prepared in D.I. water. 5 mL of the EDTA standard solution was derivatized by 3 mL of ferric chloride solution (3.2 mg/mL) in 50 mL volumetric flask. The mixture was shaken and kept in the oven at 70°C for 20 min, and finally the

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volume was made up with D.I. water. The derivatized EDTA solution was diluted and used for a calibration curve.

Sample preparation: ~500 mg of samples was mixed with 5 mL of ferric chloride solution (3.2 mg/mL) in 10 mL volumetric flask. The mixture was shaken well and kept in the oven at 70°C for 20 min, then cooled to room temperature, made with D.I. water and filtered for HPLC analysis. The amount of ferric chloride for standard and samples was assured to be in excess for the derivatization.

High Performance Liquid Chromatography Analysis (HPLC-ELSD) for Polysorbate 80

Apparatus: Agilent HPLC 1100 with Alltech 2000ES Evaporative Light Scattering detector (ELSD)

Column: Kinetex, particle size 2.6 μ m, 150 \times 4.6 mm, 100A

ELSD conditions: Impactor On mode, 60°C drift tube temperature, 2.0 L/min nitrogen flow rate

Injection volume: 10 μ L

Column temperature: 30°C

Column flow rate: 0.6 mL/min

Run time: 50 min

Mobile phase A: D.I. water with 0.1% Formic Acid

Mobile phase B: Acetonitrile with 0.1% Formic Acid

Gradient Elution:

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	70	30
30	0	100
45	0	100
45.1	70	30
50	70	30

Sample preparation: about 1 g of each sample was dissolved individually with 5 mL of methanol and sonicated for 10 min at room temperature. After thoroughly mixing, the sample solution was filtered prior to injection into the HPLC-ELSD. 57 mg of Polysorbate 80 standard was dissolved in 25 mL methanol and diluted to 1000 – 3000 μ g/mL as calibration standards.

HPLC-ELSD Analysis for Glycerin

Instrument: Agilent 1100 equipped with Alltech 2000 evaporative light scattering detector (ELSD)

Column: Imtakt Unison UK-Amino, 250 mm \times 4.6 mm, 3 μ m

Column Temperature: 37°C

Injection Volume: 20 μ L

Mobile phase: A: D.I. water; B: Acetonitrile

Gradient: Isocratic 80% A, 20% B

Run time: 30 min

Flow rate: 1.0 mL/min

ELSD parameters: Impactor ON mode

Tube temperature: 42°C

Gas flow rate: 1.5 L/min

Sample preparation: About 1 gram of sample was dissolved with 5 mL of methanol, sonicated for 10 min at room temperature. The sample solution was filtered prior to injection into the HPLC-ELSD. Glycerin standards in methanol in the range of 1000 to 6900 µg/mL were prepared for calibration.

Determination of Microcrystalline Cellulose with Small Amount of Carboxymethyl Cellulose

The amount of microcrystalline cellulose was determined by loss of solvent washing and drying. Sample (around 600 mg) was accurately weighed in a tared Eppendorf tube, the tube was centrifuged at a speed of 14000 min⁻¹ for 20 minutes. The supernatant was removed using a pipette and the residue was washed with D.I. water 1 mL, after the supernatant was removed, the residue was continued to be washed with methanol (2 x 1 mL) and D.I water (3 x 1 mL), the supernatant was removed and the residue was dried over nitrogen and weighed. The difference of tared empty Eppendorf tube and the residue with empty Eppendorf tube is the weight for microcrystalline cellulose. This method included small amount of carboxymethyl cellulose.

Particle Size Distribution by using ZetaPALS:

A small aliquot of the nasal spray samples were diluted individually in 5 mL of ultrapure water to form a slightly hazy solution. The sample was analyzed using a ZetaPALS particle size analyzer for the particle size distribution.

Particle Size Distribution by using Light Microscope:

A small aliquot of the nasal spray samples were analyzed by using Nikon TE2000 inverted microscope for particle size distribution.

Determination of the pH Value of the Samples

The pH value of samples was measured individually by the PH meter.

Results

Quantitation of Ethylenediaminetetraacetic Acid (EDTA)

HPLC chromatogram of EDTA standard and calibration curve for EDTA standard are displayed in Figure 2. EDTA was found in sample 3 based on the match of retention time and HPLC chromatogram of sample 3 was displayed in Figure 3. The weight percentage of EDTA in the sample 3 is listed in Table 2. EDTA in samples 1, 2, 4, 5, 6 are found below the limit of detection (1.5 ppm) and HPLC chromatogram of sample 1, 2, 4, 5, 6 were displayed in Figure 3.

Testing of Polysorbate 80 in the Samples

Expanded HPLC chromatogram of polysorbate 80 standard was displayed in Figure 4. Polysorbate 80 was found in all of the samples based on the match of retention time and HPLC chromatogram of samples were displayed in Figure 5.

Quantitation of Glycerin

HPLC chromatogram of glycerin standard and calibration curve for glycerin standard are displayed in Figure 6. Glycerin was found in samples based on the match of retention time and HPLC chromatogram

of samples was displayed in Figure 7. The weight percentage of glycerin in the samples were listed in Table 2.

Quantitation of Microcrystalline Cellulose with Small amount of Carboxymethyl Cellulose

The amount of microcrystalline cellulose was determined by weight loss through solvent washing and drying. FTIR was used to characterize the microcrystalline cellulose in the sample. The FTIR spectrum for microcrystalline cellulose standard, samples and overlaid FTIR spectrum for the microcrystalline cellulose and samples were displayed in Figure 8. Sample 2 and sample 6 showed some trace of carbonyl group at $\sim 1700\text{ cm}^{-1}$, indicating presence of small amount of carboxymethyl cellulose.

Particle Size Distribution by using ZetaPALS:

Results for the particle size mean diameter (nm) of the samples is listed in the Table 2. The distribution data for each sample was displayed in Figure 9.

Particle Size Distribution by using Light Microscope

Results for the particle size mean diameter (μm) of the samples is listed in the Table 2. The distribution data and image for each sample were displayed in Figure 10.

pH Value of the Samples

Results for the particle size mean diameter (nm) of the samples is listed in the Table 2.

Figures

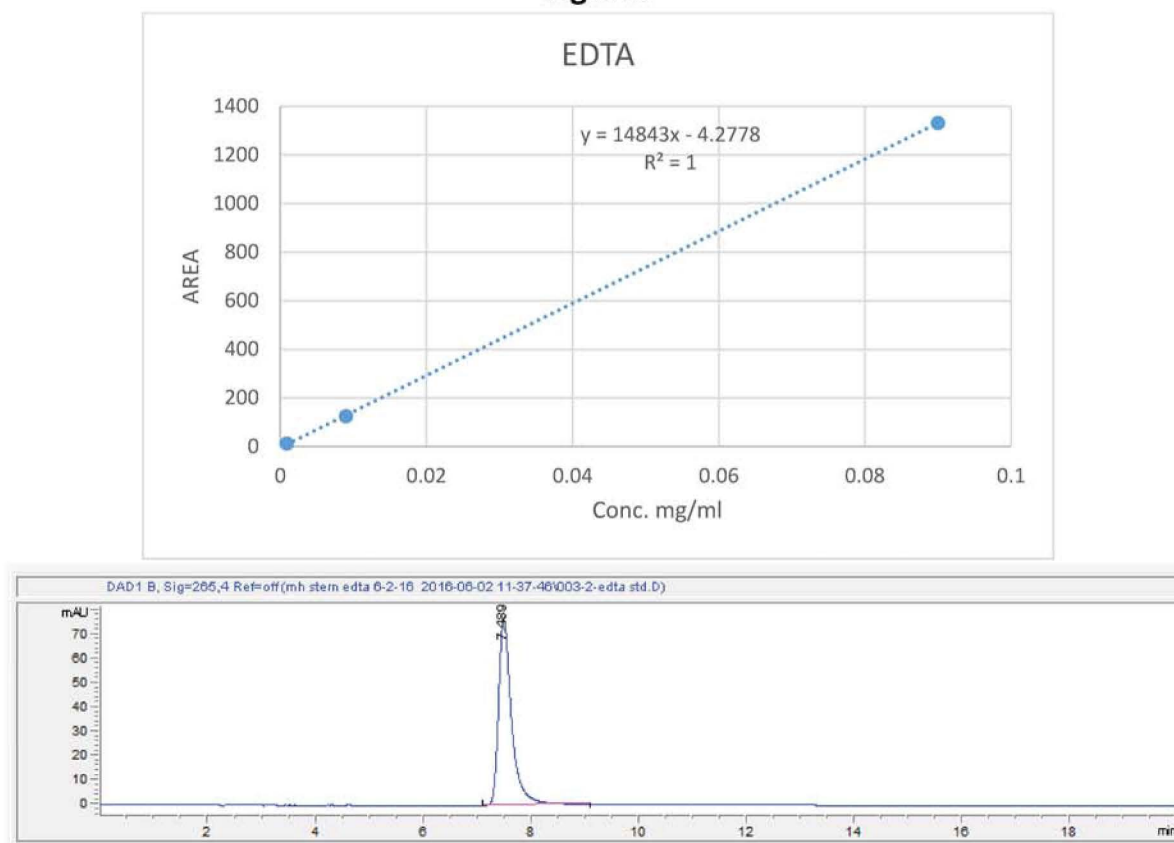


Figure 2: Calibration curve for EDTA standard (top) and HPLC chromatogram of EDTA standard (bottom)

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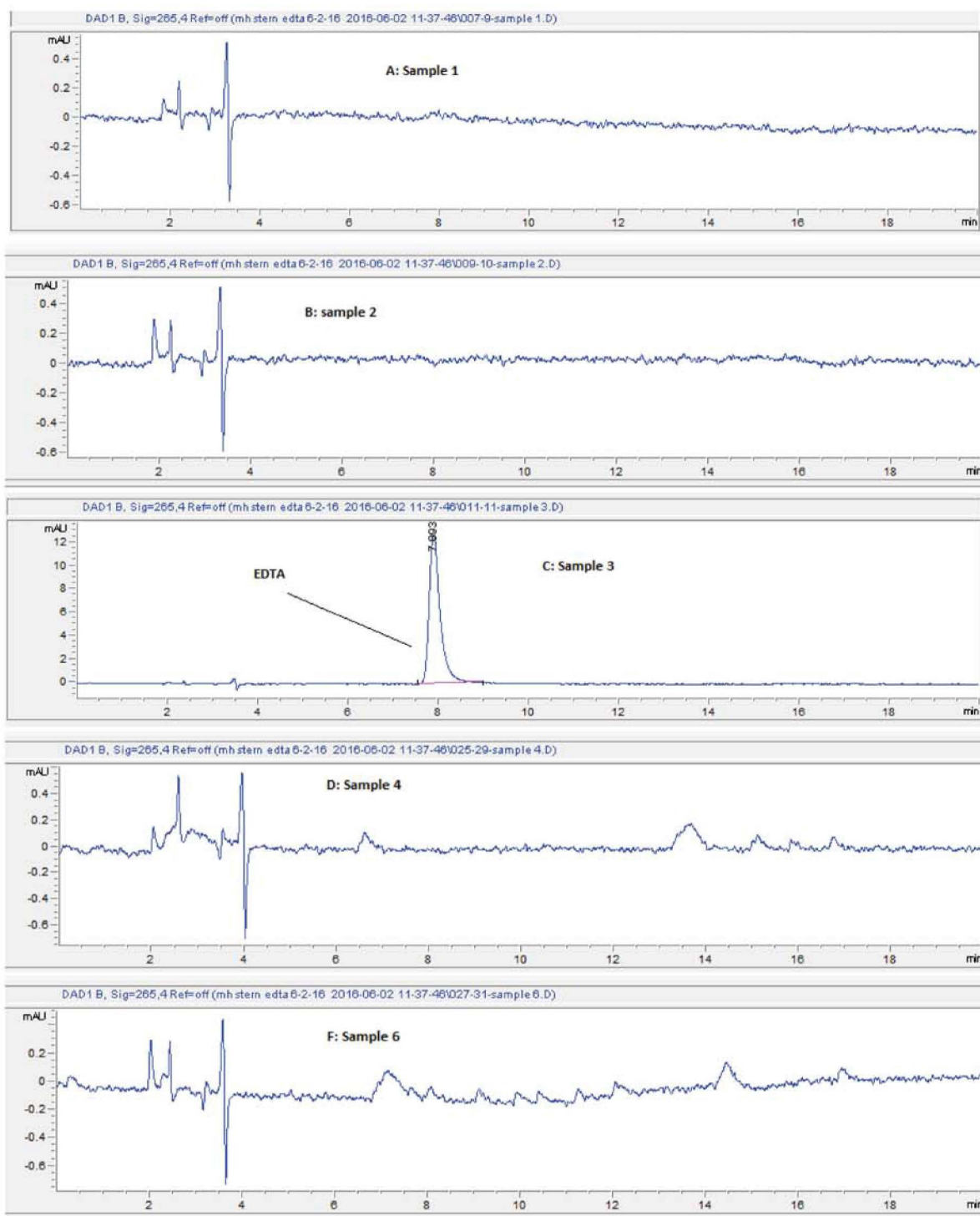


Figure 3: HPLC chromatogram of sample 1(A), sample 2(B), sample 3(C), sample 4(D), sample 5(E) and sample 6(F)

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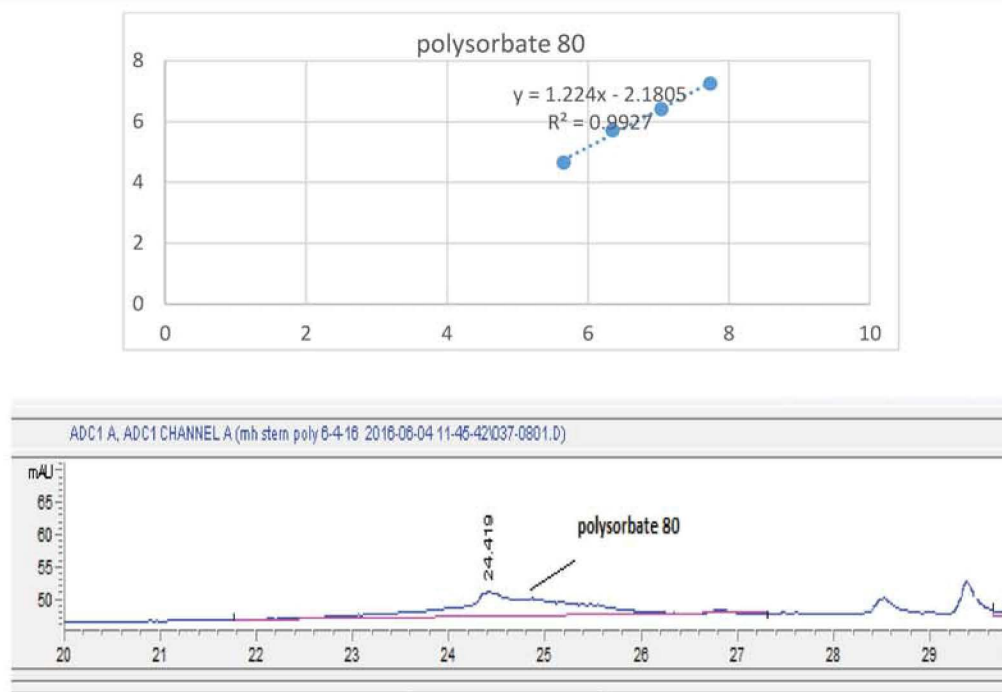


Figure 4: Calibration curve for polysorbate 80 standard (top) and expanded HPLC chromatogram of polysorbate 80 standard (bottom)

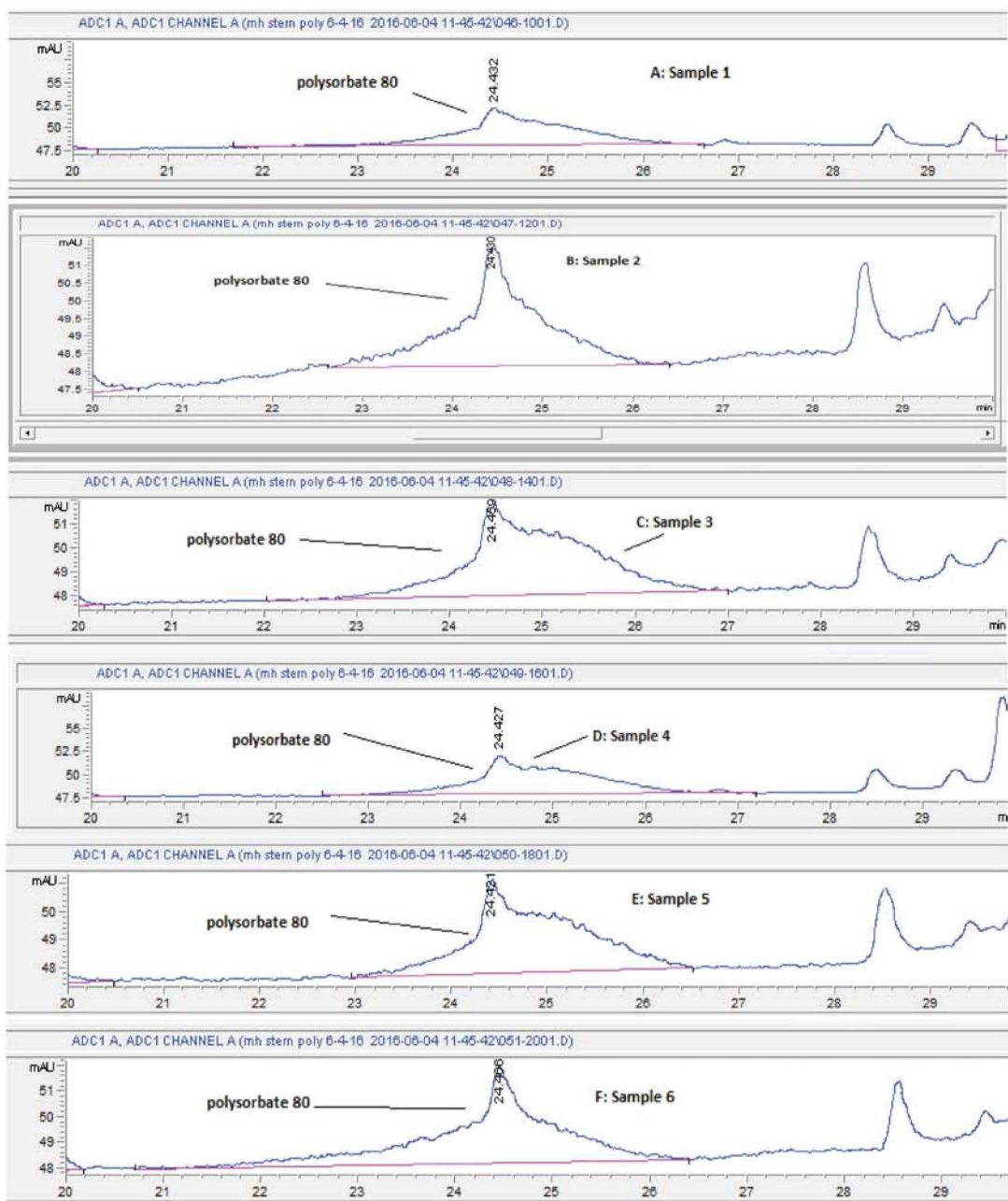


Figure 5: Expanded HPLC chromatogram of Polysorbate 80 in sample 1(A), sample 2(B), sample 3(C), sample 4(D), sample 5(E) and sample 6(F)

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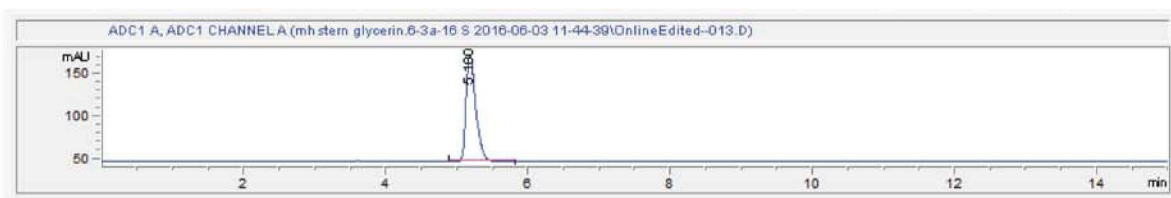
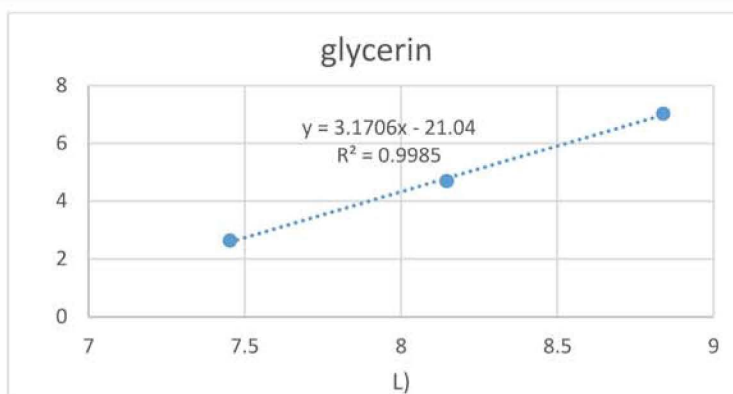
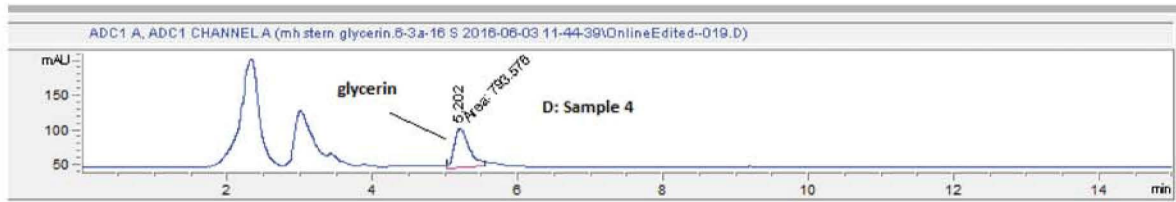
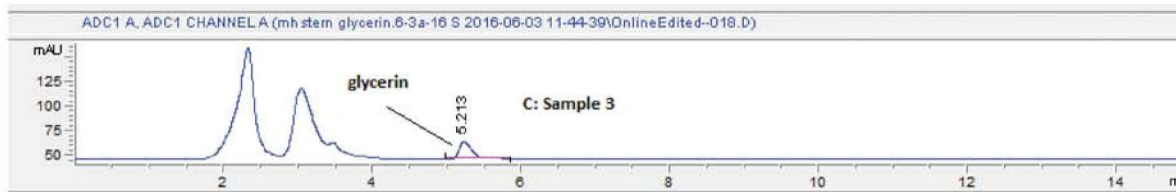
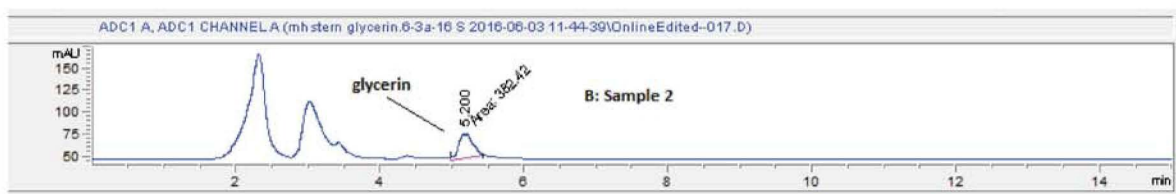
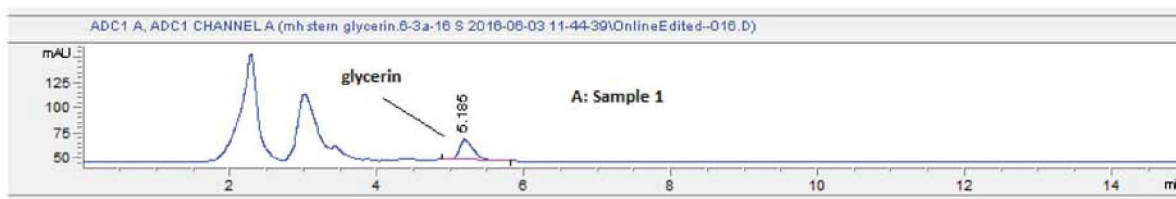


Figure 6: Calibration curve for glycerin standard (top) and HPLC chromatogram of glycerin standard (bottom)



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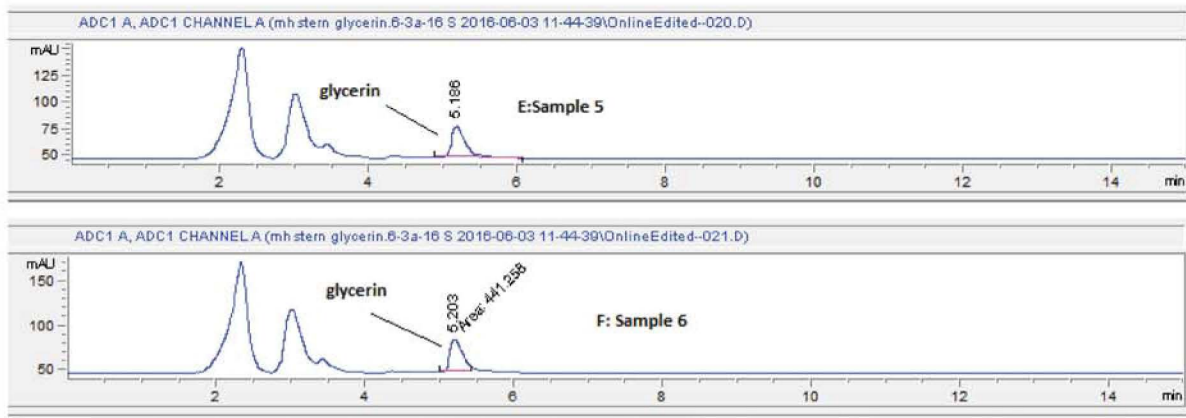
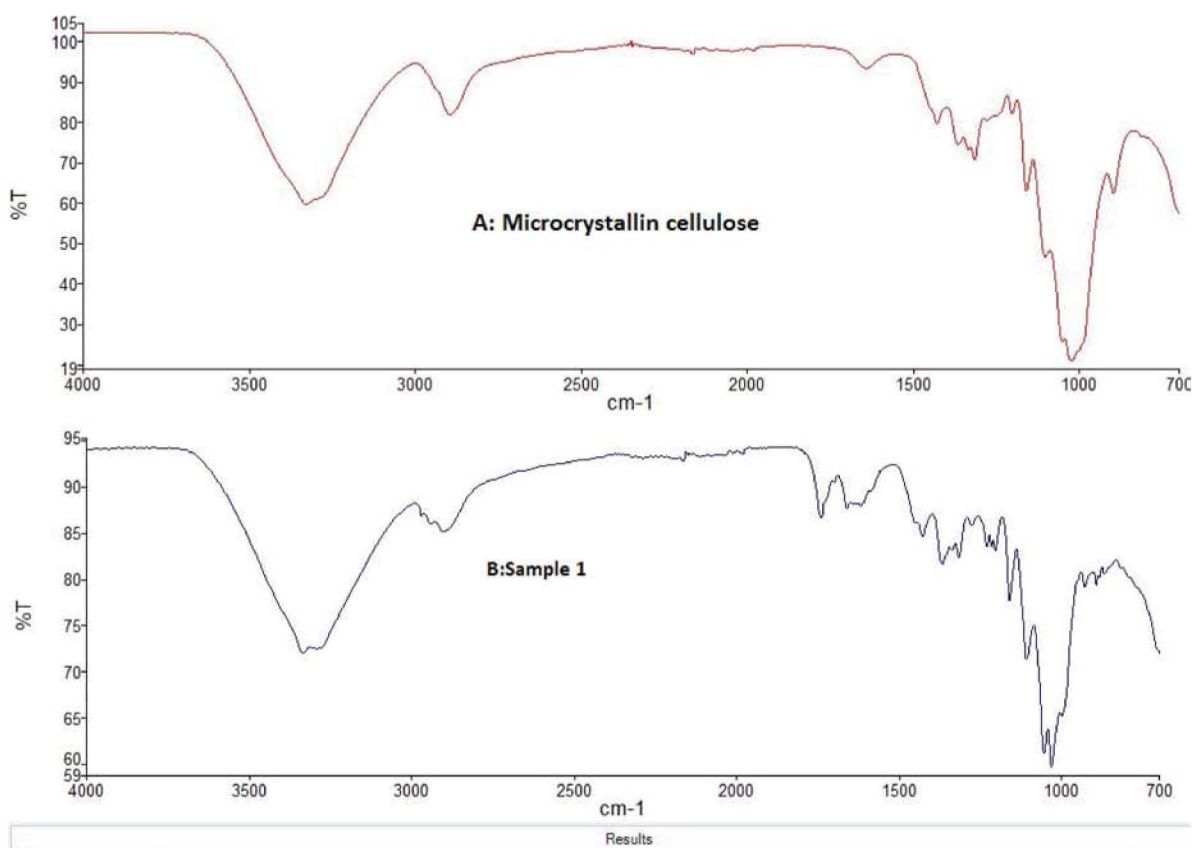


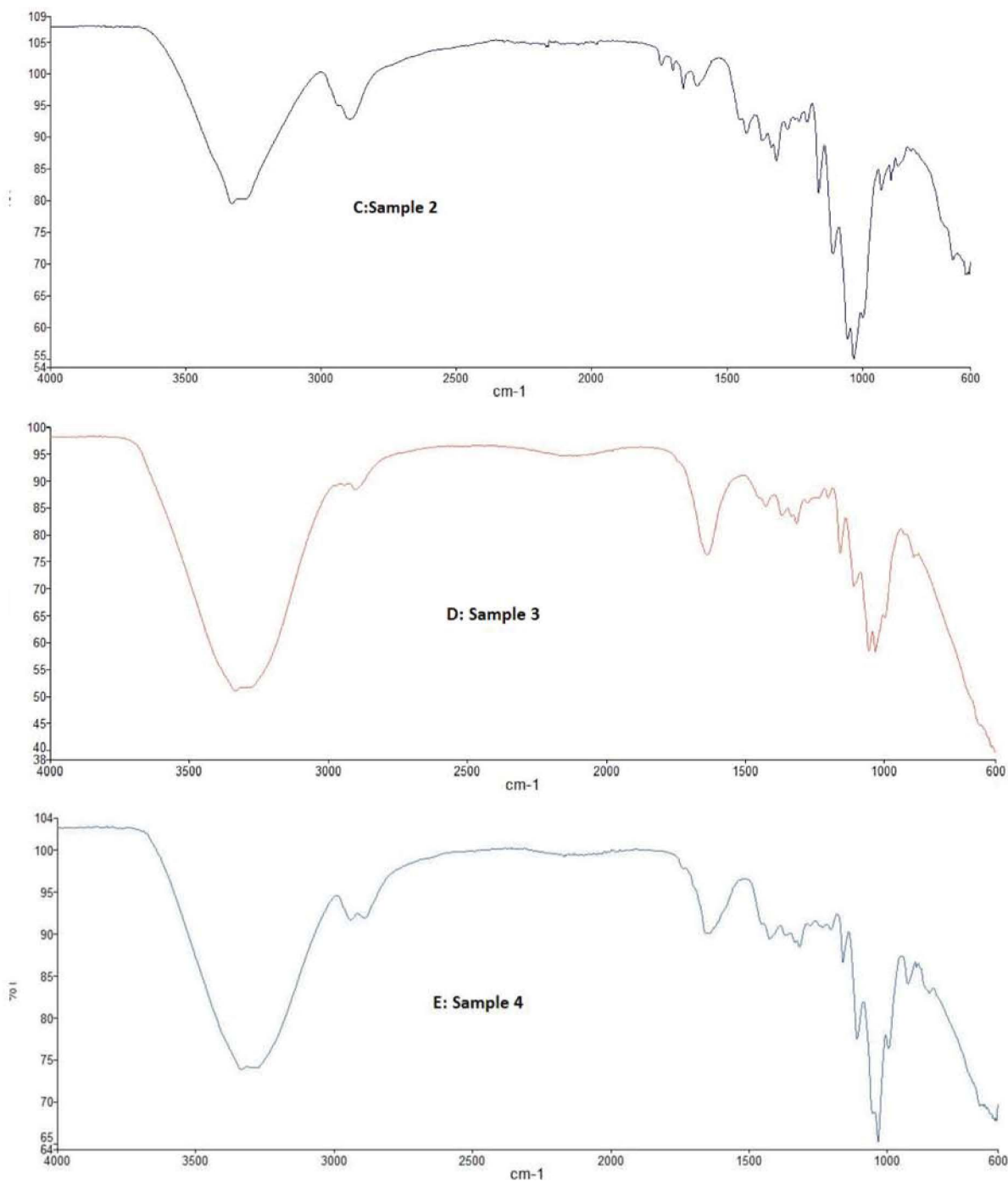
Figure 7: HPLC chromatogram of glycerin in the sample 1(A), sample 2(B), sample 3(C), sample 4(D), sample 5(E) and sample 6(F)



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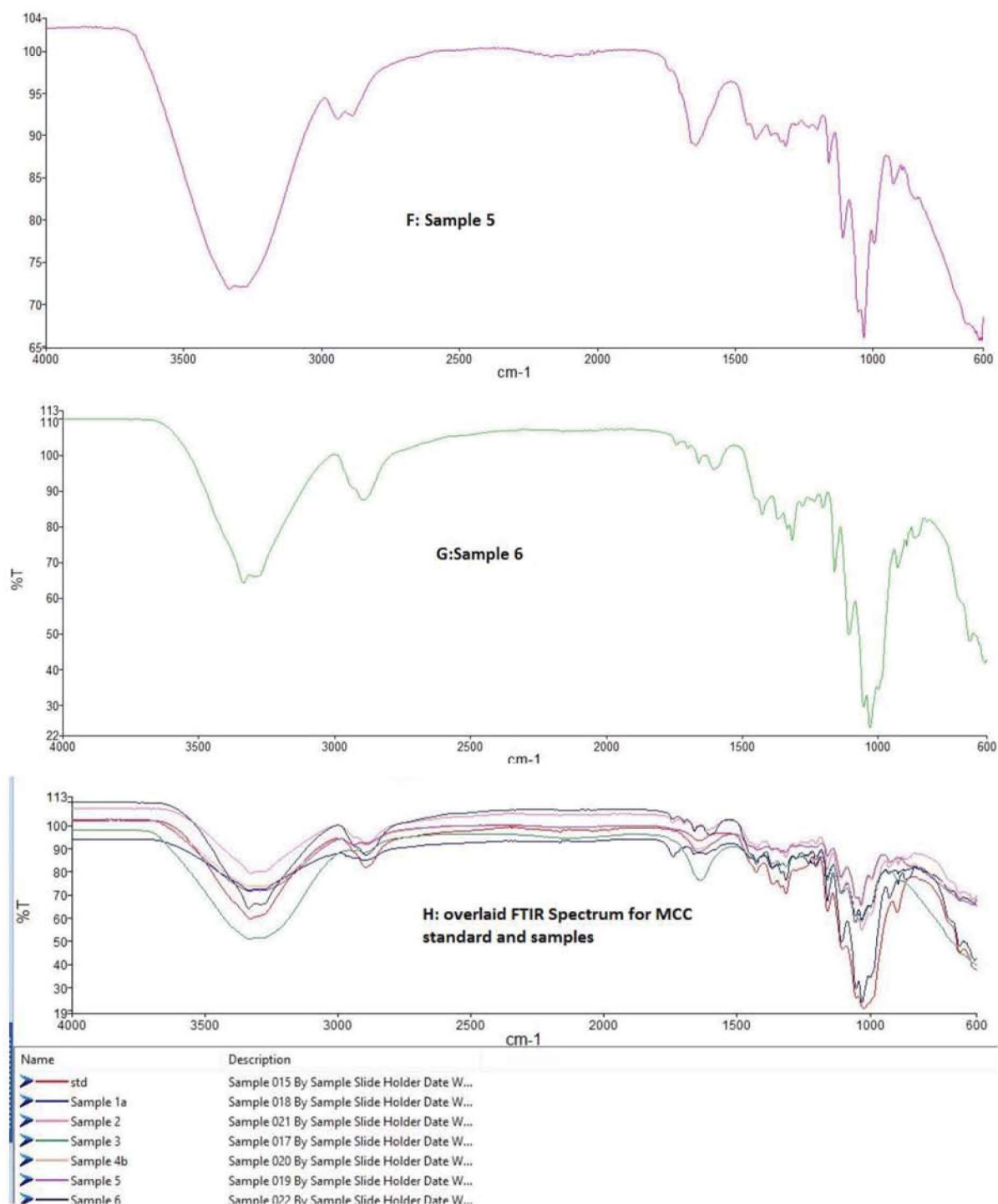
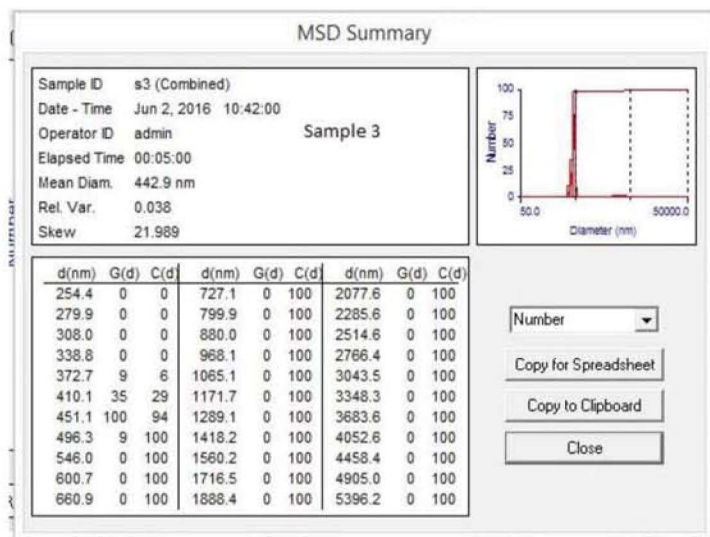
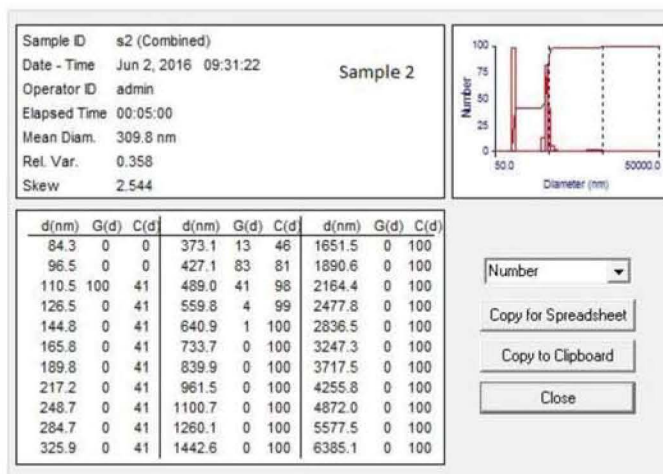
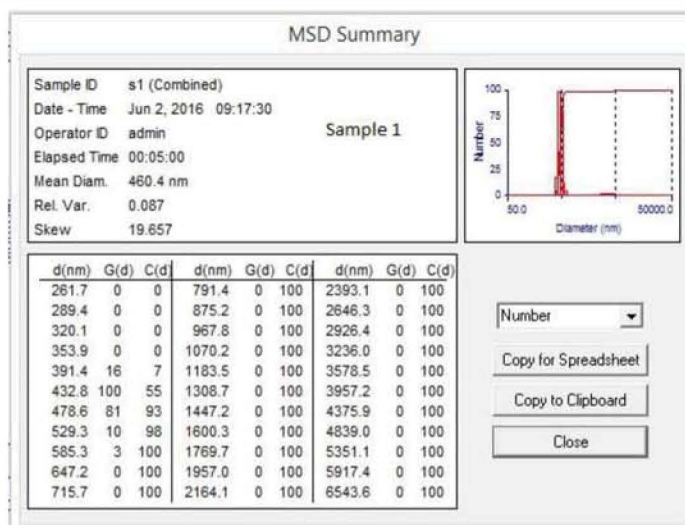


Figure 8: The FTIR spectrum for microcrystal cellulose standard (A), sample 1(B), sample 2(C), sample 3(D), sample 4(E), sample 5(F) sample 6(G) and overlaid FTIR spectrum for MCC standard and samples.

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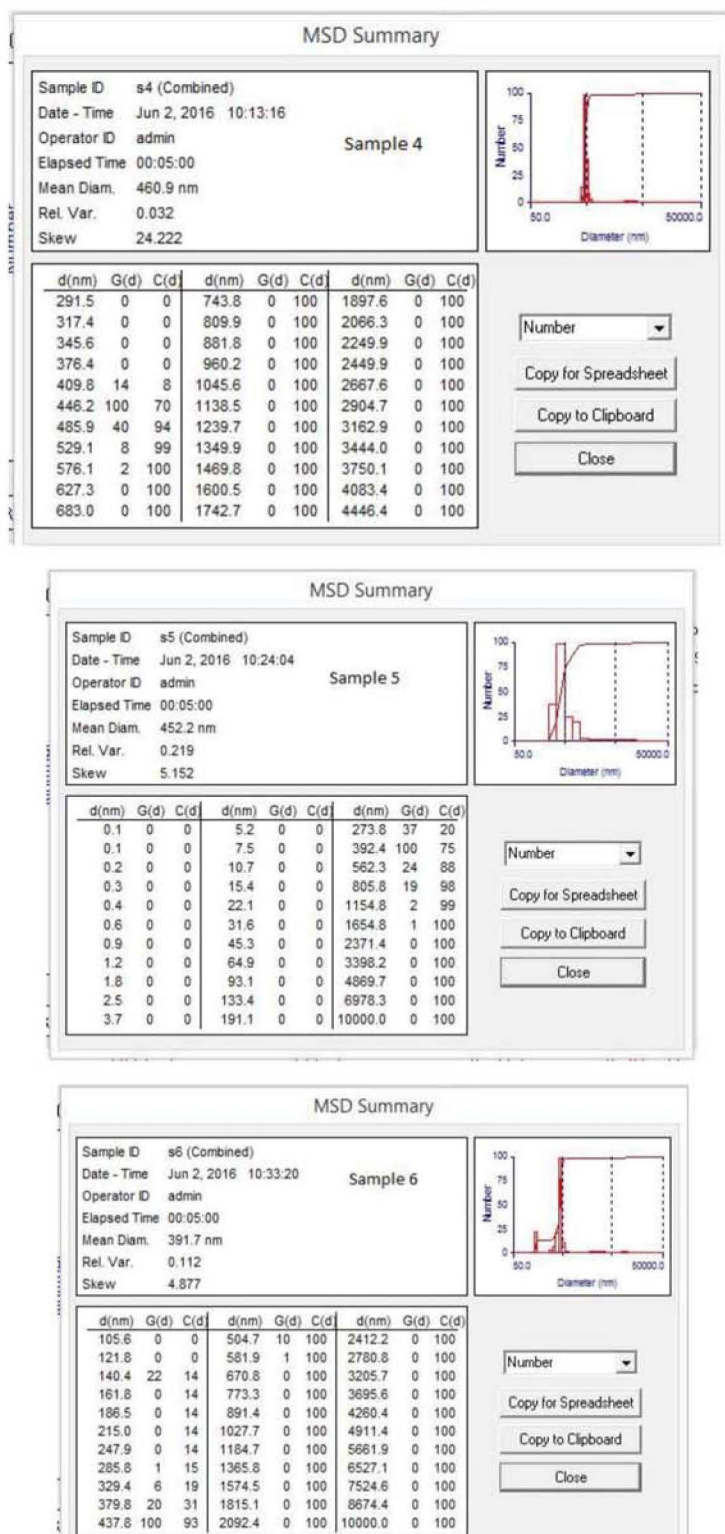
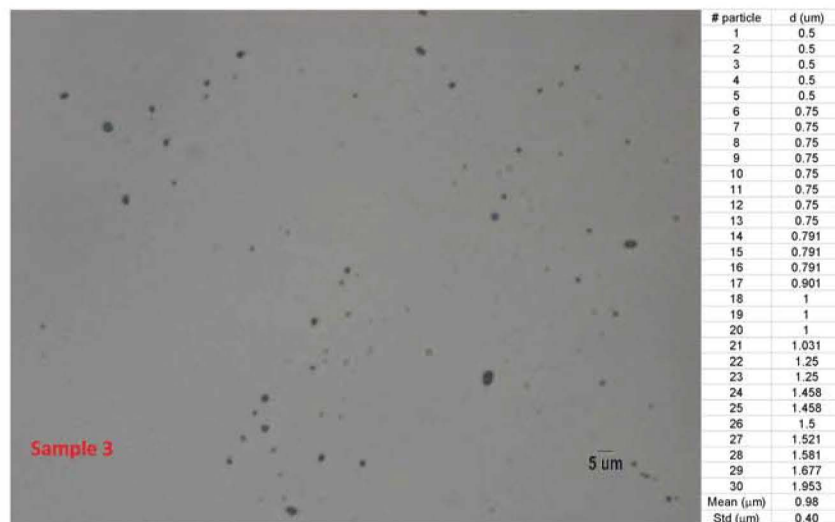
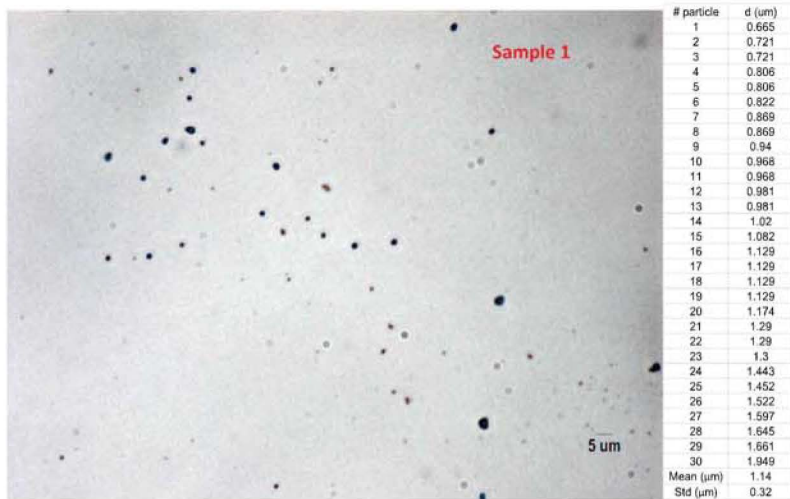


Figure 9: ZetaPALS particle size distribution of sample 1, sample 2, sample 3, sample 4, sample 5 and sample 6

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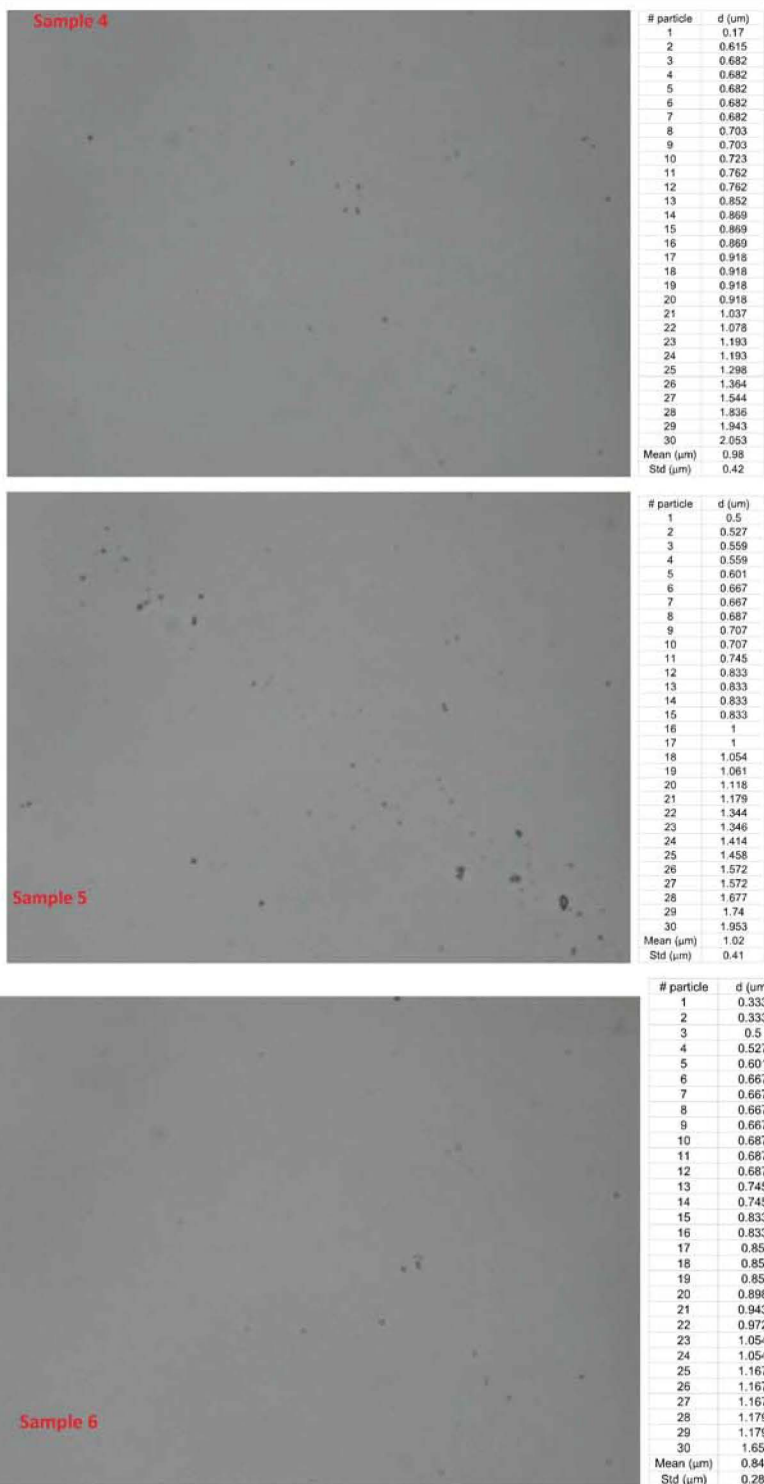


Figure 10: The distribution data and representative image of sample 1, sample 2, sample 3, sample 4, sample 5 and sample 6

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Description of Instrumentation Used

Gas Chromatograph (GC): GC analysis is commonly used to separate and analyze vaporized volatile compounds. This system uses an inert gas to carry the sample through a separatory column, and then detects the retention time of different compounds in the column. Avomeen's scientists often use gas chromatography to help in the identification of an unknown compound, or mixture of compounds. Avomeen's Gas Chromatography capabilities include autosampling, pyrolysis, flame ionization detection, thermal conductivity detection, and the use of a range of polar and non-polar columns.

Reverse Phase High Performance Liquid Chromatography (rpHPLC): Avomeen uses Agilent 1100 series instruments with quaternary pumps. Detection modules include Refractive Index, Evaporative Light Scattering, UV variable wavelength and UV Diode Array Detectors. The quaternary pumps allow the use of variable solvent chemistry to optimize resolution and run time. Diode Array detection allows for collection of data from multiple wavelengths simultaneously. The system is optimized for reverse phase chromatography, which allows the analyst to utilize a highly polar mobile phase solution that carries the compound of interest through the chromatography column. The column contains a non-polar stationary phase that interacts with the compound of interest as it is pumped through the column. The compound eventually is released from the column and travels to the detector where a signal arises based on the compound's characteristic absorbance and retention time. The analog signal is converted to a usable chromatogram where the information about the compound can be analyzed with high accuracy and precision.

Dynamic Light Scattering (DLS): DLS is a photometric technique for determining the size distribution of suspended particles in a liquid medium. The instrument reads the scattering pattern of light created by Brownian motion of suspended particles and calculates the corresponding size distribution. Results can be reported in terms of volume, intensity or number with volume being the primary reporting method for pharmaceutical work. If additional characteristics of the particles are known, the approximate weight of the particles can also be calculated.

Wrap Up

Testing results relate only to items tested. Test report shall not be reproduced, except in full, without approval from Avomeen, LLC in writing.

Thank you for consulting with Avomeen Analytical Services. If you have any questions regarding this analysis, or if we can be of any further assistance, please call us at (800) 930-5450. Following the receipt of this final report, a final invoice indicating the remaining payment will be sent to you. We will safely and securely dispose of all samples and confidential information in our possession in 30 days, unless otherwise instructed by your company.

It has been a pleasure working with you and we look forward to serving you again.

Sincerely,

Avomeen Analytical Services

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