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Preparation and Characterization of the novel MOF Fe_3O_4@chitosan@Trp for the drug delivery system of Levodopa

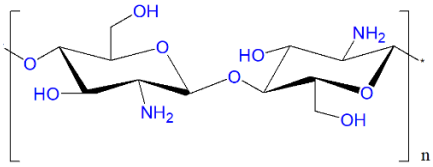
Mohammad Amin Chavoshian[1], Manouchehr Fadaiean[1], Mohammad Reza Zand Monfared[2]
[1,2] Department of Chemistry, Islamic Azad University, Qom, Iran
[1] Corresponding author: +98 2537780045; fax: +98 9128236206; E-mail: fadaeian_m@yahoo.com
Postal address: Department of Chemistry, Qom Branch, Islamic Azad University, Post Box: 37491- 13191, Qom, I. R. Iran.

Abstract
Nowadays, MOFs have been spaciously applicated as drug carriers owing to their advantages. In this project, we have explored the novel metal-organic framework containing Fe_3O_4@chitosan@Tryptophan prepared via the novel method, and plus drug loading of Levodopa was performed. Also, the structure of the nanocarrier was characterized by using different Fourier-transform infrared spectroscopy (FT-IR), Energy-dispersive X-ray spectroscopy (EDX), X-ray crystallography (XRD), Scanning electron microscope (SEM), and Brunauer–Emmett–Teller (BET) analysis. The results indicated that the drug (L-DOP) was loaded on the synthesized framework with an excellent percentage. Drug release was done in about 80-85 percent at pH: 5.5-7.4 within 8-24 hours.

Key words; Metal-organic frameworks, Tryptophan, Chitosan, Levodopa, Drug delivery

1. Introduction

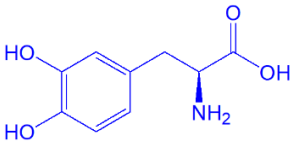
Recently, drug delivery systems have attracted much interest due to their potential applications and functionality in pharmaceuticals Industries [1, 2]. Nowadays, the disadvantages and advantages have been studied for some compounds such as micelles, liposomes, graphene and etc as drug carriers.[3-4]
A category of hopeful porous nanomaterials for biomedical applications is metal-organic frameworks (MOFs) much attention in recent years.[1,3] The MOFs are crystalline solids made of metal ions and organic ligands.[4-5] To construct the MOFs, metal ions such as Zr^{2+}, Fe^{2+}, and Zn^{2+} and ligands such as terephthalic acid and etc are applied that can have a one, 2, and 3D structure.[6] MOFs with special properties (adjustable size and figures, Easy operation, easy biodegradability, great porosity, and high design capability, etc.) can be excellent candidates for therapeutic projects such as drug delivery [3-10] which after the hydrolytic decomposition of Drug/MOF composites happens rapid release of drugs in high supersaturation in gastric media.[6,10-11]
Chitosan (CS) can be outstanding, immensely known, and used in biomedicine owing to its biocompatibility, biodegradability, eco-friendly, non-toxicity, high chemical, and thermal stability, and antifungal, antibacterial, antioxidant, and adhesiveness, among other favorable properties[12]. Also, the presence of amine (NH_2) and hydroxyl (OH) functional groups generates suitable arrangements to coordinate different metal ions. [13-14] (**Scheme 1**)



Scheme 1. Structure of Chitosan

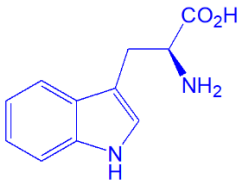
Parkinson's disease is a neurodegenerative disorder and late-onset, and progressive neurological

disease with undetermined causes worldwide. [15-16] Classical symptoms contain tremors, decreased ability, slowed movement, small handwriting, walking disorder, disbalance, flexed state, and probable dementia among older patients. [15,17] Patients are identified as having low concentrations of dopamine (DA) in the central nervous system attributed to neurons that generate dopamine. [15,18] DA precursor levodopa is advised **(Scheme 2)**. The drug's active transport across the blood-brain barrier quickly makes dopamine via an enzymatic reaction that has been catalyzed. Also, a direct neuro-modulatory is levodopa that can cause antiparkinsonian results. [15] It is a useful therapy to decrease the symptoms of PA for example tremors, stiffness, spasms, and weak muscle control. [15, 21] It treats same muscular problems included via medicines such as perphenazine, chlorpromazine, and fluphenazine. [15,20] Long-term utilization of levodopa may generate side effects like dyskinesia and paranoia schizophrenia. So, the specific concentration of this therapeutic drug is significant to control its dosage via an easy and exact analytical way. [15,21]



Scheme 2. Chemical structure of Levodopa

L-Tryptophan (Trp) is known as a chiral molecule. Trp is the least plenty necessary amino acid plant-derived required for protein synthesis and other important metabolic functions, and its supply in humans is exclusively provided via dietary intake. After consumption, it is metabolically transformed into bioactive metabolites, containing serotonin, melatonin, and the vitamin niacin (nicotinamide). [35-38] Some of the benefits of L-tryptophan including environment-friendly, less expensive, and easy availability. [22-26] (**Scheme 3**)



Scheme 3. Structure of L-Tryptophan

In the current research, a nanocarrier composed of three components of Fe_3O_4, Chitosan (CS), and L-tryptophan (Trp) was synthesized. The aim of this research is the synthesis of a metal-organic framework with amino acid tryptophan and chitosan for the purpose of better drug loading and appropriate release of levodopa.

2. Experimental

2.1. Materials

In this work, Chemicals materials, containing Terephthalic acid (BDC, 98%), $FeCl_3.4H_2O$, Chitosan, Tryptophan, and ethanol (99.9%), were bought from Merck Co, and Sigma-Aldrich as well as levodopa were purchased from in Iran Co. FT-IR spectroscopy was determined via PerkinElmer 1600 FTIR spectrometer (KBr pellets). The morphology and particle size of the samples were investigated via scanning electron microscopy (SEM). The crystals were obtained by X-ray diffraction (XRD) and The compositional analysis was operated via Energy-dispersive X-ray (EDX) and Brunauer-Emmett-Teller (BET).

2.2. Preparation of metal-organic framework of Fe_3O_4@CS@L-Trp nanocarrier

Briefly, tryptophan (0.3 g) were dissolved in terephthalic acid 0.01 M (10 ml) stirred at 60 °C, and the white precipitate was obtained. 0.01 mol $FeCl_3.4H_2O$ were dissolved in ethanol, then added to the mixture. This solution were stirred at 60 °C for 12 h. At this stage, the present product was dried for

two days at 45 °C after washing three times with water and ethanol. About 0.03 g of the mixture was dissolved in ethanol, and then 0.03 g of chitosan in 2% acetic acid were dissolved and added to the mixture. This solution were stirred for 30 min, and the final product was obtained.

2.3. Loading Levodopa on the Fe_3O_4@CS@L-Trp

For drug loading, 0.1 g of pure levodopa (L-DOP) powder was dissolved in deionized water 5ml, then 0.05 g of Fe_3O_4@CS@L-Trp were added, solution were stirred at room temperature for 5 days then washed three times by water and ethanol. Finally, the product were dried overnight at 40 °C. According to the following equation, the amount of drug loading was 98%.

$$\text{Drug loading (\%)} = \frac{\text{TC weight in sample}}{\text{Total weight of sample}} \times 100\%$$

2.4. Drug release from Fe_3O_4@CS@L-Trp

The release of the levodopa (L-DOP) were performed in two buffers, in phosphate buffer and acetate buffer (pH: 7.4-5.5). In this method, Fe_3O_4@CS@Trp (0.02 g) were added to each buffer (50 ml) separately. After, the solution was stirred at 37 °C for 3d. Each time, the solution (5 ml) were deleted and rapidly replaced by the same amounts of fresh buffer. The amount of drug released from MOF were studied via UV–Vis spectrometer at 360 nm.

$$\text{Release percentage (\%)} = \frac{\text{mr (amount of released TC)}}{\text{ml (amount of loaded TC}} \times 100\%$$

3. Results And Discussion

The Fourier Transform Infrared Spectroscopy（FTIR) were employed to check the functional group in the Fe_3O_4@CS@Trp and Fe_3O_4@CS@L-Trp@L-DOP composite (Figure. 1a, b). Figures 2a and b show an absorption band of 3410, and 3427 cm^{-1} belonging to the O-H, and N-H groups, in CS, while the peak 1680, and 1678 cm^{-1} belonged to the C=O stretching vibration of the amide group. The peaks corresponding to the C-O stretching vibration of C-OH bending stress are observed at 1018 cm^{-1}, while the bending vibration of the amino group appeared at 1574 cm^{-1}. [13] The absorption related at 546 and 553 cm^{-1} belongs to the Fe-O vibration. [13, 27] The absorption peaks are the aliphatic C–H and C=O group at 2925, and 1604 cm^{-1} in tryptophan respectively (Figure. 1a, b). [28] The spectrums appeared in Figure 2(b) (Fe_3O_4@CS@Trp@L-DOP) confirms the presence of L-DOP in the MOF. The absorption band O–H at 2980 cm^{-1}, and C=C vibrations at 1406, 823, and, 669 cm^{-1} appeared for levodopa in Figure 2b. [29]

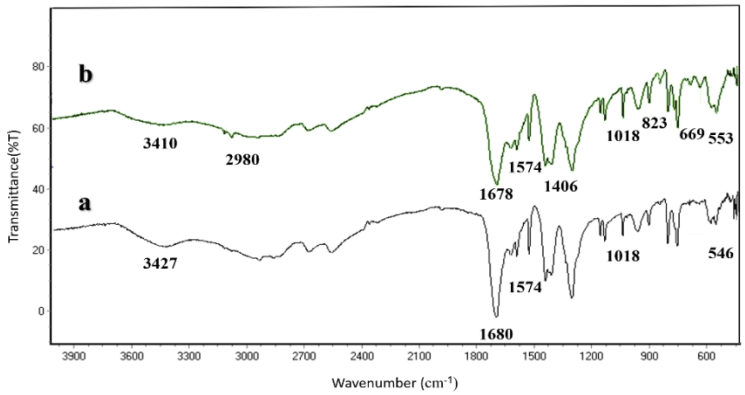


Figure 1. FT-IR spectra of a) Fe_3O_4@CS@L-Trp, b) Fe_3O_4@CS@L-Trp@L-DOP

The elements of Fe_3O_4@CS@L-Trp were investigated using energy-dispersive X-ray spectroscopy. The results displayed that main elements were C, N, O, and Fe, which confirmed that tryptophan was well attached to the chitosan substrate. (Figure. 2)

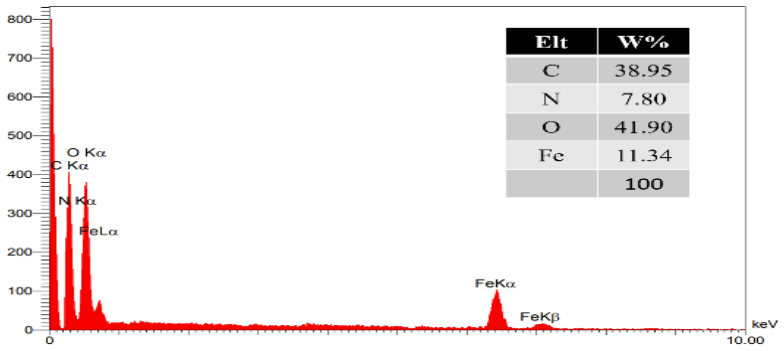


Figure 2. EDX of Fe_3O_4@CS@L-Trp

By using SEM (Scanning electron microscope), the morphology, and size of the particles can assigned. SEM images are investigated after drug loading in Figure. 3. According to the SEM images, spherical morphology was considered for most particles. The average particle size was measured to be about 37.8 nm and spherical morphology was confirmed.

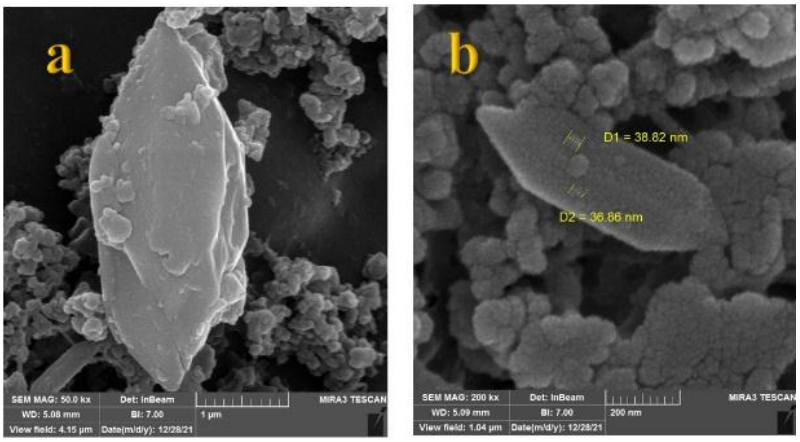


Figure 3. FE-SEM of Fe_3O_4@CS@L-Trp

The XRD patterns of Fe_3O_4@CS@L-Trp confirm the structure of matter and fuzzy composition (Figure 4). Characteristic peaks are observed for Fe_3O_4 were observed at 2θ = 30.20, 35.60, 43.15, 53.70, 57.20, and 62.90° degrees. [10,24] Also, the observed peaks display that the structure of Fe_3O_4 have not changed during the loading of the drug.

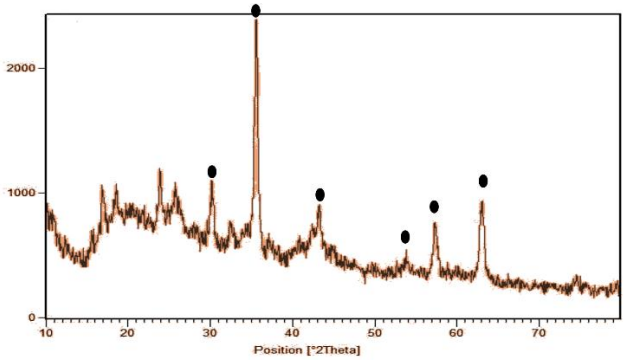


Figure 4. XRD of Fe_3O_4@CS@L-Trp

In the BET-Plots, the available surface area before loading L-DOP is about 12.694 m^2g^{-1} (Fig. 5a) In addition, a pore volume of 0.056 cm^3g^{-1} is demonstrated in Fig. 5 a. The BJH analysis illustrates that the average pore diameter is 1.64 nm, which discloses the microporosity of the composition (Fig. 5 b).

As shown in Fig. 5c, the adsorption-desorption isotherm for Fe_3O_4@CS@L-Trp is a type II sorption isotherm.

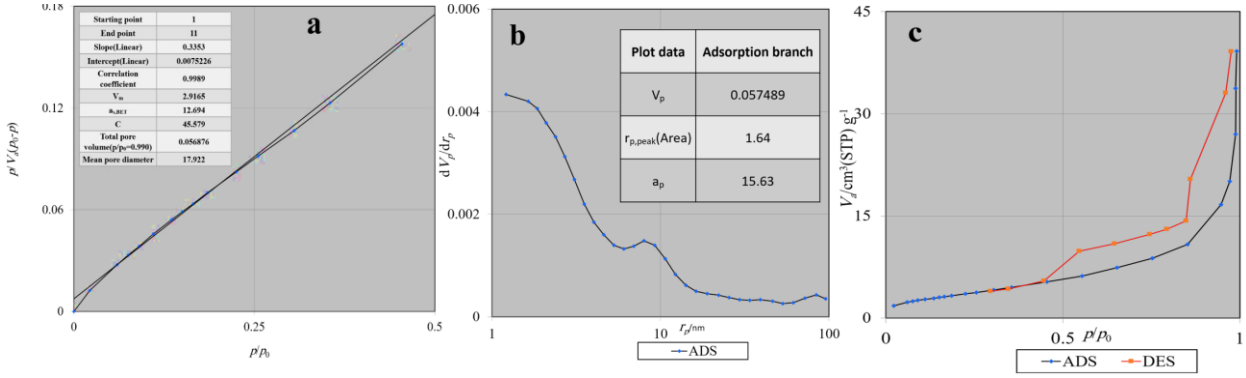


Figure 5. (a) BET of Fe_3O_4@CS@L-Trp analysis, (b) BJH of Fe_3O_4@CS@L-Trp, (c) Adsorption/desorption isotherm of Fe_3O_4@CS@L-Trp

3.1. Study on drug release

Drug release (L-DOP) was carried out, in phosphate buffer and acetate buffer in pH: 7.4-5.5 via a UV–V device at a wavelength of 360 nm, then their calibration curve was plotted. Figure 6. The framework of Fe_3O_4@CS@L-Trp@L-DOP is unstable in acidic conditions (pH: 5.5) and degraded very quickly (85% after 8 h). As a result, drug release at pH: 5.5 is fast. The release becomes stable after 24 hours, and it is about 80%. (pH: 7.4).

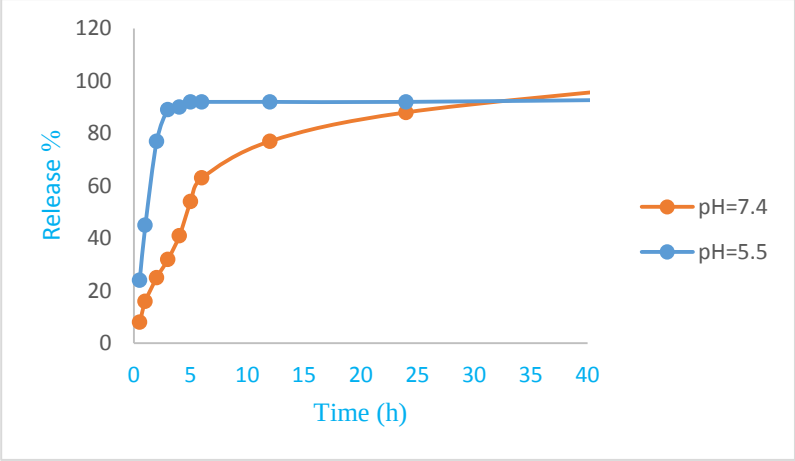


Figure 6. The release of L-DOP from Fe_3O_4@CS@L-Trp in two buffers at pH: 7.4 and pH: 5.5

4. Conclusion

In summary, we designed and fabricated a novel nanostructure of Fe_3O_4@CS@L-Trp@L-DOP for the first time. After confirming the nanocomposite structure, the drug (L-DOP) has loaded on the MOF. based on the characterization and structure confirmed via FT-IR, SEM, EDX, XRD, and BET analysis. Furthermore, Fe_3O_4@CS@L-Trp @L-DOP release was tested in both pH (7.4, 5.5) with high loadings (80-85%).

Disclosure statement

The authors stated that they had no financial or personal interest in preparing the material reported in this article.

ORCID Id

Manoochehr Fadaeian*[a] https://orcid.org/0000-0001-7928-0698

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