Short Communication

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Preparation Of Nano Medicines from Deer Antones in Azerbaijan and Study of Quality Criteria

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ABSTRACT

One of the priorities for the development of nanotechnology in pharmacy is the targeted delivery of drugs. In this respect, it is important to create new drug forms based on deer antlers, which is one of the natural raw materials of Azerbaijan, with low side effects, high bioavailability and high therapeutic effect. Considering this, nanocapsules, nanoemulsions and nanogels were prepared to hide the bad odor and taste of the extract obtained from deer antlers and to provide long-term storage. Analysis of the amount of active pharmaceutical ingredient in deer antler extract was important. Extraction from deer antlers was carried out in a high-intensity ultrasonic disperser. Alcohol-propylene glycol (50% ethyl alcohol-10% propylene glycol 90:10 ratio) mixture (sample -1) and 80% propylene glycol (sample 2) were used as extractants. Extraction was done once. Sample-1 was analyzed as powder (evaporation in a water bath) and Sample-2 was analyzed as liquid. The amino acid content of secondary metabolites in the samples was analyzed. Amino Acid Screening by LC-MS / MS includes qualitative and quantitative analysis of amino acid compounds (15 compounds in total). Parent ions, fragmentation ions, collision cell potentials, LOD-LOQ, regression coefficient, calibration interval and quantitative results of the analytes were examined. A comparative analysis showed that more amino acids were released in Sample 1. In this example, high amounts of glycine, proline, alanine, glutamine, aspartame were obtained.

Keywords: Drug Delivery Systems; Active Pharmaceutical Ingredients; Deer Antler Extract; Amino Acids; Liquid Chromatography (Spark Holland); Tandem Mass Spectroscopy (AB SCIEX 4000 QTRAP)

Abbreviations: MRM: Multiple Reaction Monitoring; ESI: Electrospray Ionization; EDA: Extracts From Deer Antlers; TDS: Targeted Delivery System; API: Active Pharmaceutical Ingredients

Introduction

Today, more than 50% of pharmaceutical companies use nanotechnology to develop systems to deliver active pharmaceutical ingredients (APİ) to target organs and tissues. Over the past 20 years, nanotechnology has made significant progress in the development of drug delivery systems that improve the solubility and bioavailability of API and help reduce side effects. Specific forms and small sizes of drugs allowed to deliver various therapeutic agents to difficult-to-achieve targets, for example, to cross the blood-brain barrier or to deliver active substances to the cell nucleus [1-5]. Targeted delivery of drugs is a system of active nanoobjects, a way to fully convey the properties of this system to the tissue (organ). Targeted delivery system (TDS) has the following requirements: it must circulate in the blood for a long time, accumulate in the site of inflammation, effectively transfer molecules of active substances to cells and its organelles, be compatible with peptides, nucleic acids and fully maintain physical stability in the blood. should give. It should be noted that the TDS has the ability to carry a marker that can be used to monitor the accumulation of API in the site of inflammation in real time, the size of which can vary from 10 to 300 nm. The use of delivery systems is aimed at reducing the negative side effects of drugs (TDS). To date, there are 5 main areas of application of nanotechnology in medicine and pharmacy: API, new treatments at the nanometer level, in vivo and in vitro diagnostics, medical implants. Nanotransmission systems depend on the nature of the carrier: organic and inorganic; Depending on the state and morphological characteristics of the aggregate are classified as liposomes, micelles, fullerenes, dendrimers, clusters,

nanospheres, nanocrystals. A nanoparticle usually consists of a molecule from which a fraction is formed; API is a surface changer that provides delivery to the target. The following types of nanomaterials are known: nanoporous structures, nanoparticles, nanotubes and nanofields, nanodispersions (colloids), nanostructured surfaces and films, nanocrystals and nanoclusters. Depending on the state and morphological properties of the aggregate, nanosuspensions, liposomes, mixed micelles, crystal structures (liotropes), microemulsions, nanoemulsions, nanocapsules, surfactants, polymer nanoparticles, solid lipid nanoparticles; organic metal nanoparticles are known [1,3,5-8].

It should be noted that the main concepts in the creation of nanopreparations are molecular objects - drugs and targets. The target is a macromolecular biological structure, which is associated with a specific function, the violation of which causes the disease, in which case it is necessary to take appropriate approaches. The most common targets are receptors and enzymes. APİ is a chemical compound (usually low molecular weight) that specifically interacts with the target to change the reaction of the target cell in one way or another. If a receptor acts as a target, then the drug will most likely be its ligand, i.e the compound specifically interacts with the active area of the receptor. One of the central research topics in the field of nanotechnology is the synthesis of high-quality nanoparticles with precise control over the size, shape, structure and composition of particles. Of particular interest for inorganic nanoparticles are nanoclusters and nanocrystals (usually 2-100 nm) in the measuring range of ~ 2 nm. The most widely used in recent years are magnetically controlled nanotoxes, which allow to create the optimal concentration of the drug in the therapeutic effect zone, operating on the principle of «drug - target organ», which reduces systemic toxicity by reducing the total dose and prolonged retention in the affected organ. significantly lowers. Thus, the use of nanotechnologies for the development of the composition and technology of pharmaceuticals allows the creation of high-performance nanopreparations that deliver active pharmaceutical ingredients to the site of inflammation [1,3,7-9].

Taking into account the above, it was considered expedient to conduct research in the field of preparation of nanopharmaceutical forms based on extracts from natural raw materials (deer antlers, clays, medicinal plants). For many years, many countries around the world have been developing and manufacturing various medicines and cosmetics from different parts of the deer (antlers, tails, blood, etc.) [10,11]. Despite all this, the development of new forms of medicine from deer antlers that deliver the active substance to the target and provide long-term effects remains relevant. Therefore, we have conducted research to obtain extracts from deer antlers grown in Azerbaijan with the participation of various solvents and to prepare nanocapsules, nanoemulsions Figure 1. The size of the forms developed as a drug delivery system during the research was proved by SEM and TEM analysis methods [12-14]. This article is devoted to the analysis of the chemical composition of extracts from deer antlers (EDA).

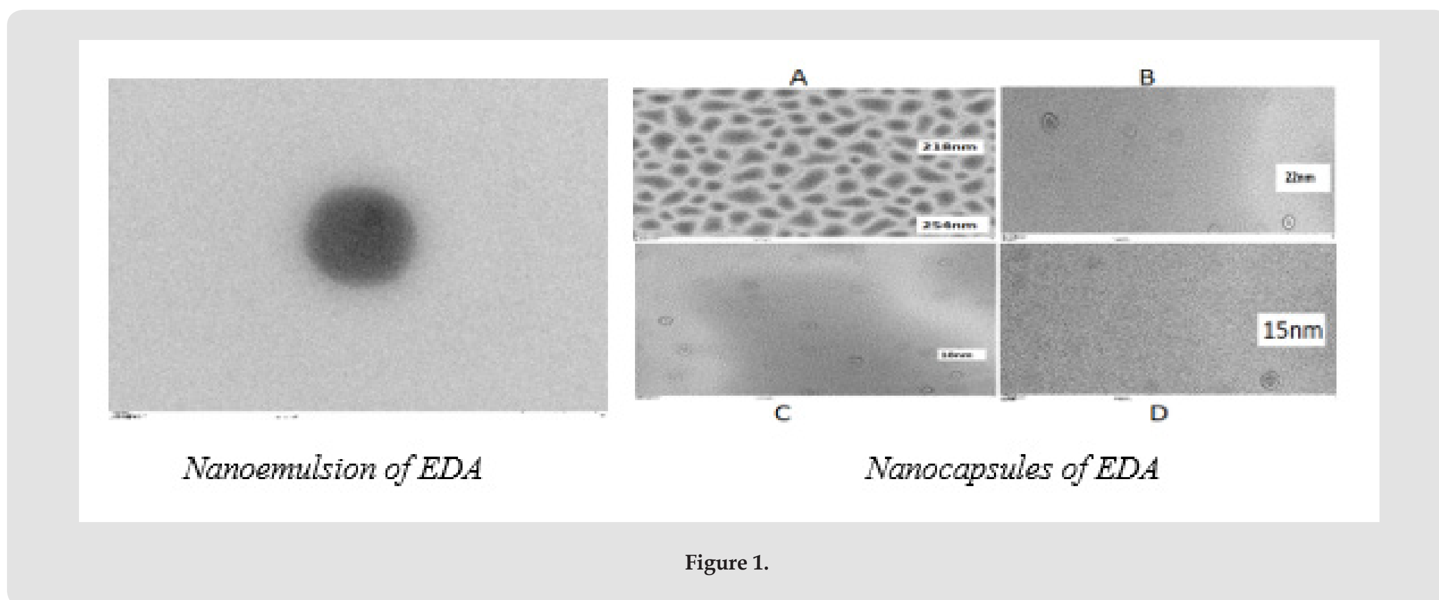

Figure 1.

The Objective of the Study

Is to test the amount of secondary metabolites as a biologically active ingredient in extracts from deer antlers by modern methods.

Materials and Methods of Research

The research was carried out at the Laboratory of Pharmaceutical Technology of the Azerbaijan Medical University and the Central Application and Research Laboratory of the Chechen University of

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Agri Ibrahim, Turkey. Deer antlers grown in Azerbaijan were used as the object of research. Extraction from deer antlers was performed in a high-intensity ultrasonic disperser. Alcohol-propylene glycol (50% ethyl alcohol-10% propylene glycol 90:10 ratio) mixture (sample -1) and 80% propylene glycol (sample 2) were used as extractants. The extraction process was performed once. Sample-1 was analyzed as a powder (evaporated on a water bath), and Sample-2 was analyzed as a liquid. Amino acid content from secondary metabolites was analyzed in the samples.

Chemicals and Reagents

All reference standards and formic acid (purity 95% ≤) were purchased from Sigma-Aldrich. LC-MS grade methanol was purchased from Isolab. The deionized water was obtained by (Millipore Direct-Q® 3 UV) water purification system.

Sample Preparation

The weighed samples were placed in teflon vessels for hydrolysis. Then, 8 mL of 6 M Hydrochloric acid solution was added to the vessels and the vessel lids were closed. Temperature-controlled microwave operation was carry out through microwave digestion system (Milestone Start D). Conditions for microwave operation are given in Table 1. The solutions in the vessels, which were cooled to room temperature after microwave treatment. Deionized water was added to the solution to be a total volume of 50 ml. After appropriate dilutions were made, it was filtered through a PTFE filter (Isolab 0.45 µm). The filtered solution was transferred into capped vials for LC-MS/MS analysis [15].

Table 1: Conditions of temperature-controlled microwave operation.

	Stage 1	Stage 2
Power (%, 800 W)	100	80
Preparation time (min)	5	5
Fixed dwell time (min)	20	10
Temperature (max, °C)	100	155

Note: Weight of Sample 1: 361.8 mg, Weight of Sample 2: 403.1 mg.

Amino Acid Screening by LC-MS/MS

This method includes qualitative and quantitative analysis of amino acid compounds (15 compounds in total). Analyzes were performed using a liquid chromatography (Spark Holland) and tandem mass spectroscopy (AB SCIEX 4000 QTRAP) combined system. Chromatographic separation was carried out with a C18 type column (Inertsil ODS-3V 250 mm x 4.6 mm, 5 µm). Gradient system conditions were set as indicated in Table 2. 0.1% (v/v) formic acid solution (A) and methanol (B) were used as mobile phase. In addition, the injection volume was set to 10 µL, the flow rate was set to 0.700 mL/min, and the column furnace temperature was set to 30°C. The chromatographic screening time was set to 15 minutes. Multiple Reaction Monitoring (MRM) mode was used for the qualitative and quantitative determination of the analytes. Electrospray ionization (ESI) was used as an ionizer technique and the ionization conditions were given in Table 3.

Table 2: Gradient system conditions.

Time (h:m:s)	Flow (mL/min)	Mobil Phase A (%)	Mobil Phase B (%)
0:00:00	0.7	95	5
0:05:00	0.7	70	30
0:08:00	0.7	50	50
0:10:00	0.7	40	60
0:12:00	0.7	20	80
0:13:00	0.7	40	60
0:14:00	0.7	95	5
0:15:00	0.7	95	5

Table 3: Electrospray ionization conditions.

Parameter	Value	Unit
Ions Source	Turbo Spray	Unit
Curtain Gas (CUR)	10	psi
Collision Gas ((CAD)	Medium	
Ion Spray Voltage (IS)	4500	V
Temperature (TEM)	100	°C
Ion Source Gas 1 (GS1)	40	psi
Ion Source Gas 2 (GS2)	60	psi
Interface Heater (IHE)	On	

Results

Belong to samples and standard mixture (20000 ppb) chromatograms were given in Figures 2-4. Parent ions, fragmentation ions, collision cell potentials, LOD-LOQ, regression coefficient, calibration range and quantitative results of the analytes are given in Table 4. A comparative analysis showed that more amino acids were released in Sample 1. In this sample, high amounts of glycine, proline, alanine, glutamine, and aspartame were obtained. In our future research, it is planned to use an alcohol-propylene glycol mixture as a solvent in the extraction of deer antlers and to create nano-drug forms based on it.

Table 4: Secondary metabolite screening results.

No	Analytes	Retention Time	Parent Ion (m/z)[a]	Fragment Ions (m/z)[a], (CE)[b]	LOD/LOQ [c] (ng/mL)	R^2	Calibration Range (ng/mL)	Quantification (mg analyte/G extract)	
								Sample 1 (Solid sample)	Sample 2 (Liquid sample)
1	Lysine	2.56	147.12	83.9 (23), 130.1 (13)	7.02/21.28	0.9998	39.06-2500	17.15 ± 0.19	ND[e]
2	Histidine	2.59	156.08	110.2 (21), 83.2 (35)	6.61/20.03	0.9992	39.06-625	5.78 ± 0.04	ND[e]
3	Glycine	3.23	75.97	76.0 (5), 30.1 (17)	3.79/11.50	0.9996	1250-20000	103.66 ± 0.38	D[d]
4	Serine	3.24	106.11	60.3 (19), 88.2 (19)	6.58/19.92	0.9986	39.06-1250	14.31 ± 0.44	ND[e]
5	Alanine	3.33	90.16	44.2 (17), 45.1 (41)	7.00/21.22	0.9992	1250-20000	66.53 ± 0.38	D[d]
6	Glutamate	3.47	148.04	84.2 (21), 130.1 (13)	12.31/37.29	0.9936	1250-20000	62.31 ± 4.08	ND[e]
7	Cystine	3.55	122.3	76.2 (19), 59.2 (31)	8.25/24.99	0.999	39.06-1250	D[d]	ND[e]
8	Aspartate	3.57	134.06	74.1 (19), 88.2 (15)	1.06/3.21	0.995	1250-20000	35.93 ± 0.50	ND[e]
9	Proline	3.66	115.99	70.2 (19), 43.4 (45)	1.25/3.78	0.9998	1250-20000	75.66 ± 0.12	D[d]
10	Methionine	4.68	150.1	104.0 (15), 133.2 (13)	2.49/7.57	0.998	39.06-1250	D[d]	D[d]
11	Leucine	6	132.12	86.3 (13), 44.2 (35)	4.33/13.11	0.9998	39.06-1250	9.53 ± 0.04	ND[e]
12	Isoleucine	6.45	132.12	86.2 (13), 69.3 (27)	12.52/37.95	0.999	39.06-2500	24.27 ± 0.52	0.99 ± 0.005
13	Tyrosine	6.58	182.14	136.3 (17), 91.2 (37)	9.57/29.01	0.9966	39.06-1250	2.01 ± 0.03	0.29 ± 0.014
14	Phenylalanine	9.23	166.11	120.1 (15), 103.3 (37)	6.36/19.28	0.9999	39.06-1250	12.53 ± 0.01	D[d]
15	Tryptophan	11	205.13	188.2 (15), 146.3 (25)	4.62/14.01	0.9992	39.06-1250	D[d]	D[d]

Note:

a Molecular and fragment ions of the standard compounds (mass to charge ratio).

b (CE), refers to collision energies of related fragment ions.

c Limit of Detection / Limit of Quantification.

d Peak observed, however concentration was lower than Limit of Quantification.

e Not detected.

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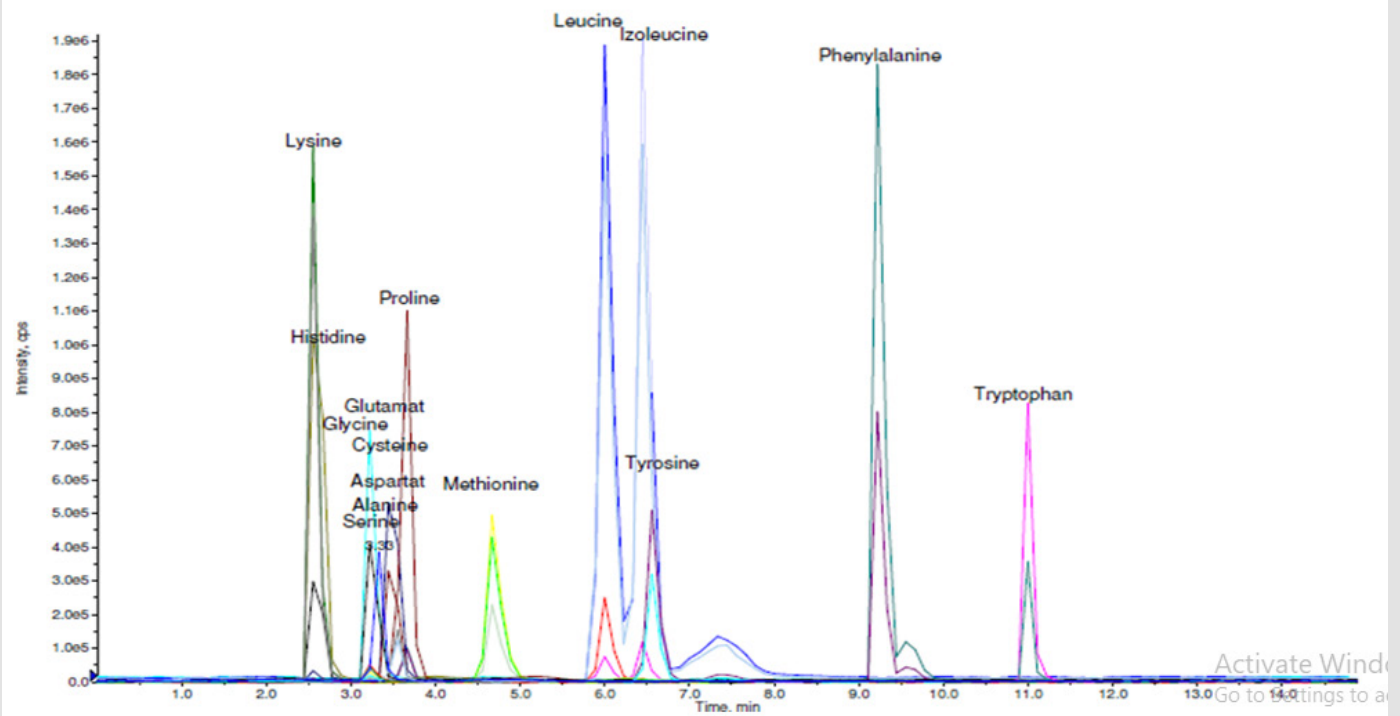

Figure 2: Standard Chromatogram (20,000 ppb).

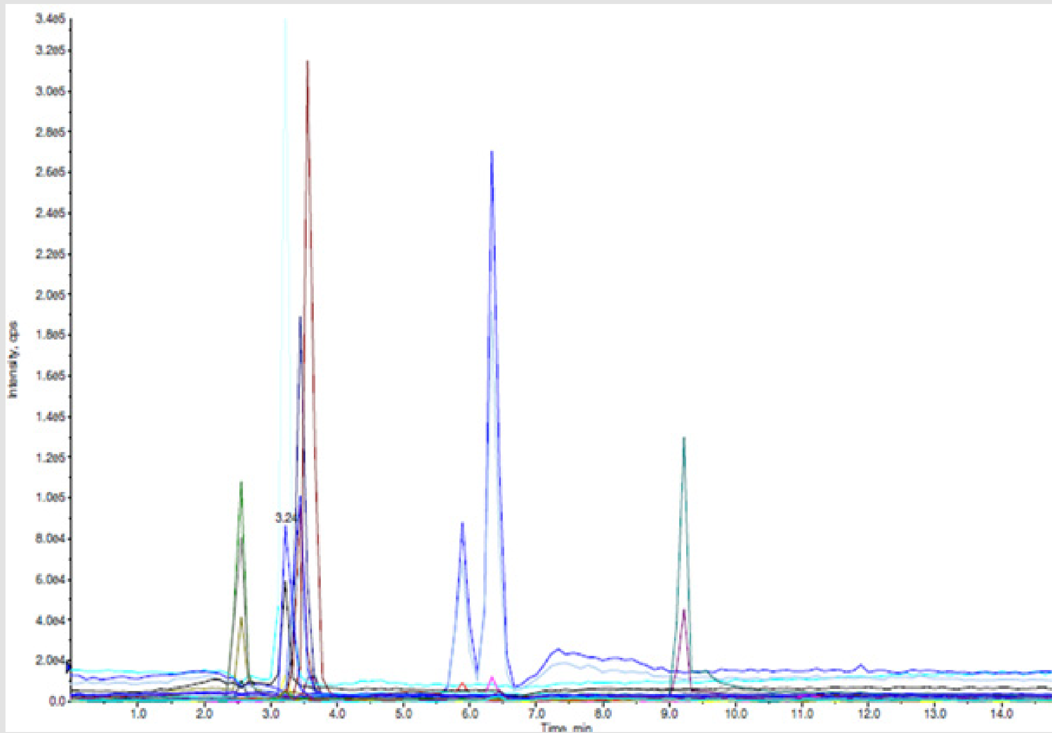

Figure 3: Sample 1 (solid sample).

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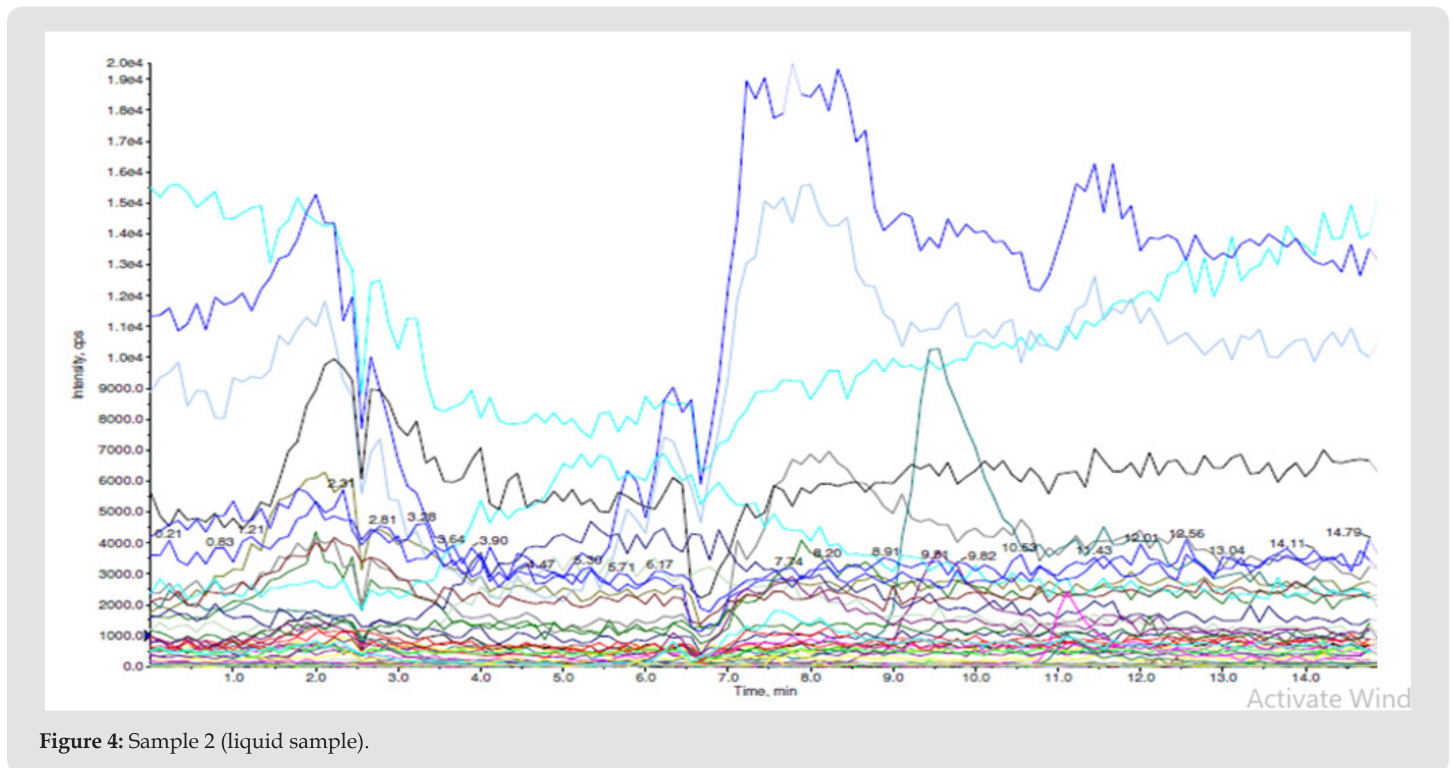

Figure 4: Sample 2 (liquid sample).

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