

Development of conditions for extraction of clozapine and olanzapine drugs from aqueous media using organic solvents and study of factors affecting them

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Abstract:

The article presents information on the therapeutic and toxic properties of the drugs clozapine and olanzapine and their analogues registered in the Republic of Uzbekistan. Factors influencing the extraction of clozapine and olanzapine from aqueous media, including the effect of organic solvents and pH of the medium, were also studied. Qualitative and quantitative analysis was carried out using a previously developed UV spectrophotometric method.

Keywords:

Clozapine, UV spectrophotometry, absorption spectrum, specific absorption index, molar absorption index, validation parameters, calibration graph.

INTRODUCTION

Psychotropic drugs of the neuroleptic group are widely used in medical practice. These drugs form the "basis" of pharmacotherapy in modern psychiatry. Such drugs, in addition to normalizing the pathological process in the body, in some cases, as a result of excessive use or as a result of their accumulation in the body, can lead to severe poisoning. These drugs include clozapine and olanzapine.

In recent years, due to the abundance of relatively cheap generic drugs on the pharmaceutical market, cases of poisoning with antipsychotic drugs have been increasing, both in the treatment of mental illnesses and in non-medical situations. Poisoning with antipsychotics in patients with mental and behavioral disorders is often intentional, but occasionally poisoning occurs due to improper use or overdose. According to the State Register of Medicines and Medical Devices, more than 100 names of neuroleptic drugs are used in Uzbekistan. This group of drugs also includes clozapine and olanzapine. In Uzbekistan, 3 clozapine preparations (clozalan, leponex, azaleptol), 9 olanzapine preparations (olanzapine LEK, olanzapine J LIFE, egolanza, zyprexa, olfex, ozapex, zolaxa, olzap, jubrexa) are registered. [1] Despite the relatively low toxicity of these drugs, acute poisoning has been reported even when taking therapeutic doses. Most often, poisoning occurs when antipsychotics are taken against the background of alcohol or drug intoxication for self-treatment (eliminating psychoses, eliminating withdrawal symptoms) or for enhancing the intoxicating effect. Despite the complete knowledge of the pharmacological properties and toxicity of atypical antipsychotics, they are often found in the diagnosis of patients with acute poisoning, which continues to attract the attention of researchers. For many modern atypical antipsychotics, there is no information in the scientific

literature about the available methods of isolation and identification. The available experimental data are inconclusive and insufficient to obtain a universal method for the detection of these drugs. Difficulties arise when trying to separate antipsychotics from each other and from other psychoactive substances. Clozapine is a pale yellow crystalline powder. Olanzapine is a yellow crystalline powder. Both of drugs insoluble in water, soluble in alcohol.

MATERIALS AND METHODS

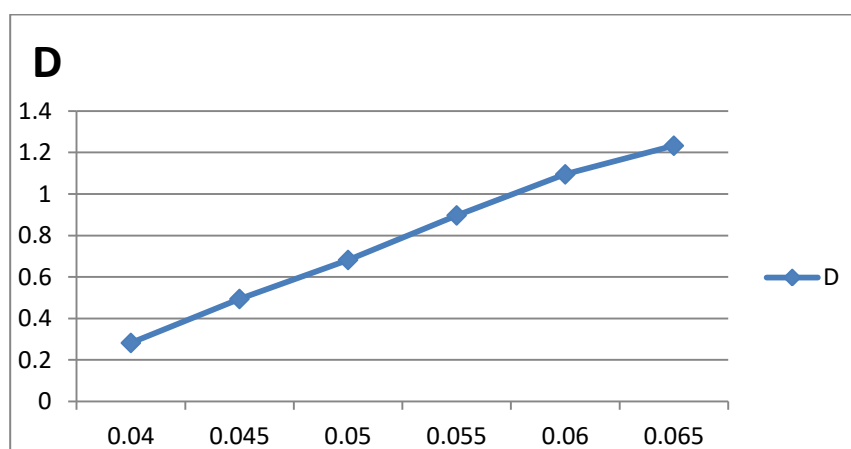
Taking into account the increasingly widespread use of Clozapine and Olanzapine in medical practice and the fact that its toxicity and chemical-toxicological aspects have not been fully studied, it is important to study the effect of organic solvents and pH on the extraction process of Clozapine and Olanzapine, and to solve the issues of forensic examination. was taken as a basis for creation.

Solvents such as benzene (GOST 5779-78), ethylacetate (GOST 12375-76), chloroform (R 76.822.279), petroleum ether and acetone (GOST 6933-75) were used to study the influence of the nature of the organic solvent on the extraction process. To carry out the analysis, 9 ml of solutions with different pH values were taken in 250 ml conical flasks with a capacity of 250 ml, 1 ml of the working solution containing 125 µg/ml of clozapine was added to it, and 10 ml of organic solvent was added and shaken uniformly for 15 minutes on a mechanical shaker.

The flasks were left for 5 minutes to separate the layers. After complete separation of the layers, the organic solvent layer was filtered through filter paper soaked in solvent into dry porcelain bowls with 5 g of anhydrous sodium sulfate in advance using a separatory funnel. The filter paper was washed with 3-5 ml of organic

solvent and the test was added to the main extract. The organic solvents from the extract were evaporated to a dry residue under a stream of hot air. The dry residue was dissolved in 95% ethyl alcohol, brought to 5 ml and

analyzed by UV spectrophotometric method. The amount of clozapine in the aqueous medium was determined based on a previously prepared calibration graph.

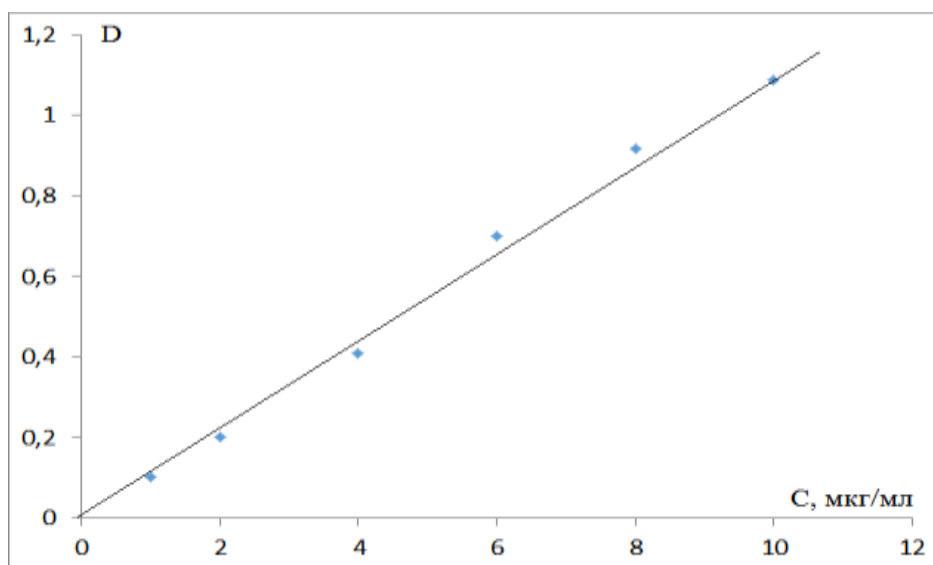


1 - picture. Calibrated plot of clozapine obtained at UV wavelength

The same extraction conditions were carried out separately for each organic solvent.

To study the effect of organic solvents on the extraction process of olanzapine, 9 ml of solutions with different pH values were taken in 250 ml conical flasks, 1 ml of working solution containing 15 µg/ml of olanzapine was added to it, and 10 ml of organic solvent was added, and mechanically stirred for 15 minutes shaken evenly in a shaker.

The flasks were left for 5 minutes to separate the layers. After complete separation of the layers, the organic solvent layer was filtered through filter paper soaked in solvent into dry porcelain bowls with 5 g of anhydrous sodium sulfate in advance using a separatory funnel. The filter paper was washed with 3-5 ml of organic solvent and the test was added to the main extract. The organic solvents from the extract were evaporated to a dry residue under a stream of hot air. The dry residue was dissolved in 95% ethyl alcohol, brought to 5 ml and analyzed by UV spectrophotometric method (Figures 15-27). The amount of olanzapine in the aqueous medium was determined on the basis of a previously prepared calibration graph.



2 - picture. Calibrated plot of olanzapine obtained at UV wavelength

The same extraction conditions were carried out separately for each organic solvent.

2.2 To study the effect of pH environment on the extraction process of Clozapine and Olanzapine

The pH value of the medium has a great influence on the process of extracting the tested substances from the aqueous medium. Therefore, the effect of pH on the extraction of clozapine and olanzapine from aqueous media was studied. For this, using standard fixanals (GOST 8.135 - 74, pH metric standard - titer), the pH of the environment is 2.56; 6.86; Solutions of 9.18 and 12.45 were prepared and analyzed under the above extraction conditions.

The results of the experiment are presented in Tables 1.1 and 1.2

Table 1.1.
The results of studying the effect of organic solvent and pH on the extraction of clozapine residues from aqueous medium

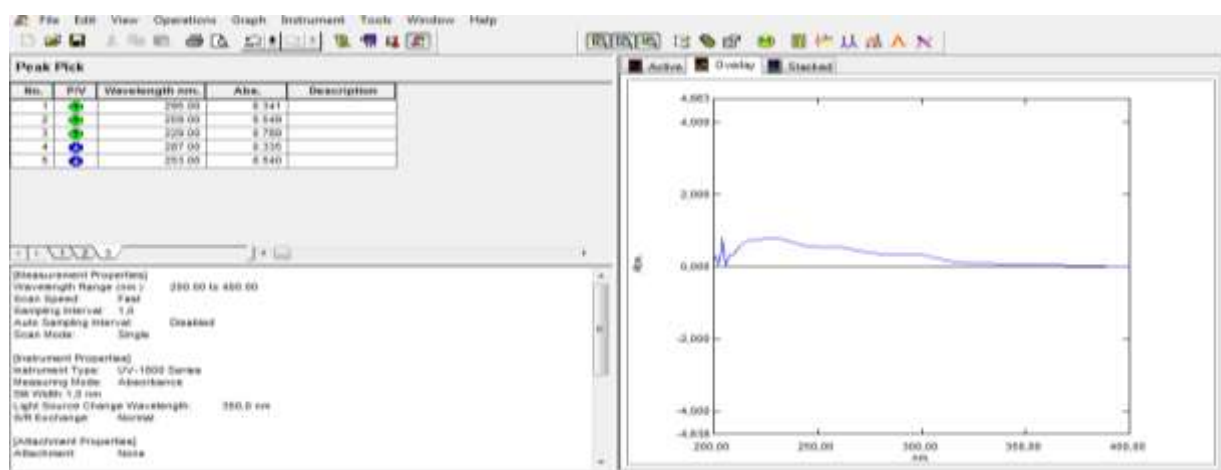
pHindicator	aqueous medium							
	Organic solvents							
	chloroform		ethyl acetate		acetone		benzene	
	extracted							
	µg	%	µg	%	µg	%	µg	%
2,56	53,0	42,4	49,0	39,3	48,0	38,4	48,6	38,9
6,86	67,0	53,6	56,0	44,8	49,5	39,6	55,0	44,0
9,18	55,0	44,0	51,5	41,2	55,5	44,4	46,4	37,2
12,45	59,0	47,8	50,0	40,0	31,0	24,7	25,1	20,2

From the data presented in the table above, it can be seen that clozapine is transferred to the chloroform layer in a maximum amount of 53.6.0% during a single extraction from the aqueous medium at a pH of 6.86.

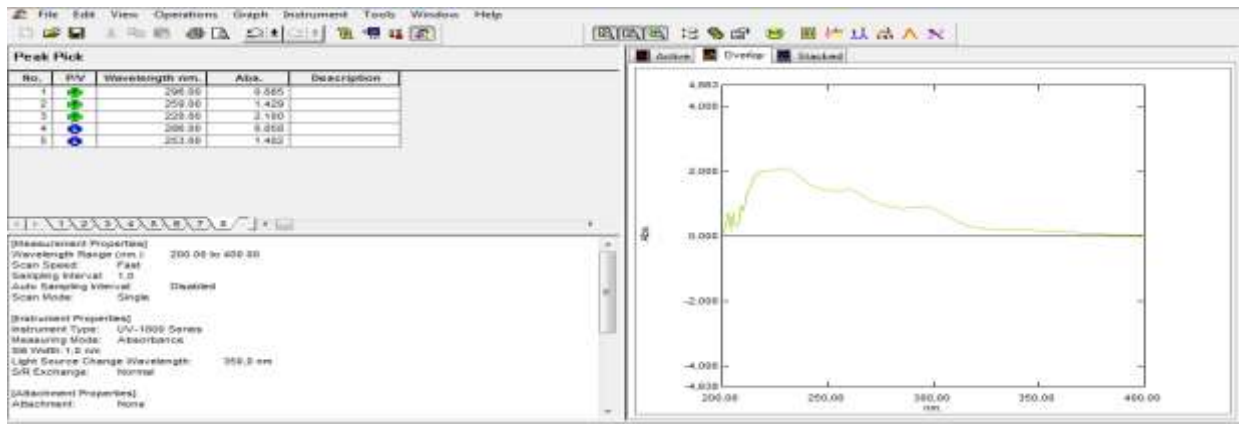
Table 1.2.
Results of the study of the effect of organic solvent and pH on the extraction of olanzapine residues from aqueous media

pH indicator	aqueous media							
	Organic solvents							
	chloroform		ethyl acetate		acetone		benzene	
	extracted							
	µg	%	µg	%	µg	%	µg	%
2,56	5,5	36,7	3,1	20,7	3,9	26,0	6,1	40,7
6,86	5,85	39,0	5,9	39,3	3,2	21,4	3,9	26,0
9,18	6,5	43,3	5,8	38,7	4,8	32,0	6,5	43,3
12,45	6,9	46,0	6,2	41,3	5,6	37,3	6,0	40,0

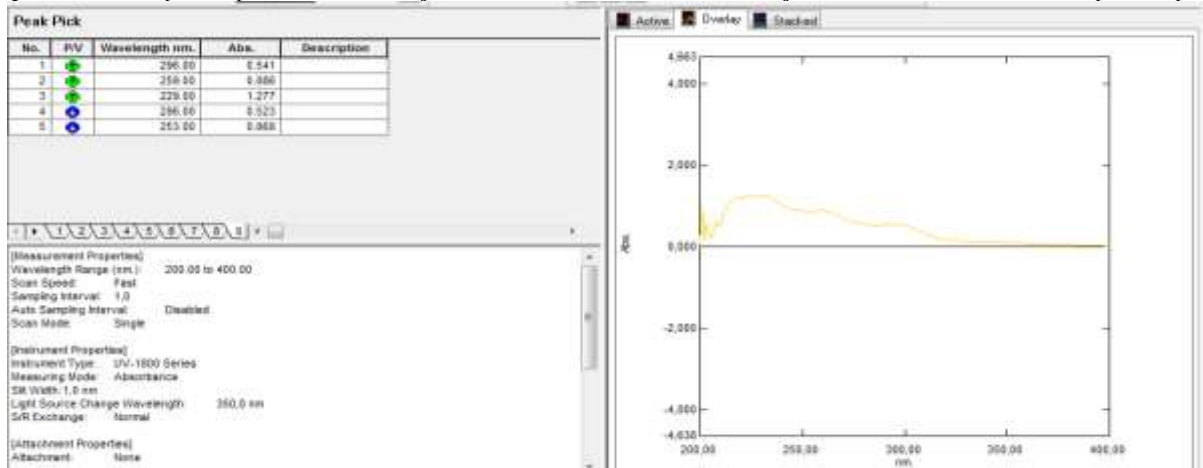
From the data presented in the table above, it can be seen that clozapine is transferred to the chloroform layer in a maximum amount of 53.6.0% during a single extraction from the aqueous medium at a pH of 9-13.



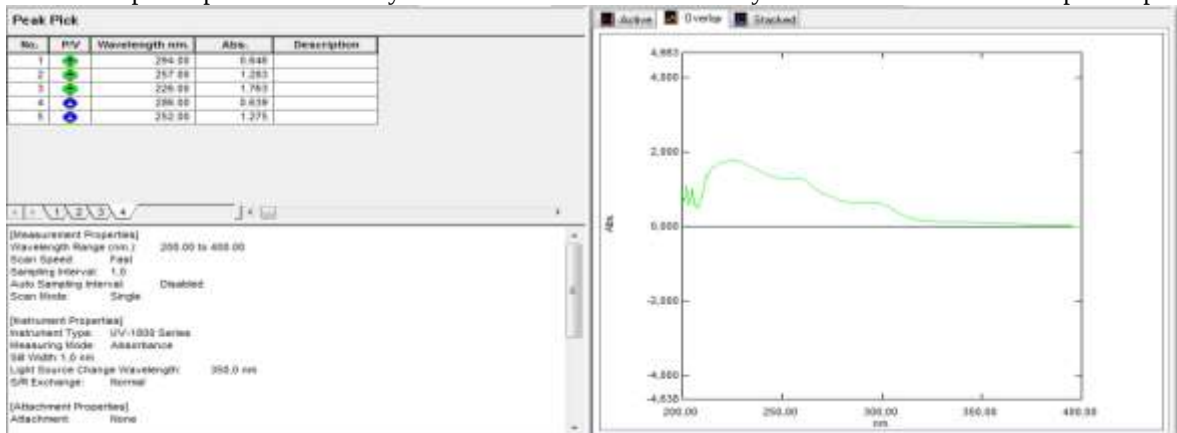
3-picture. Absorption spectrum of the dry residue of the extract obtained by benzene extraction of clozapine in pH-2.5



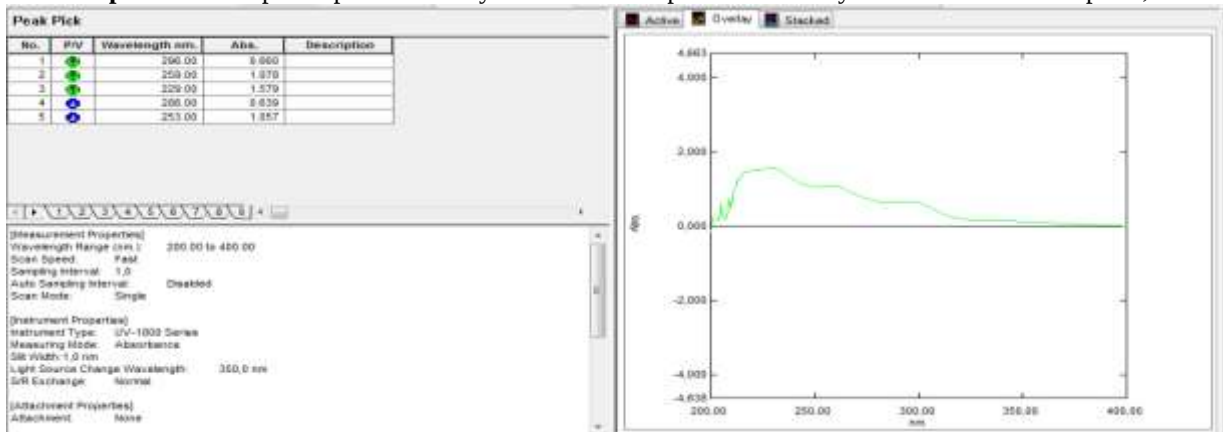
4- picture. Absorption spectrum of the dry residue of the extract obtained by benzene extraction of clozapine in pH-7



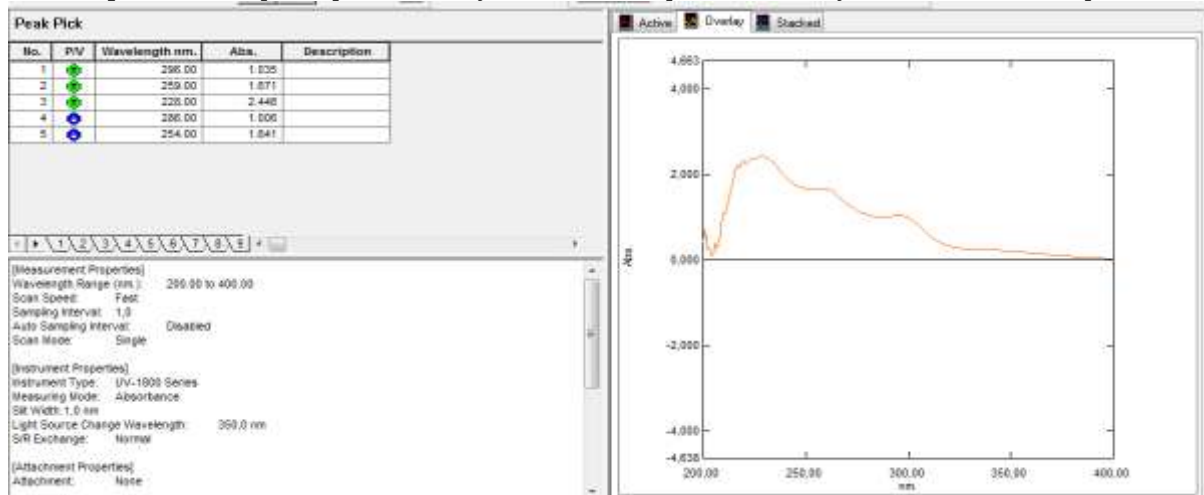
5- picture. Absorption spectrum of the dry residue of the extract obtained by benzene extraction of clozapine in pH-9-12



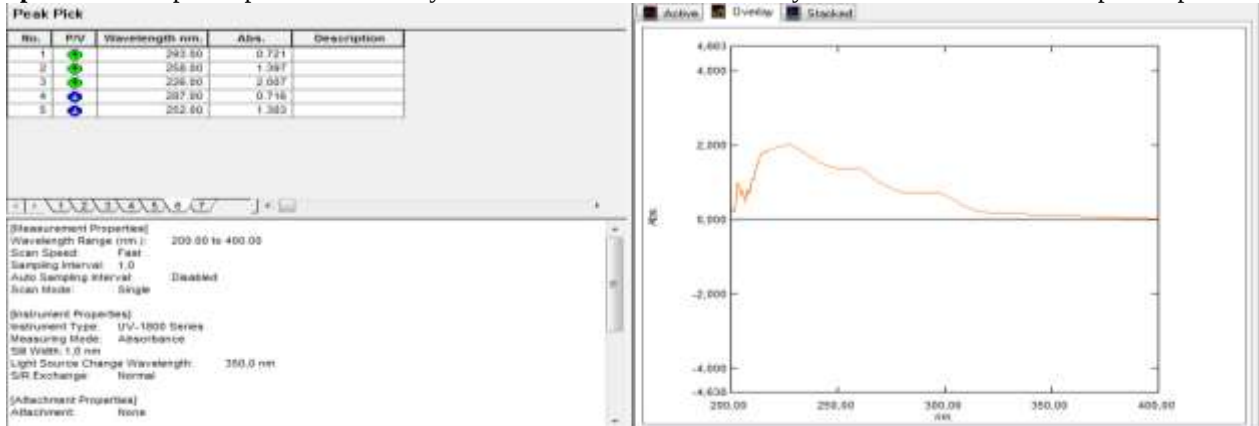
6 - picture. Absorption spectrum of dry residue of clozapine extracted by acetone extraction in pH-2,5



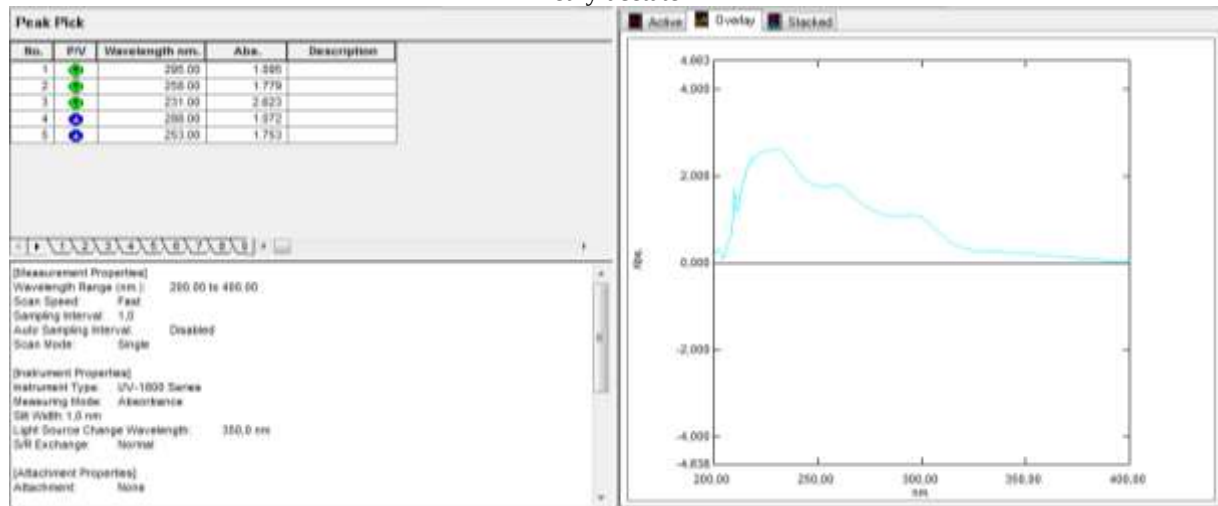
7- picture.Absorption spectrum of dry residue of clozapine extracted by acetone extraction in pH-7



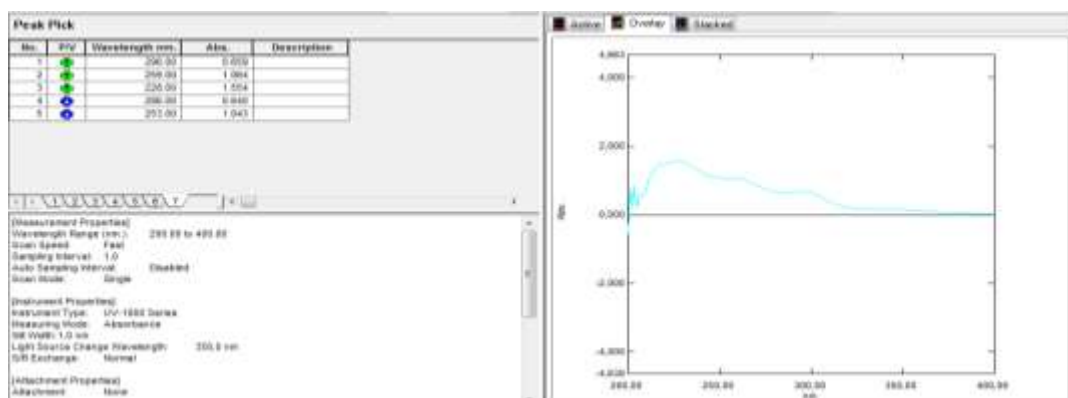
8-picture.Absorption spectrum of the dry residue of the extract obtained by acetone extraction of clozapine in pH-9-12



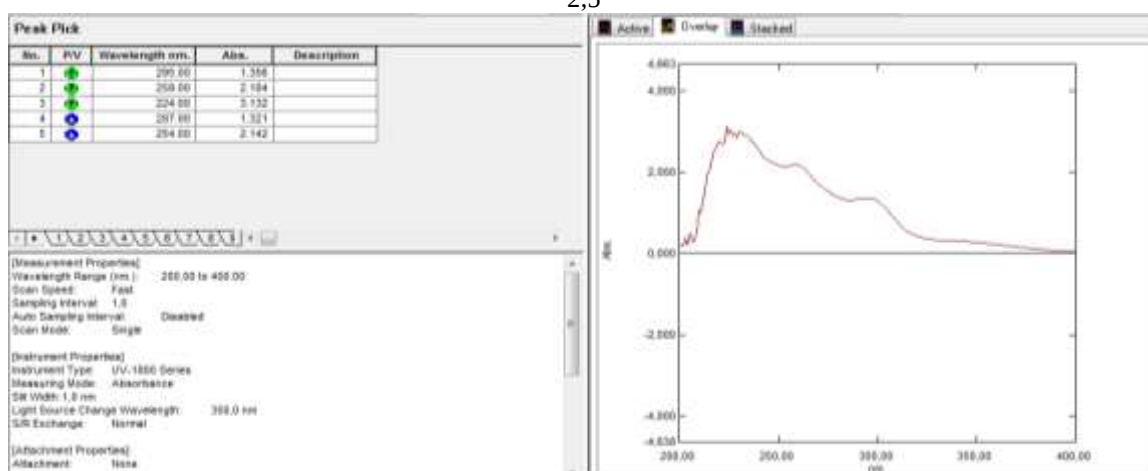
9-picture.Absorption spectrum of the dry residue of the extract obtained by extraction of clozapine in pH-2.5 with ethylacetate



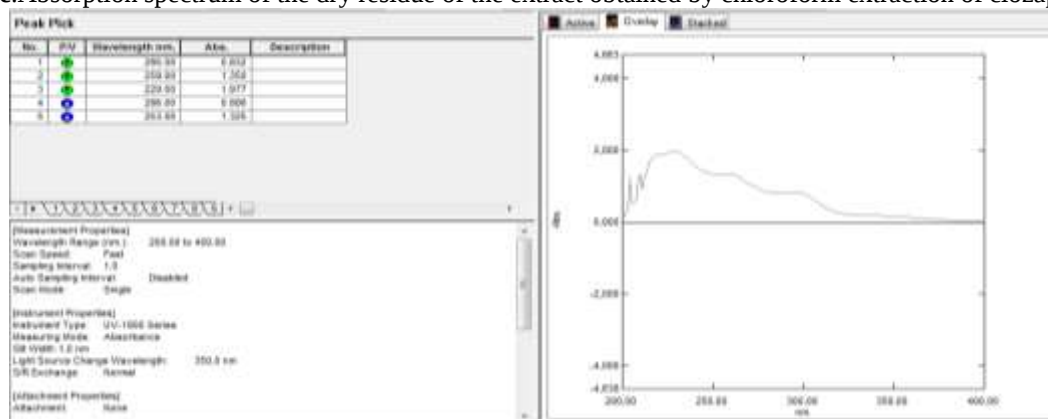
10- picture.Absorption spectrum of the dry residue of the extract obtained by extraction of clozapine in pH-7 using ethylacetate



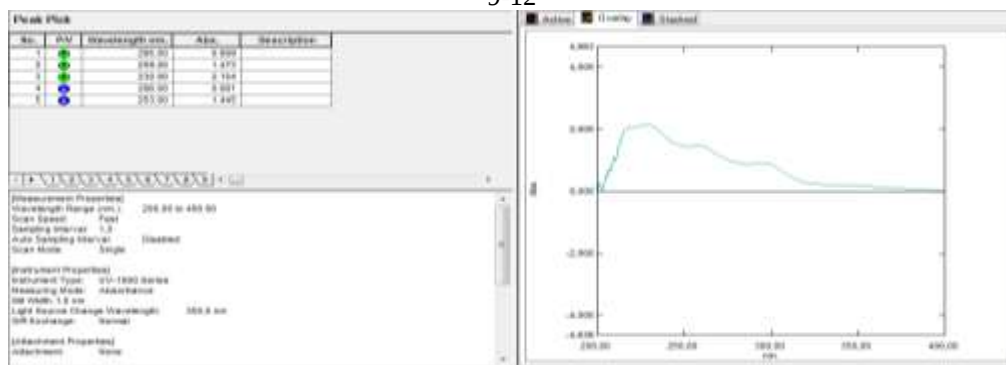
11- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of clozapine in pH-2,5



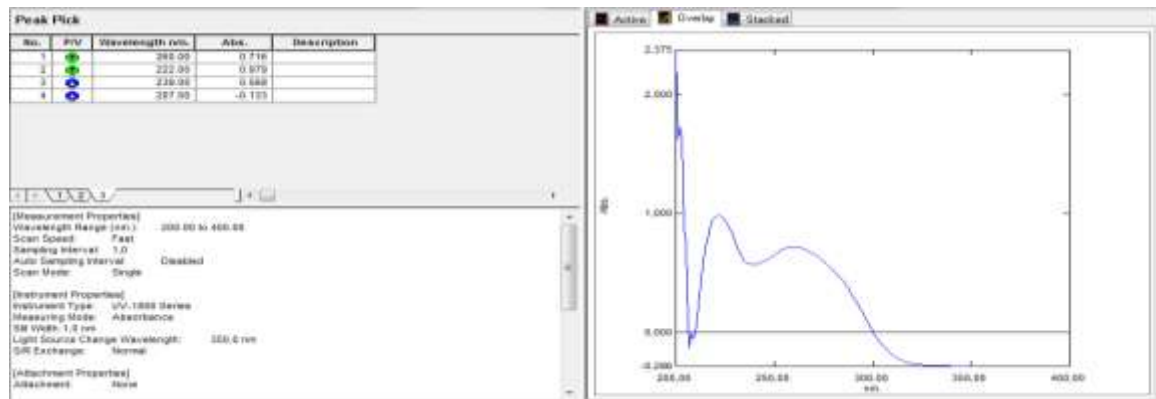
12- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of clozapine in pH-7



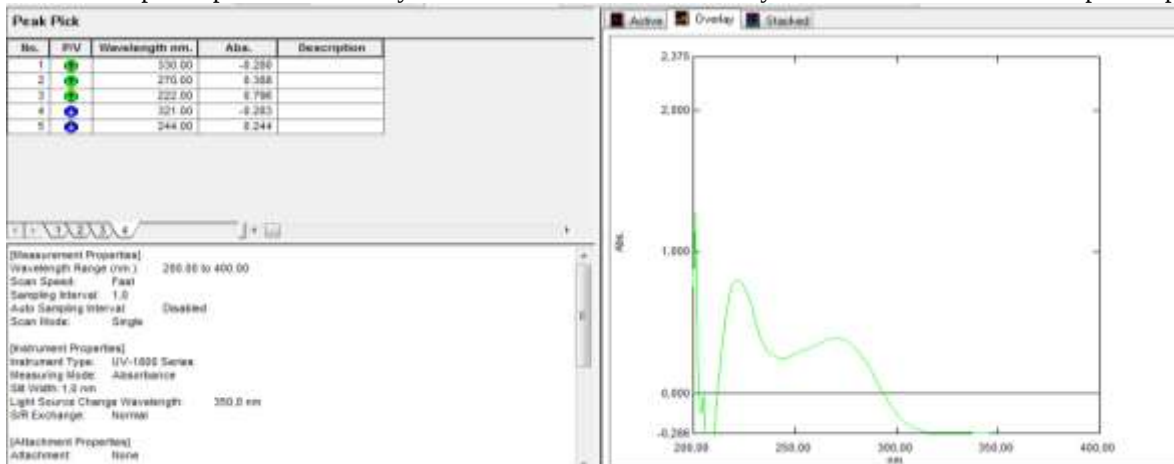
13- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of clozapine in pH-9-12



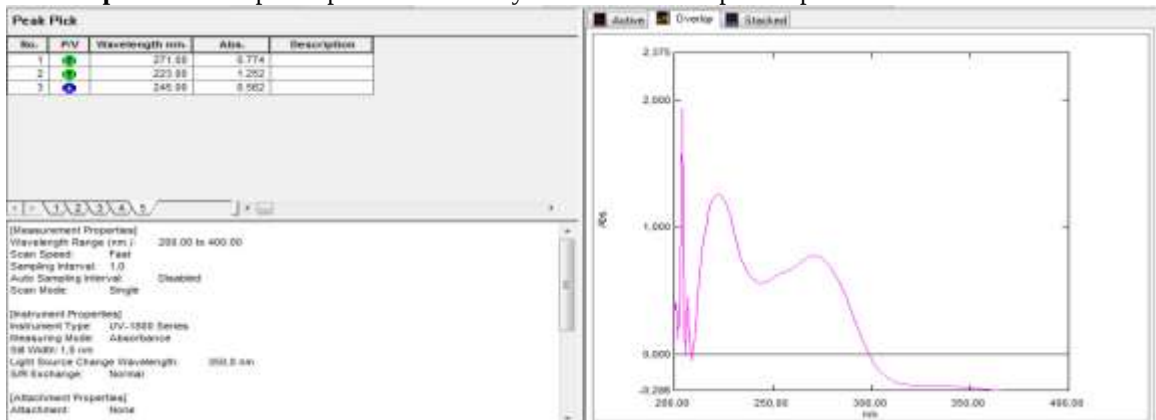
14- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of clozapine in pH-13



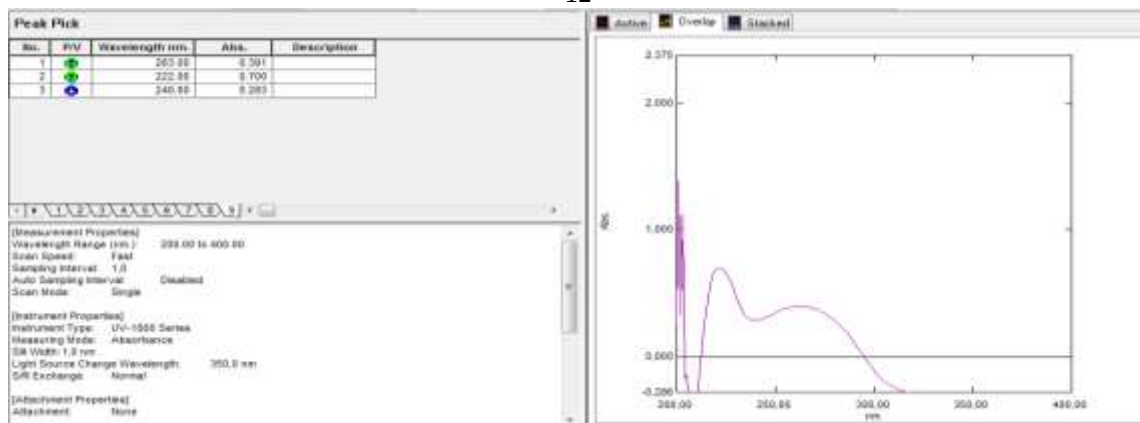
15- picture. Absorption spectrum of the dry residue of the extract obtained by benzene extraction of olanzapine in pH-2,5



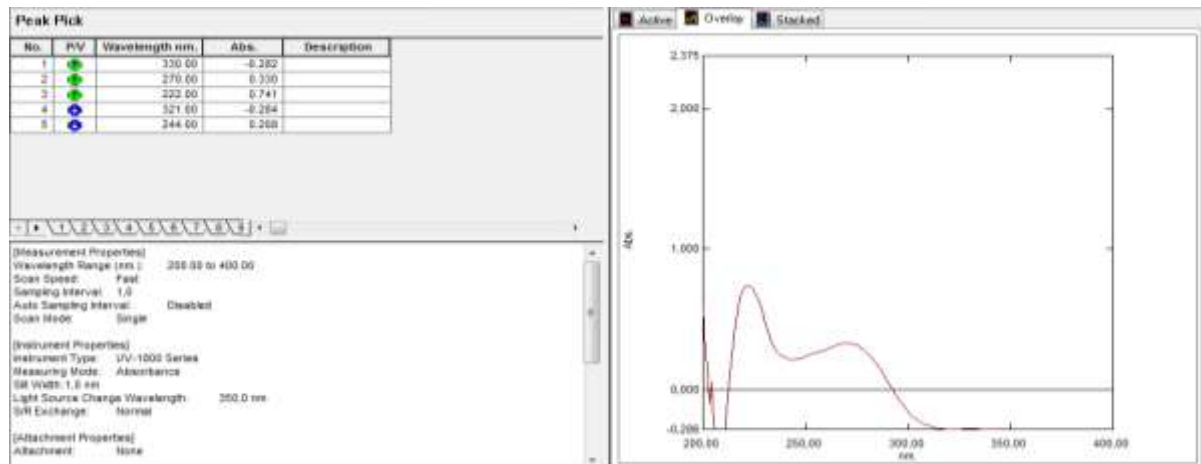
16- picture. Absorption spectrum of the dry residue of Olanzapine in pH-7 extracted with benzene



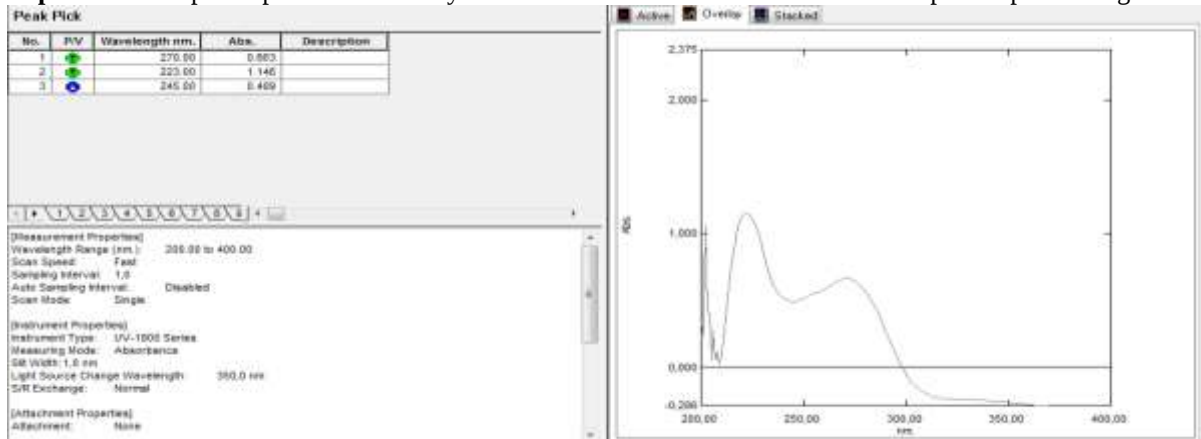
17- picture. Absorption spectrum of the dry residue of the extract obtained by benzene extraction of Olanzapine in pH-9-12



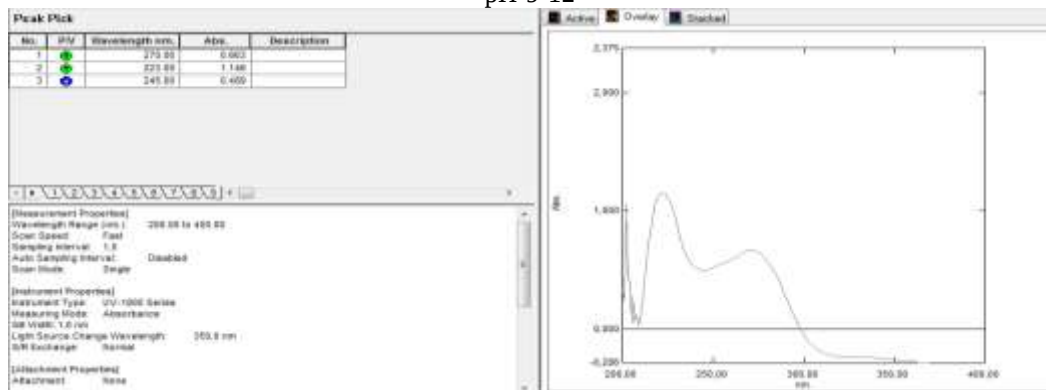
18- picture. Absorption spectrum of the dry residue of the extract extracted from olanzapine in pH-2,5 with acetone



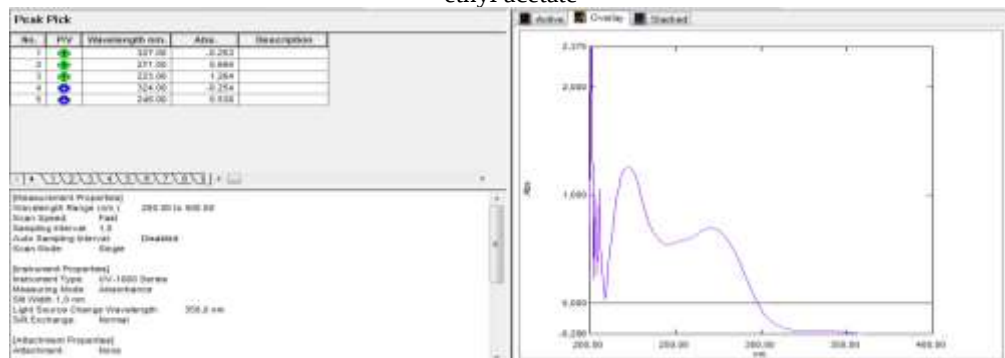
19- picture. Absorption spectrum of the dry residue of the extract extracted from olanzapine in pH-7 using acetone



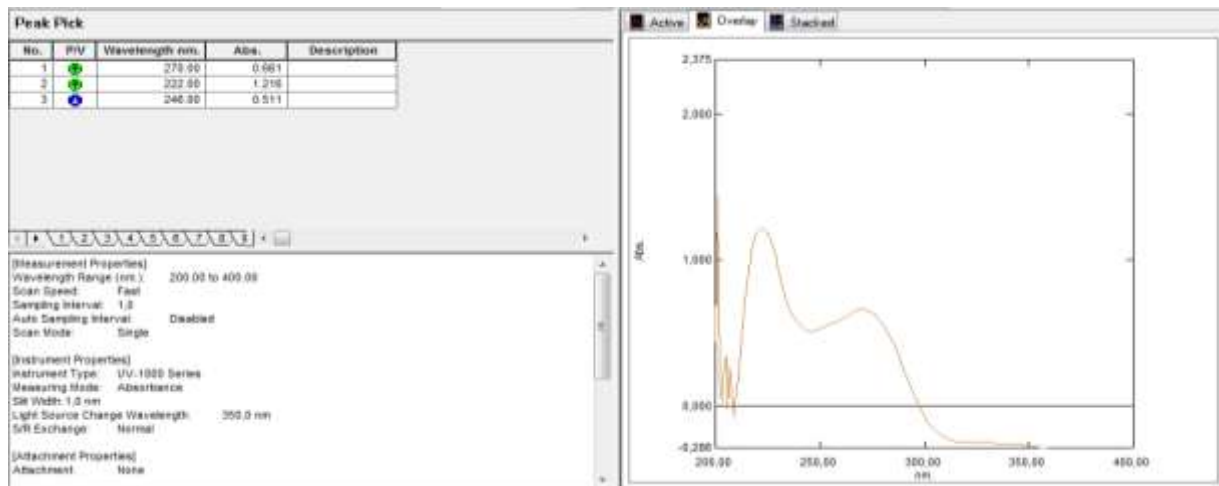
20- picture. Absorption spectrum of the dry residue of the extract obtained by extraction with acetone in olanzapine in pH-9-12



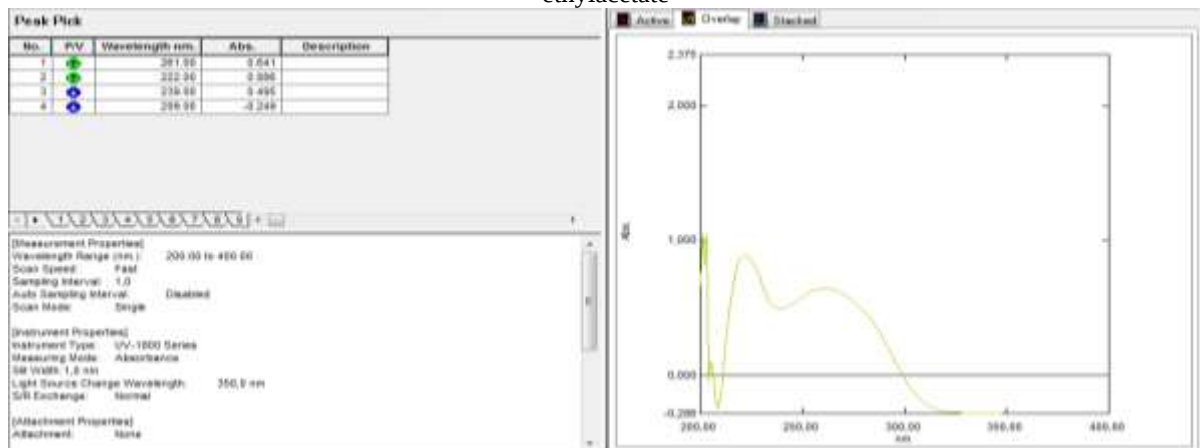
21- picture. Absorption spectrum of the dry residue of the extract obtained by extraction of olanzapine in pH-2.5 with ethyl acetate



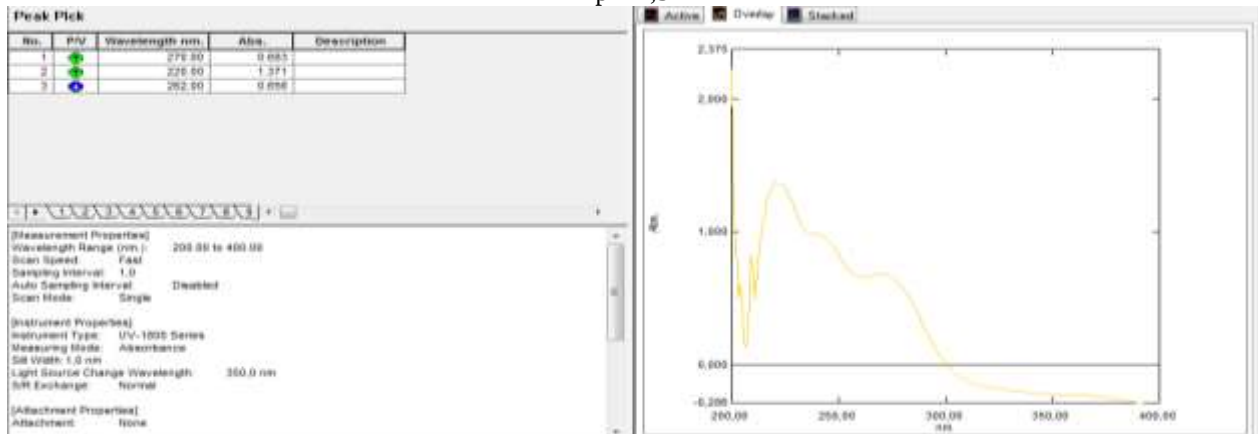
22- picture. Absorption spectrum of the dry residue of the extract extracted from olanzapine in pH-7 using ethylacetate



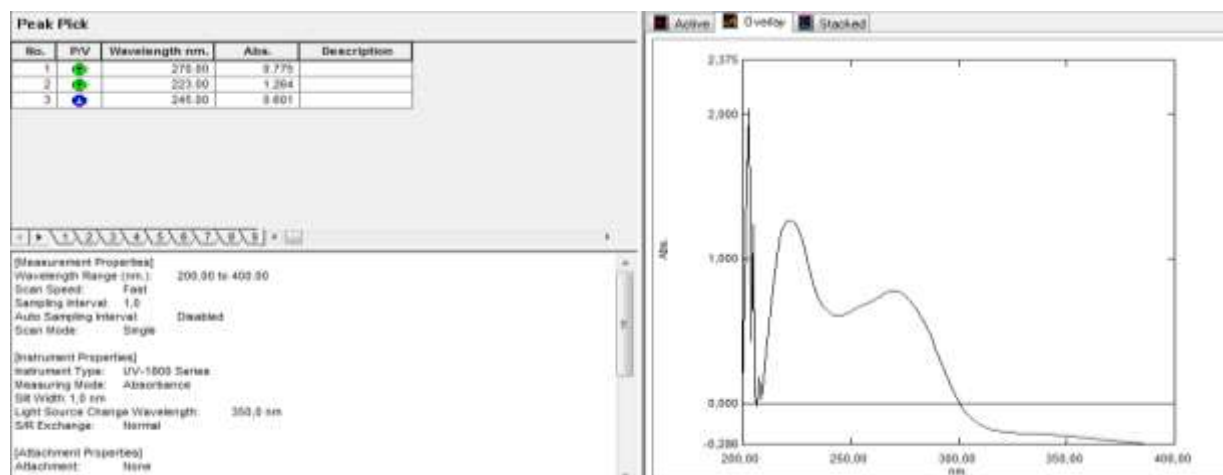
23- picture. Absorption spectrum of the dry residue of the extract extracted from olanzapine in pH-9-12 using ethylacetate



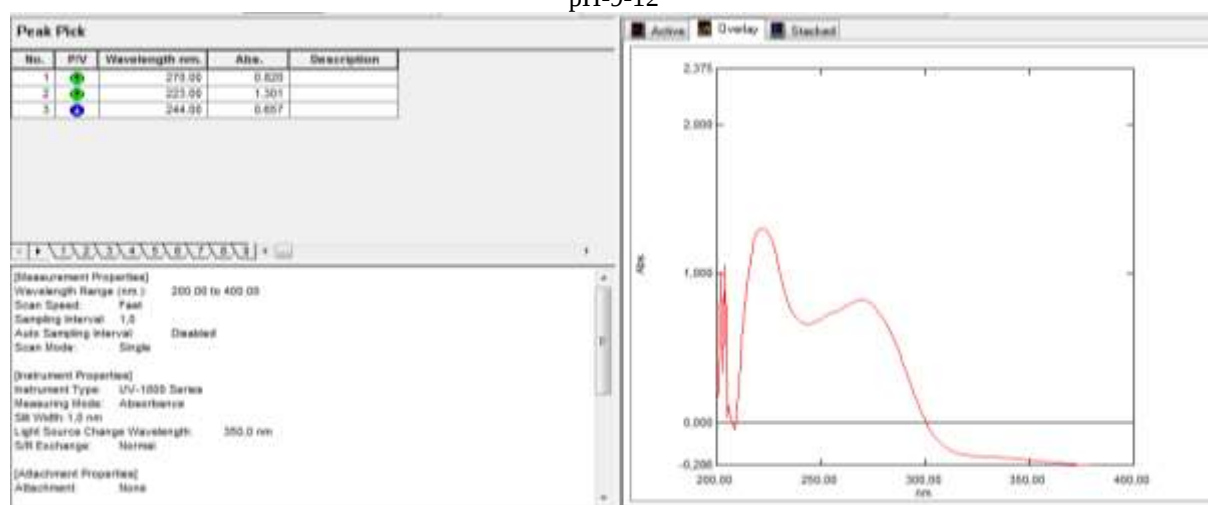
24- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of olanzapine in pH-2,5



25-picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of olanzapine in pH-7



26- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of olanzapine in pH-9-12



27- picture. Absorption spectrum of the dry residue of the extract obtained by chloroform extraction of olanzapine in pH-13

RESULTS AND DISCUSSION:

The effect of different pH media on the extraction process of clozapine and olanzapine drugs from aqueous media was studied using organic solvents: benzene, petroleum ether, acetone, ethylacetate and chloroform. Solvents such as benzene, ethylacetate, chloroform, petroleum ether and acetone were used to study the influence of the nature of the organic solvent on the extraction process. To carry out the analysis, 9 ml of solutions with different pH values were taken in 250 ml conical flasks with a capacity of 250 ml, 1 ml of the working solution containing 125 µg/ml of clozapine was added to it, and 10 ml of organic solvent was added and shaken uniformly for 15 minutes on a mechanical shaker.

The flasks were left for 5 minutes to separate the layers. After complete separation of the layers, the organic solvent layer was filtered through filter paper soaked in solvent into dry porcelain bowls with 5 g of anhydrous sodium sulfate in advance using a separatory funnel. The filter paper was washed with 3-5 ml of organic

solvent and the test was added to the main extract. The organic solvents from the extract were evaporated to a dry residue under a stream of hot air. The dry residue was dissolved in 95% ethyl alcohol, brought to 5 ml and analyzed by UV spectrophotometric method. The amount of clozapine in the aqueous medium was determined based on a previously prepared calibration graph.

A working solution containing 15 µg/ml olanzapine was used to study the effect of organic solvents on the extraction process of olanzapine.

The pH value of the medium has a great influence on the process of extracting the tested substances from the aqueous medium. Therefore, the effect of pH on the extraction of clozapine and olanzapine from aqueous media was studied. For this, using standard fixanals the pH of the environment is 2.56; 6.86; Solutions of 9.18 and 12.45 were prepared and analyzed under the above extraction conditions.

CONCLUSION

The influence of organic solvents and pH environment on the extraction process of clozapine drug was studied and analysis by UV-SF method was carried out during the quantitative analysis. During the analysis, 95% ethyl alcohol was used. It was observed that clozapine was released into the chloroform layer in a maximum amount of 53.60% during a single extraction under the conditions of pH equal to 6.86.

2. The influence of organic solvents and pH environment on the extraction process of olanzapine drug was studied and analysis by UV-SF method was carried out during the quantitative analysis. During the analysis, 95% ethyl alcohol was used. In this case, it was observed that olanzapine drug was released into the chloroform and ethylacetate layer in a maximum amount of 43-46.0% when it was extracted once from the aqueous medium under the conditions of pH 9-13.

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