Improvement of Citalopram Purity by Adsorption on Zeolite Solid Phase

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Abstract

**Introduction:** Citalopram Hydrobromide is one of the antidepressant medications that belong to the family which are the Selective inhibitors of serotonin reuptake. Due to having minimal side effects this medication is now under a huge consideration from psychiatrics and also patients. Citalopram Hydrobromide is among the most important salt that are produced from Citalopram and its high degree of purity will cause more effectiveness and less side effects.

**Aim:** to reach to a final product -citalopram hydrobromide - with 99% purity by using activated natural Zeolite named clinoptilolite as an adsorptive solid phase for citalopram and elimination of its impurities.

**Method:** In this method produced Citalopram is solved in an Acid and then it is purified by adding Clinoptilolite that is an activated Zeolite then citalopram will be extracted, and finally its bromide salt has been prepared in a solvent. The product purity is being measured with high performance liquid chromatography (HPLC) device.

**Results and Discussion:** the results of experiments have been inspected before adding Zeolite and after that. The results showed that adding Zeolite cause the degree purity to by increased from 93.75 to 99.45 and total amount of impurities decreased from 0.25% to 0.064%. Other properties of product are in complete agreement with the standards of pharmacopoeia of America.

**Conclusion:** Analysis shows that in this method the degree of purity is increased and the amount of impurities is decreased. Besides the most important advantage of this method is that less amount of solvent is consumed

**Keywords:** Citalopram, Purification, Recrystallization, Zeolite, antidepressant, Adsorption

Introduction

Citalopram hydrobromide (Figure1) is a selective serotonin reuptake inhibitor antidepressant drug recently has been considered by psychologist due to its less adverse reactions. It is one of the most important acidic salts of citalopram which is crystallized in a class B solvent according to the Pharmacopoeia but its purity is low. Recrystallization
method is very useful, but high volumes of class B solvents such as ethanol and acetone are consumed in this method.\textsuperscript{[2]} Solid phase zeolit has been utilizing for selective adsorption in different industries for several years. The studies based on adsorption of some medication such as aspirin and metronidazole on Zeolites and carrying them by nanoZeolite has been illustrated in literatures.\textsuperscript{[3]} In this study using Zeolite as an adsorptive solid phase for improvement of citalopram purity by cheap and recyclable solvents will be discussed.

\textbf{Main impurities of citalopram}

Most of citalopram impurities are produced in cyaniation step which is one of the final steps in citalopram synthesis.\textsuperscript{[4]} Two kinds of impurities\textsuperscript{[5]} (Figures 2) are produced in final step, both of them and their quantities affected the final purity of citalopram. This effect has been analyzed in the present study.

\textbf{Utilization of Zeolit in medicine industries}

Zeolites are crystallized hydrated alluminosilicates of group I and II elements of periodic table especially Na, K, Mg, Ca, Sr, and Ba. They occur naturally and synthetic and crystallographically have a cellular unit formula of $M_{x/n}[(Al_2O_3)_{x/3}(SiO_2)_{y/3}]nH_2O$ where $M$ is a cation from group I and II elements with $n$ valency. Clinoptilolite, chabazite, and mordenite are inorganic Zeolite and $A$, $X$, and $Y$ zeolites are synthetic zeolites.\textsuperscript{[6,7]} Because of their selective adsorption ability, zeolites are known as molecular sieves and their advantages over other common adsorbents such as activated carbon, activated earths, and silica gel are due to organized crystalline structure and consequently uniformities of cavities and channels sizes in whole of zeolite mass.\textsuperscript{[8,9]} Zeolites are used in synthesis of sustained-
release drugs, purification of some intermediates, and also as an additive in pharmaceutical formulations.[10]

In adsorption of citalopram on clinoptilolite and increasing its purity, manufactured citalopram is dissolved in a water soluble inorganic or organic acid solution such as hydrochloric or acetic acid respectively followed by addition of activated clinoptilolite considering its suitable Si/Al ratio for adsorption of organic molecules. After mechanical stirring, the mixture is neutralized by an alkali and after filtration of resulted solid; it is extracted by toluene several times. After evaporation of toluene, resulted purified citalopram is converted to its hydro bromide salt with 99% purity by addition of hydrotropic acid in a class C solvent such as acetone. Prescribing clinoptilite for mouses with different kind of tumors has been shown that their health is improved afterwards and they live longer.[11]

Recently in surpex technology zeolits is used for separation of xylene, alkin, alkan isomers and fructose form glucose.[12]

Material and Method

Experiments

Preparation of Zeolite: 100 Gms clinoptilolite (particle size ≤ 170 meshes) was added to a 250 ml flask and its content was refluxed for 12 hrs with distilled water. After activation and drying at 200 °C, it was prepared as powder.

Adsorption of citalopram on Zeolite solid phase: In a 250 ml beaker, 10 Gms of impure citalopram was dissolved in 100 ml hydrotropic acid followed by addition of 30 Gms prepared clinoptilolite and reaching the pH of the content to 9 by a 5% ammonium hydroxide solution. The beaker content was mechanically stirred for 3 hrs and filtered. The remaining solid was purified citalopram-adsorbed Zeolite.

Extraction: Filtrate from previous step was added to 100 ml toluene in a two-necked round-bottomed flask. The mixture was mechanically stirred for 2 hrs at 60 °C followed by cooling at room temperature and filtration. The toluene phase was decanted. Extraction was repeated for further 3 times, each time with 100 ml toluene and finally the resulted 400 ml extract was evaporated to obtaining an oily extract.

Synthesis of citalopram hydro bromide: 100 ml of acetone was added to oily extract from previous step in a 250 ml flask followed by reaching the pH to 2.5 by addition of a 48% (w/w) hydrotropic acid solution at 40 °C. Flask content was stirred for 10 hrs followed by cooling at 5 °C and filtration. The resulted crystals was washed with 5 ml acetone and dried at 40 °C in an oven. Weight of dried citalopram hydro bromide crystals was 7 gms.

Results and discussion

Results of experiments before and after addition of Zeolite and after obtaining product (citalopram hydro bromide) were analyzed by HPLC as it is observed according to chromatogram 1 and 2 the purity of citalopram is 93.5% when only one solvent of group 2 has been used, but by using of solid phase zeolit the purity percentage increases to 99.45%. Reduction in quantities of mentioned impurities from 0.25% to 0.064% was also determined by HPLC (Chromatograms 3 and 4). It is necessary to mention that other pharmaceutical tests such as melting point, optical rotation, and organic volatile impurities of finished product is consistent with U.S. Pharmacopoeia standers.

The main and most important advantages of using solid phase zeolit are:
1. Utilization of less amount of solvent comparing to general methods of separation
2. Increasing of the purity percentage of the medication
3. Decreasing the amount of main impurities and elimination of some other impurities
As disadvantages of the solid phase method expenses for extraction of citalopram form zeolite and decreasing of 3 to 5 percent in performance of final product can be mentioned.

Chromatogram 1 - Citalopram purity before purification (93.5%).

Chromatogram 2 - Citalopram purity after purification by zeolite (99.45%).
Chromatogram 3 - Citalopram impurities before purification (0.25%).

Chromatogram 4 - Citalopram impurities after purification by zeolite (0.064%).
Conclusions
The present study indicates that zeolite can be used for improvement of citalopram hydrobromide purity and reduction of its impurities. In this method, according to the instrumental analysis done, elimination of impurities has resulted in improvement of product purity. For industrialization of the present method, batches pilot tests should be done.

References: