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Application of magnetic Montmorillonite as a recyclable heterogeneous catalyst in the synthesis of Levofloxacin

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Abstract

Levofloxacin, a chiral carboxycinolone, is a synthetic antibiotic with a broad spectrum effects. One of the challenges in the synthesis of this compound is efficient catalytic synthesis of their key structural intermediates (Q-acid). Several methods have been reported for the synthesis of this active pharmaceutical ingredient in which toxic and expensive solvents have been used. Therefore, alternative and cost-effective methods are still needed. In this study, focusing on the last step in the synthesis of levofloxacin using commercial Q-acid, an attempt was made to replace the previous methods using commercial catalysts with Lewis acid character and the use of safe solvents. In this study, magnetic montmorillonite (MM) was first synthesized and purified. The reaction of methylpiperazine with Q-acid intermediate for levofloxacin synthesis was also performed under different conditions. The best results were obtained using methylpiperazine and Q-acid with a molar ratio of 1.2:1 in the presence of catalytic amounts of MM in ethanol solvent (95%) at 70 °C for 8 h. At the end of the reaction, MM was recovered using a magnet and a simple filtration and dried for 2 h at 100° C for activation and used for 5 consecutive reactions to evaluate levofloxacin synthesis without significant decrease in efficiency. In total, taking into account factors such as raw material consumption, solvent type and simple recycling conditions, operating temperature and energy consumption, type and amount of catalyst and its recovery, solvent and catalyst biocompatibility, production of levofloxacin hemihydrate in the method presented in this study, are associated with lower cost, and its production at increased scales will have good economic benefits.

Keywords

Levofloxacin, Q-acid, Magnetic Montmorillonite, Active Pharmaceutical Intermediate, Heterogeneous Catalysis.

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1. Introduction

The development of new methods for the efficient synthesis of pure medicinal raw materials is of great importance. Using available raw materials and optimal reaction conditions, the goal is to achieve these products with greater purity and lower costs. Tricyclic fluoroquinolones, including levofloxacin, are known to have broad-spectrum antibacterial agents against gram-positive and gram-negative bacteria [1]. Levofloxacin is one of the most potent antibacterial drugs on the market in the world of quinolones. Levofloxacin is used as a drug in the treatment of bacterial infections of the skin, sinuses, kidneys, bladder and prostate. It is also used to treat anthrax and plague.

Sterile eye drops of this drug is used in eye infections. Levofloxacin belongs to the quinolone antibiotic group. These drugs work by killing or preventing bacterial infection by killing the bacteria or preventing them from growing. Levofloxacin and other fluoroquinolones as antibiotics kill bacteria by preventing them from replicating DNA [2]. Levofloxacin, ad a chiral fluorinated carboxyquinolone, is a broad-spectrum synthetic antibiotic. Levofloxacin enantiomer S of the racemic mixture of ofloxacin is an antimicrobial agent of fluoroquinolone (Figure 1).Levofloxacin has been reported in three polymorphic forms (α, β, γ, anhydrous) and two polymorphic quasi-polymorphic forms in scientific sources. Heat of the semi-aquatic form leads to the removal of hydrated water and the formation of anhydrous form and then the formation of β. Further heating leads to the formation of a dehydrated form. Heating of the monohydrate form also leads to the removal of water α of the vapor form α and hydrated α and the formation of a dehydrated form.Under normal conditions, the form of water in the air absorbs moisture quickly, and it is converted to the semi-hydrated form (hemihydrate and monohydrate, respectively).

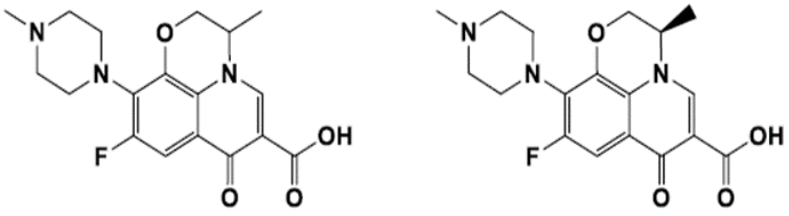


Fig. 1 - Chemical structure of levofloxacin (in the right side) and ofloxacin (in the left side)

Montmorillonite is a soil with the formula $Al_2Si_4O_{10}(OH)_2.nH_2O$ that can be used both as a catalytic substrate and as a catalyst with the property of Lewis acid for many organic reactions, including nucleophilic reactions [3]. By fixing a species with acidic properties on montmorillonite, its acidity can be increased. Montmorillonite has the ability to exchange its ions with other metals, which changes its acidic property [4].

One of the properties of montmorillonite as a catalyst is that it reacts at reduced temperatures and the non-toxic nature of this catalyst. Montmorillonite has the ability to exchange its ions with other metals, which changes its acidic property.

One of the properties of montmorillonite as a catalyst is that it reacts at reduced temperatures and the non-toxic nature of this catalyst. Today, the use of magnetic nanoparticles with different composites has become very popular due to the effects of Lewis acid and easy separation in the purification stage of the product. Iron oxide compounds such as γ-Fe_2O_3 and Fe_3O_4 [5], spinel ferromagnets such as Mg Fe_2O_4, $MnFe_2O_4$ and $CoFe_2O_4$ [6], and alloys such as FePt [7] are some of the examples [8].

2. Methods

2-1 Chemical materials and the devices

Chemical raw materials and solvents were prepared by Merck and Sigma Aldrich Companies and used without purification. Product specifications were compared with physical and spectral data with known samples in the sources. Progression of the reactions was followed by thin layer chromatography (TLC). The melting point of the products was measured with a melting point measuring device. The model Fourier transfer spectrophotometer in Bruker Equinox 55 model was used to study the infrared spectrum using potassium bromide tablets and NMR device in Brucker Avance DPX, 400 MHz Model was used to identify hydrogen and carbon of the product and tetramethyl silane (TMS) was used as the internal standard. A magnetic heater and 50- and 500-ml glass balloons were used with relevant equipment for the experiments.

2-2 Method of synthesis of levofloxacin drug raw material using Montmorillonite catalyst

Levofloxacin hemihydrate in one step is starting from 9-(R), 10-d-fluoro-3-methyl-7- oxo-3, 7- di-hydro-2H-[1,9] oxazinone [2,9,10] quinoline-6-carboxylic acid (I) as the starting material in 95% ethanol solvent at 70 ° C for 8 hours using Montmorillonite catalyst (Figure 2).

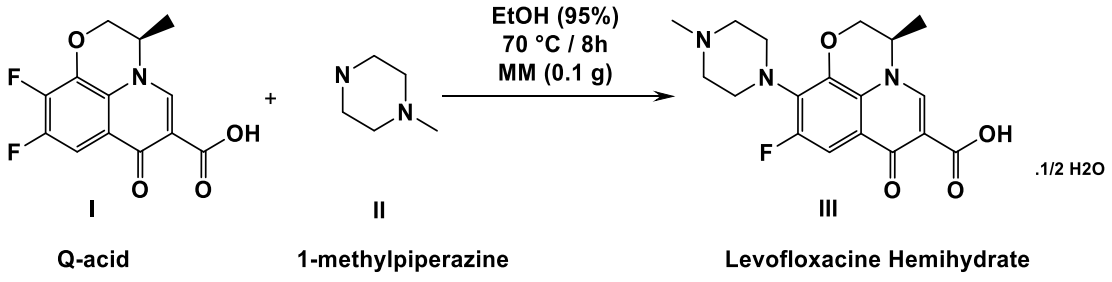


Fig. 2 - Synthesis of elevated scale levofloxacin hemihydrate using catalysts MM

In a 500 ml glass reactor equipped with a coolant and thermometer, a mixture of 95% ethanol solvent (200 ml) and n-methyl p-pyrazine (11.2 ml, 0.12 mol) was mixed to reflux temperature. Q- Acid I (28.1 g, 0.1 mol, white powder) and magnetic montmorillonite (2.0 g) was added to the mixture and left to mix for 70 hours at 70 ° C until complete (TLC control). Then 50 ml of water was added and heated to reflux temperature, at which time the montmorillonite was separated using a magnet and simple filtration, and the solution was cooled to ambient temperature. The filtered vacuum precipitates were crystallized in 200 ml of isopropanol. It was then dried in an oven at 60 ° C for 6 hours. The 25.5 g of yellow levofloxacin hemihydrate powder were obtained with a melting point of 225-230 ° C, purity of 99.3 (by HPLC technique) and 69% efficiency.

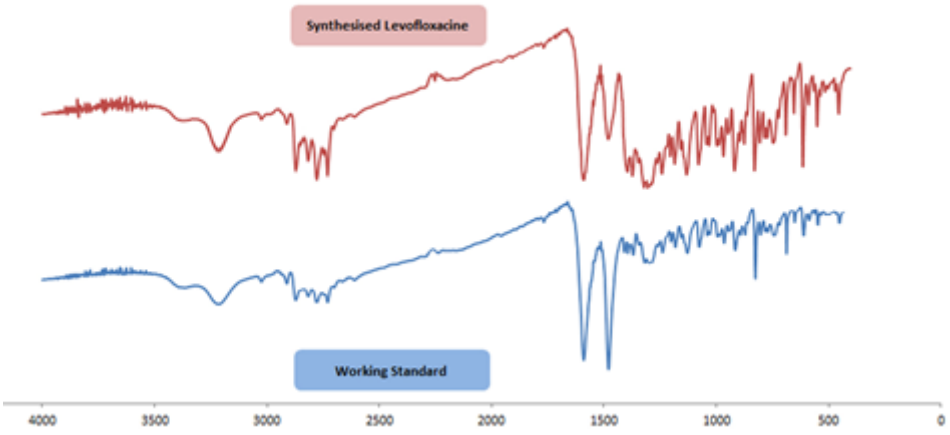
3. Results

3-1 Catalyst Reusability

The reusability of the catalyst was also examined as an important aspect for commercial and industrial applications. In the reaction of Q-acid and methylpyrazine, the catalyst can be recovered at the end of the reaction using a magnet and a simple filtration. The recycled catalyst was washed with ethanol and dried for activation for 2 hours at 100 ° C and used to evaluate its re-efficacy in subsequent reactions. The activated catalyst was used in 5 consecutive levofloxacin synthesis reactions without significant reduction in efficiency.

3-2 Analysis of levofloxacin

In order to identify the product structure and confirm the proposed structure, various analyzes were performed and indicates the similarity of the structure of these two compounds in comparison of the FTTR spectral image of this drug raw material with the FTTR standard sample spectrum image (Figure 3).



Wavenumber (cm^{-1})

Fig. 3 - Synthesized FTIR spectrum of levofloxacin (up) and comparison with standard samples used in the pharmaceutical industry (dawn)

(–)-(*S*)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido [1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, hemihydrate; $C_{18}H_{20}FN_3O_4$.½H_2O; Pale or bright -yellow crystalline powder; mp: 225 – 230°C; MW: 370.38; soluble in Water.
FTIR (KBr) $\bar{\upsilon}(cm^{-1})$: 925, 1086, 1238, 1294, 1452, 1535, 1618, 1724, 2847, 2931, 3080, 3266, 3401.
^{1}HNMR (400 MHz, $CDCl_3$) δ(ppm): 1.45 (d, 3H), 2.25 (s, 3H), 2.50 (m, 4H), 3.28 (m, 4H), 3.36 (d, 2H), 4.36 (dd, 1H), 4.58 (dd, 1H), 4.94 (m, 1H), 7.54 (d, 1H), 8.97 (s , 1H).
^{13}CNMR (100 MHz, $CDCl_3$) δ(ppm): 18.4, 46.5, 50.5, 55.3, 68.5, 103.6, 107.1, 119.9, 125.2, 132.4, 140.4, 146.5, 154.6, 157.1, 166.5, 176.7.

4. Discussion

Optimization of synthesis using MM catalysts

Methyl-p-pyrazine reaction experiments were performed with Q-acid intermediates under different conditions, the results of which are shown in Table 1. For this purpose, 5 mmol of Q-acid (1.4 g) and 7.5 mmol methylpyrazine (0.75 g) were first added to 10 ml of solvent in which 0.1 g of catalyst was well dispersed and refluxed for 16 h. The montmorillonite was then separated using magnets and simple filtration, and the solution was cooled to ambient temperature. The precipitates were filtered and crystallized in isopropanol. It was then dried at 60 ° C for 6 hours.

Table 1- Catalytic reaction of methylpiperazin with Q-acid mediator under different conditions.

No	solvent	Cat	(T)C°	(%)
1	H_2O	-	25	-
2	H_2O	-	Ref	25
3	H_2O	$FeCl_3.6H_2O$	Ref	35
4	EtOH:H_2O 50 : 50	$FeCl_3.6H_2O$	Ref	43
5	EtOH (95%)	$FeCl_3.6H_2O$	Ref	52
6	EtOH (95%)	Fe_2O_3	Ref	40
7	EtOH (95%)	Fe_3O_4	Ref	55
8	EtOH (95%)	MM	Ref	82
9	EtOH (95%)	M	Ref	49

First, the use of water as a cheap green solvent was investigated, which was associated with low efficiency in the nucleophilic reaction between p-pyrazine and Q-acid under reflux conditions (Table 1, rows 3-1). This is probably due to the completely polar nature of the solvent and the formation of by-products through parallel unwanted reactions. In the polar water environment, the acidity of the hydrogen fluoride released during the reaction caused to destroy the product or inactivate the methylpyrazine raw material, thereby reducing the final yield. Therefore, the use of 95% ethanol was considered as the next option for commercial and environmentally friendly solvents. Overall, the replacement of ethanol with water significantly improved efficiency. The use of iron (iii) hexavalent chloride ($FeCl_3.6H_2O$) as a commercial and inexpensive catalyst with Lewis acid fluorescents was investigated in this reaction, which, of course, did not yield good results (Table 1, rows 3-5). In addition to the low efficiency, the dimensions of the dye medium in the solvent and the difficulty of purifying some impurities related to water-soluble chlorinated iron led us to look for other insoluble and recyclable iron compounds with Lewis acid properties. Therefore, the use of insoluble iron oxide, hematite (Fe_3O_3) and magnetite (Fe_3O_4) was investigated. Unlike hematite (Table 1, row 6), the use of magnetite in the above reaction was associated with relatively good efficiency (Table 1, row 7). The use of magnetized montmorillonite soil with magnetite nanoparticles as a catalyst with strong Lewis acid properties and very simple recyclability was investigated in this study, which was accompanied by a significant increase in efficiency (Table 1, row 8). In order to investigate the effect of stabilized magnetic nanoparticles on the montmorillonite substrate, a separate experiment was performed using montmorillonite soil, which was associated with a significant reduction in yield (Table 1, row 9).This observation clearly shows the effect of iron nanoparticles on the catalysis of the reaction which is probably due to the interaction of free electron pairs of fluorine atoms in the Q-acid and the orbital of the iron Fe_3O_4 and thus the activation of the C-F bond in the Q-acid to nucleophilic attack of type II nitrogen in the methylpyrazine molecule (Figure 4).

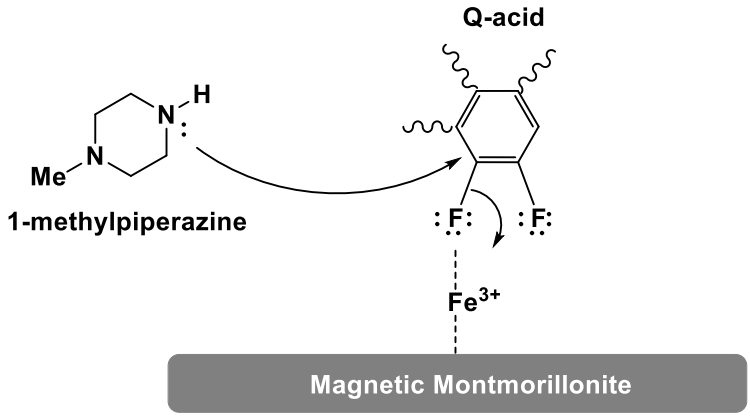


Fig. 2 - Possible mechanism of Q-acid activation by MM in levofloxacin synthesis

5. Conclusions:

Magnetic separation technology, as an easy and fast way to separate and recycle catalysts, has the advantages of catalytic with solid magnetic synthesis, which include: simple recycling of substrates, ease of use and handling, reduction of product pollution and reduction of environmental problems, greater safety, increased selectivity of reactants In terms of pores and surface adsorption, reacting at lower temperatures and increasing their reactivity due to uniform distribution on the substrate, montmorillonite soil with Lewis acidic properties, solid acid catalyst used in various organic reactions.

However, the use of 95% ethanol solvent in catalytic value of magnetic montmorillonite for the synthesis of levofloxacin, which is mentioned in this study, although not significantly effective compared to other methods, but for the following reasons this process is cost-effective to use at higher scales:

1- Using the 95% ethanol solvent due to domestic production, has the advantage of easy access and reduced production costs

2- Recovering the 95% ethanol solvent due to low boiling point is easily possible by simple distillation and can be used many times in the next process cycle.

3- Having the possibility of easy separation and recovery by the use of heterogeneous magnetic montmorillonite catalyst in the reaction process. This mineral-based catalyst does not mix with the organic reaction medium due to its heterogeneity. In addition, due to the magnetism of this catalyst, it is possible to separate it by applying a magnetic field (magnet).

4- Playing the important role from an environmental point of view, in the use of biocompatible ethanol and its replacement with highly toxic solvents. On the other hand, due to the mineral nature and biocompatibility of the magnetic montmorillonite catalyst, its use is not associated with environmental hazards, and in fact magnetic montmorillonite is a green catalyst.

5- Reaction at elevated temperatures is one of the reasons for the formation of by-products in the chemical reaction; therefore, at reduced temperatures (70 ° C) in this study, the probability of performing a parallel unwanted reaction is less and also minimized the possibility of by-products and impurities.
6- The molar ratio of methyl-p-pyrazine to Q-acid is 1: 1.2. This means that in this method, much smaller methylpyrazine are used than other methods. The minimum molar ratio of methylpyrazine to Q-acid in other methods is 1: 2.11. Because methyl-p-pyrazine is an imported substance and its preparation is associated with foreign exchange, so by reducing the consumption of this compound in the process of synthesis of levofloxacin, the production of this drug raw material will be more economic.
7- The purity of the synthesized material in this research is equal to 99.3% (with HPLC technique), which is in accordance with the USP 37 standard and suitable for drug use.

6. Acknowledgments

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