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ORIGINAL RESEARCH

The Effects Study of Isoniazid Conjugated Multi-Wall Carbon Nanotubes Nanofluid on *Mycobacterium tuberculosis*

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Background: Tuberculosis (TB) has always been recognized as one of the fatal infectious diseases, which is caused by *Mycobacterium tuberculosis* (M.tb). Isonicotinic acid hydrazide or isoniazid (INH) is one of the most commonly utilized drugs in the treatment of TB. Patients need to take 300 mg daily of INH for 6 months in combination with another anti-TB drug and tolerate several side effects of INH. On the other hand, the emergence of resistant strains of anti-TB antibiotics is one of the major problems in the treatment of this disease. So, antimicrobial drug delivery by nanofluids could improve the efficacy, and reduce the adverse effects of antimicrobial drugs. The purpose of this study was to perform a novel method to synthesize INH-conjugated multi-wall carbon nanotubes (MWCNTs) for more effective drug delivery, as well as, TB treatment.

Methods: INH-conjugated functionalized MWCNTs were prepared, using a reflux system. The characterization of the obtained nano-drug was performed by the elemental analyses of total nitrogen, hydrogen, carbon and sulfur (CHNS), Raman spectroscopy, Fourier transform infrared (FTIR), transmission electron microscopy (TEM), and scanning electron microscopy (SEM) methods. The nanofluid of nano-drug was prepared by the ultrasonic method, and the related antibacterial effect studies were carried out on the two strains of M.tb.

Results: The antimicrobial effect of INH-conjugated MWCNTs was found to be much better at low concentrations than the pure drug in all of the strains.

Conclusion: Since one of the main antimicrobial mechanisms of MWCNTs is through the destruction of the bacterial cell wall, in addition to its antimicrobial effects, it increased the drug delivery of INH at lower doses compared to drug alone. So, the nanofluid, containing INH-conjugated MWCNTs, had a better lethal effect on a variety of M.tb strains than that of the drug alone.

Keywords: isoniazid, multi-wall carbon nanotubes, *Mycobacterium tuberculosis*, nano-drug, nanofluid

Introduction

Tuberculosis (TB) has been illustrated as one of the most lethal infectious diseases in humans, which is caused by *Mycobacterium tuberculosis* (M.tb). Despite the ability of this pathogen to infect different parts of the body, the lungs are distinguished to be the most susceptible. According to the World Health Organization (WHO), about 10 million people are suffered from TB all over the world, each year.[1,2] Isoniazid or isonicotinic acid hydrazide (INH) was mentioned as one of the common drugs used in treating the infectious parts of TB. Plenty of people are healed with this safe and cost-effective drug, which was introduced in 1952,

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Table 1 Elemental Analysis of Conjugated MWCNT

Sample Name	%C	%H	%N	%S
MWCNT	96.40	0.04	0.0	0.0
MWCNT-INH	90.71	0.62	2.66	0.0

Abbreviations: MWCNTs, multi-wall carbon nanotubes; INH, isoniazid.

despite creating liver problems.[3,4] Typically, a daily administration of about 300 mg of INH was prescribed for six months with other effective medications. However, this consumption had side effects such as liver poisoning, jaundice, acute hepatic failure, and reduced blood pressure.[5] Although TB is not a chronic disease, several drugs such as INH and rifampin are used for 4 to 7 months as well as pyrazinamide for eight weeks.[6,7] Furthermore, ethambutol, streptomycin, and piperine were also demonstrated as effective drugs toward TB.[8] Unfortunately, the existence of various infections in humans has made the pathogens more resistant to antibiotics such as INH. INH is used as the first-line drug to treat this infection, and M.tb *inhA, ahpC*, and *fabD* mutational genes are the common targets of this drug.[9] On the other hand, chemotherapy has been the most common method to cure TB, by its advantages and side effects. Nano drug delivery system is an emerging technique to deliver multiple drugs, in a controllable release, lower systematic toxicity, and high drug bioavailability condition, compared to chemotherapy. So, researchers successfully used and confirmed several nano vehicles for sustainable anti-TB multi-drug delivery.[10–12] Carbon nanotubes (CNTs), as biocompatible polymers, are known for the capability of high drug loading, stable release, and significant diffusion in the body.[13] Therefore, the importance of CNTs has been recognized in the pharmaceutical industry.[12,14,15] Multi-wall carbon nanotubes (MWCNTs), as drug carriers, should first be functionalized to enhance the biological function. Induction of carboxyl and chlorine on MWCNTs could increase the carrying capacity and reduce the complications symptoms on healthy cells.[16] Moreover, timely detection and the right administration of the appropriate antibiotics could enhance the ability to recover. In contrast, aging, being infected with HIV, and having

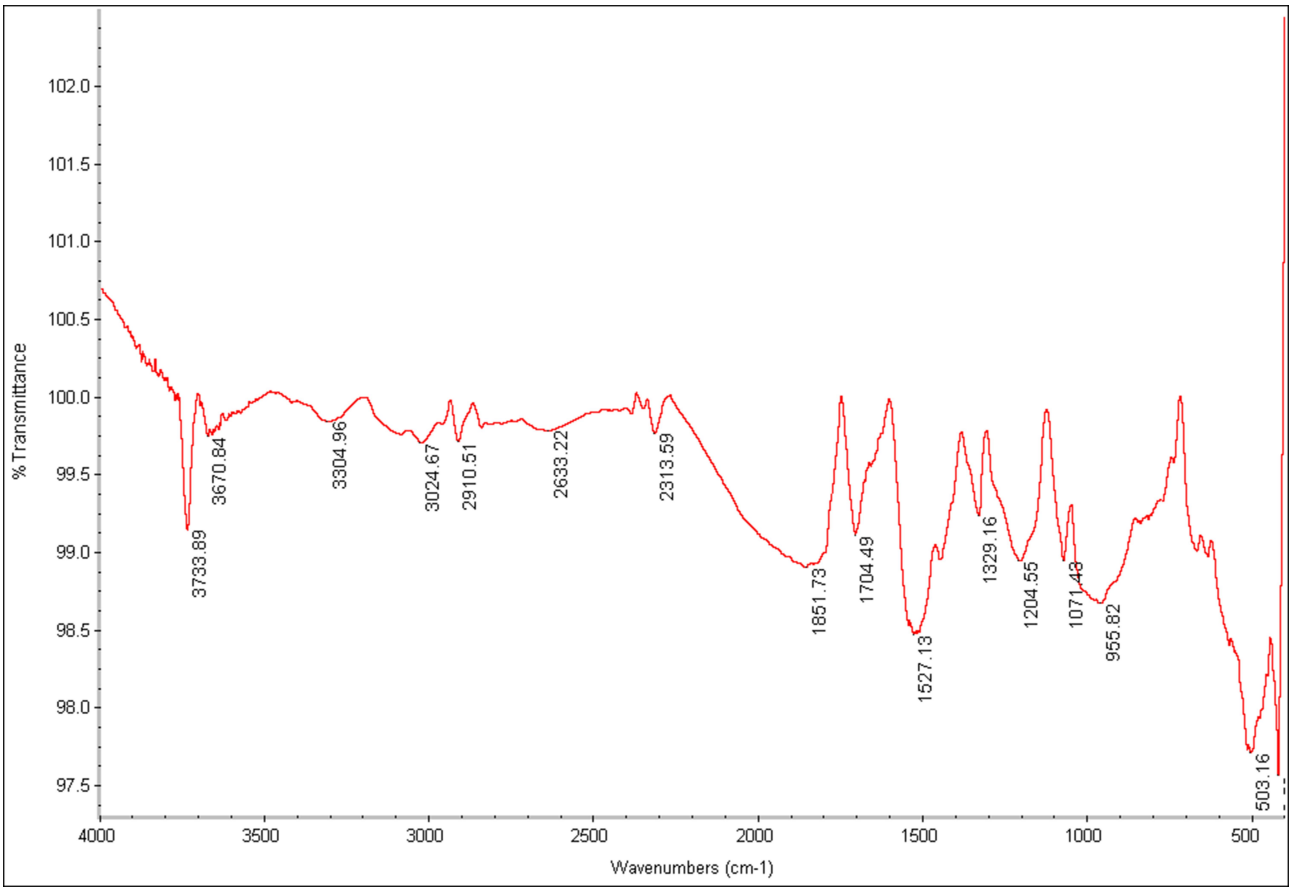


Figure 1 The infrared spectrum of carboxylated nanotubes.

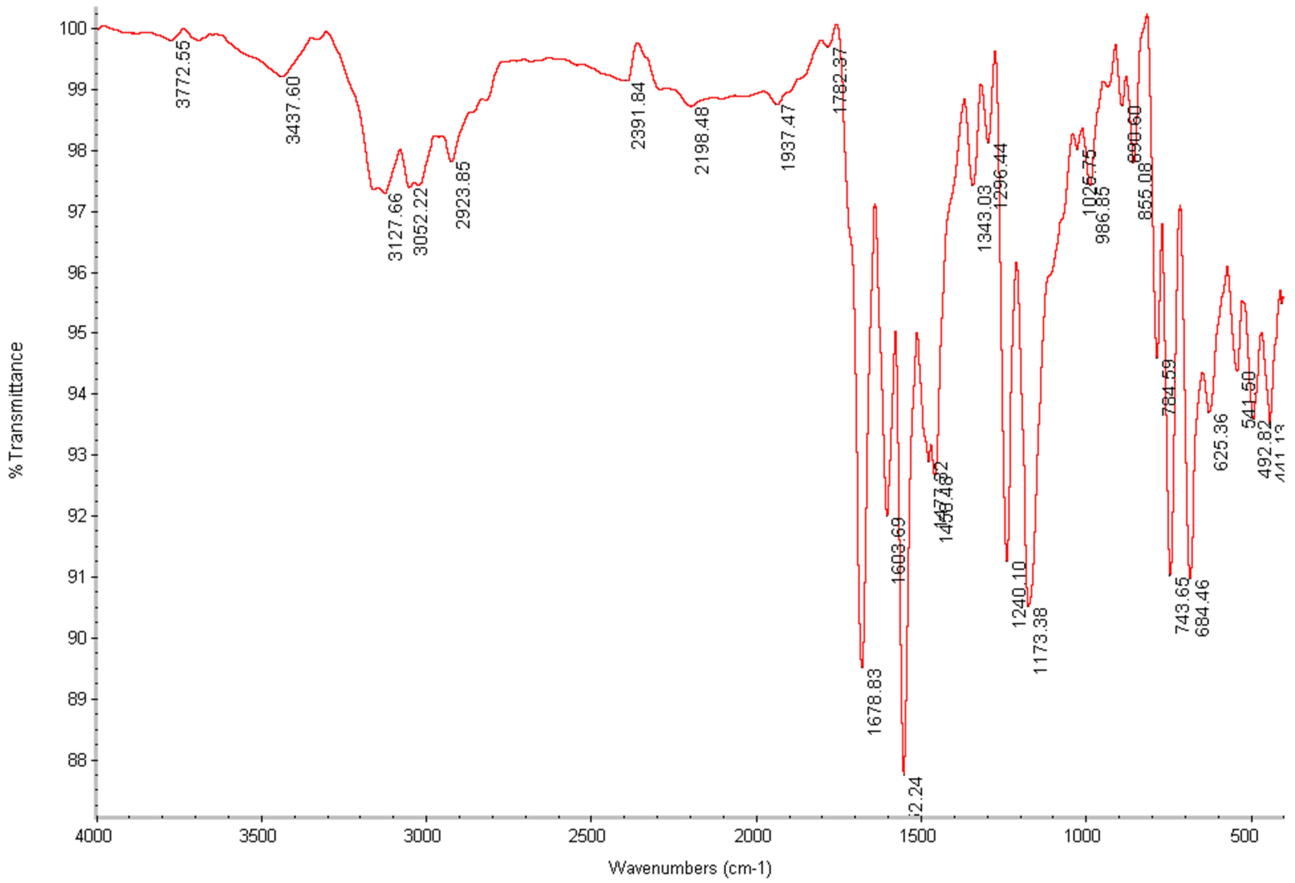


Figure 2 The infrared spectrum of nanotubes functionalized with INH.
Abbreviation: INH, Isoniazid.

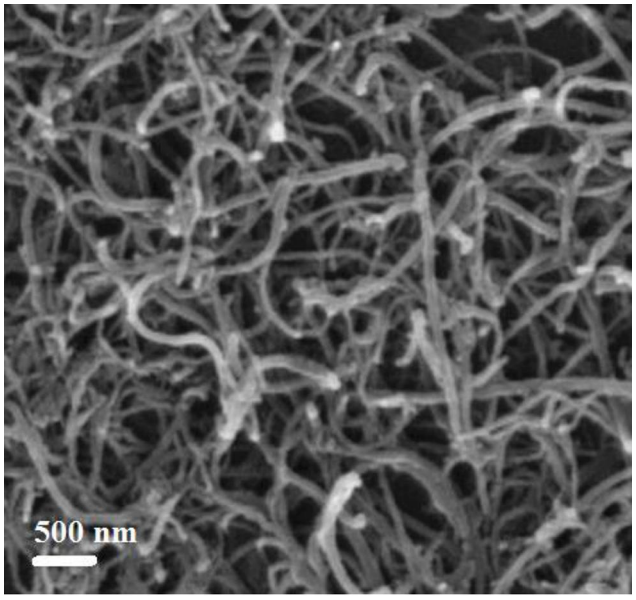


Figure 3 SEM image of the raw MWCNTs.
Abbreviations: SEM, scanning electron microscopy; MWCNTs, multi-wall carbon nanotubes.

a history of TB, are some factors which make the treatment more complex.[17] The focus of this research is on the preparation of the new nano product by chemical reactions, which may be classified in the nano-drug family. There has been no detailed study of the targeting INH with CNT at a dose much lower than the usual therapeutic dose. Therefore, this lower dose could reduce the side effects of the drug during the treatment. Rajarajeswari et al,[18] used single-wall CNTs as carriers of INH to state that this binding could enhance the efficacy of the drug. However, they did not study the microbial and did not determine the appropriate dose. In the antibacterial effect study section, the growth inhibition zone is measured based on the amount of antibacterial substance usage.[19] In this investigation, it has been attempted to confirm the antimicrobial effectiveness of conjugated MWCNTs nanofluid on M.tb by esterification reactions. Also, the prepared nano-drug was validated by the techniques such as elemental analyses of total nitrogen, hydrogen, carbon and sulfur (CHNS),



Figure 4 SEM images of MWCNTs functionalized with INH.
Abbreviations: SEM, scanning electron microscopy; MWCNTs, multi-wall carbon nanotubes; INH, Isoniazid.

Raman spectroscopy, Fourier transform infrared (FTIR), transmission electron microscopy (TEM), and scanning electron microscopy (SEM).[20,21]

Methods

Preparation of INH and MWCNTs

4-pyridinecarboxylic acid hydrazide, INH, with CAS-No: 54–853 (Merck, Germany) and MWCNTs (United States Research Nanomaterials, USA) were prepared.

Functionalization of MWCNTs

Functionalized CNTs were prepared by the use of acylation reactions.[22,23] For carboxylation of MWCNTs, 1.5 g of MWCNTs was combined with 20 mL of sulfuric acid and nitric acid at a ratio of 3:1 for 30 min in the ultrasonic device and was replaced in reflux system for 24 h at 45 ° C. Subsequently, 100 mL of H_2O_2 and HNO_3 were added to the previous phase at a ratio of 4:1, and again, placed to the ultrasonic device for 30 min.[24] The reaction mixture was centrifuged, the precipitate was separated, and the supernatant was centrifuged again by adding deionized water. After several steps of washing with the solvents at the pH up to 6, the sample was washed with methanol. The solution was filtered through a 0.2 µm polytetrafluoroethylene filter, and the black solid was dried under vacuum at room temperature. For acylation of carboxylated MWCNTs, 1 g of MWCNTs with 20 mL of thionyl chloride (Merk, Germany) was mixed at 60 °C for 14 h in the reflux system. The final product was washed and separated with tetrahydrofuran (Merk, Germany) and acetone; then, it was dried in an oven at 70 °C.

Drug Conjugation

For loading INH on CNT, 3 g of INH and 1 g of the chlorate MWCNT powder with 50 mL of dimethylformamide

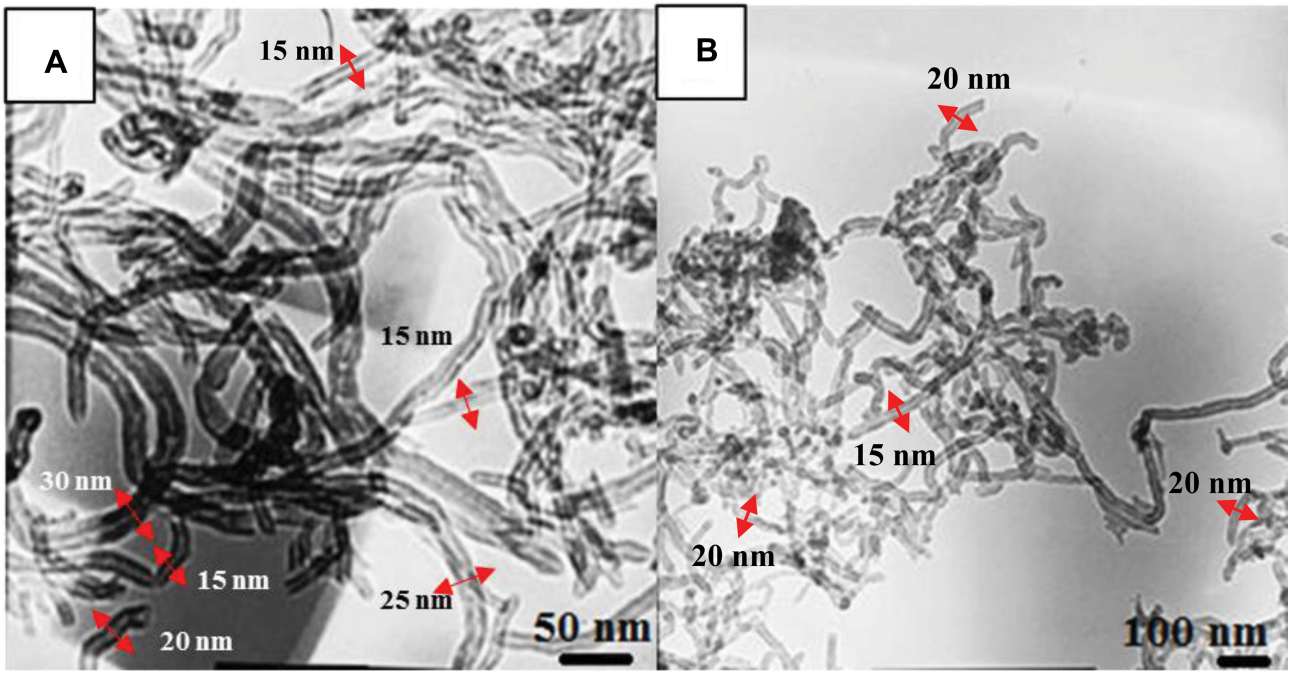


Figure 5 The TEM images of the MWCNT-COOH (**A**) and the MWCNT-INH (**B**) (The red arrows indicate the diameters).
Abbreviations: TEM, transmission electron microscopy; MWCNTs, multi-wall carbon nanotubes; INH, Isoniazid.

(DMF) solution were refluxed at 50, 60, and 70 ° C for 36 hours.[25] The solution was extracted with tetrahydrofuran, methanol, and ethanol (96%), and then the precipitate was dried at room temperature.

Nano-Drug Characterization

Elemental analysis of C-H-N-S and FT-IR were conducted to ensure the binding of INH and CNTs.[26] SEM and TEM observations were done on the functionalized nanotubes and nanotubes alone. Followed that, Raman spectroscopy was performed for MWCNTs compared to their drug conjugated form.[27–29]

Nanofluid Preparation

In this step, 0.2 g of Nano-drug powder, 6 mL of 96% ethanol, and 0.06 g of Arabic gum were added to 100 mL of deionized water, and the mixture was stirred for 20 min.[30] In the next step, the solution was placed in an ice container; then, sonication was carried out for 20 minutes at 200 W.

Microbial Testing

Two M.tb strains, H37Rv as standard, and S (sensitive to INH) were prepared from the microbial bank of the Mycobacterium and Pulmonary Research Department, Pasteur Institute, Iran. The S strain, separated from a sputum sample of TB patient, was sensitive to INH. Afterward, the microbial suspensions were prepared at 0.5 McFarland and were cultured in Lowenstein-Jensen (LJ) culture medium. Then different dilutions (1/2, 1/4, 1/8, 1/16, 1/32) from the first concentration (2mg/mL) of the MWCNT-drug complex were provided and were added for each strain and tested twice for each sample. The bacterial growth was assessed within three weeks; after this time, the final results were observed. Two repetitions for each sample which were treated by INH alone with a concentration of 2mg/mL were been used as controls.

Results

Nano-Drug Characterization

Elemental Analysis

Table 1 exhibits the elemental analysis to ensure the binding of INH to the MWCNTs. Indeed, MWCNTs have no nitrogen mass, but it could be measured in functionalized nanotubes, which indicates the binding of INH to MWCNTs.

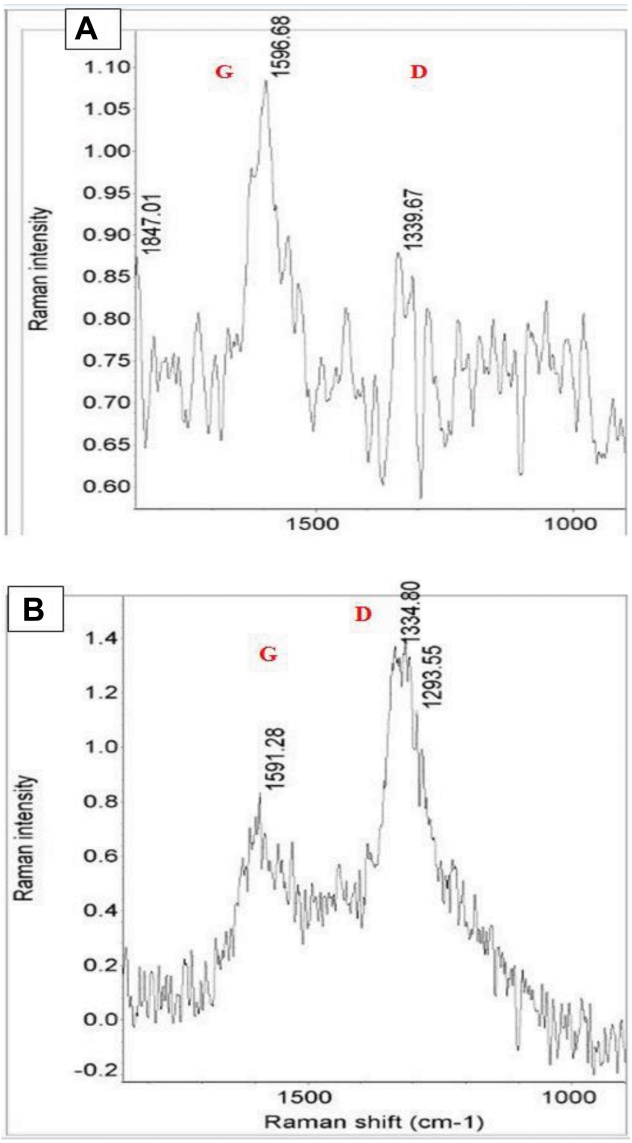


Figure 6 Raman spectroscopy of MWCNT-COOH (**A**) and MWCNT-INH (**B**). (The "G" and "D" indicators: The Raman spectra presented two strong peaks at around 1330 cm $^{-1}$ of which is the D-band and 1590 cm $^{-1}$ of which is the G-band. These are consistent with typical characteristics of CNTs).

Abbreviations: MWCNTs, multi-wall carbon nanotubes; CNTs, carbon nanotubes.

Fourier Transform Infrared

A comparison was made between the infrared spectrum of carboxylated nanotubes (Figure 1) and the infrared spectrum of the nanotubes functionalized with INH (Figure 2). Similar results with previous studies[31,32] were recorded. As shown in Figure 1, the peak at 1527 is related to the C = C bond in the wall of MWCNTs. Also, the peak at 3304 cm^{-1}correspond to the carboxylic acid group. The FTIR spectrum of INH-MWCNTs (Figure 2) confirmed the formation of amide groups on the MWCNTs surface. The peaks at 16781173 cm^{-1} were assigned to amide bond

between the drug and nanotubes. The peak at 1603 cm^{-1} peak is related to the amide bounding of the pyrimidine ring of the isoniazid drug. The peaks at 743684 cm^{-1} are also related to the vibrations of the pyridine ring of the drug.

Scanning Electron Microscopy Data Analysis

This analysis was conducted to demonstrate the evidence for the functionalization of MWCNTs by the SEM method. Figure 3 is related to the SEM images of the MWNT–COOH, and Figure 4 exhibits the nanotubes functionalized with INH.[10] The MWCNT–COOH (Figure 3) has a smooth surface. The changes in the morphology for MWCNT- INH (Figure 4) are significant. A uniform tubular layer is observable on the surface of the MWCNT (the rough part). It seems that the diameter in MWCNT- INH is slightly increased in comparison to those of MWCNT–COOH.

Transmission Electron Microscopy

The TEM images of MWCN modified with COOH and MWCNT modified by INH are given in Figure 5A and B, respectively. As it is clear in both samples the mean diameters of MWCNT are in rang of 15–20 nm. The MWCNT-COOH seemed to be a bundle or a rope of MWCNT; while, the dissociation of the bundles was observed in the MWCNT-INH. Functionalization prevented the MWCNT to aggregate in the form of bundles and enhanced their dispersibility. So, the MWCNT-INH showed a higher and more facile dispersion, in solvents, than that of the MWCNT-COOH.

Raman Spectra Analysis

Raman spectroscopy could be a powerful tool, used to provide structural information about MWCNT–COOH, before and after functionalization. As shown in Figure 6, the D and G bands of the MWCNT, are at around 1330 and 1590 cm. A and B were observed for MWCNT–COOH, and MWCNT– INH. The increase in the intensity of the defect mode at 1330 cm is related to the sp3 hybridization of carbon, which is used as evidence of the disruption of the aromatic system of π electrons by the attached molecules.

Results of Microbial Tests

The results of the study on the effects nano-drug on two strains of M.tb (S and H37Rv) are shown in Figures 7 and 8, and Table 2. The results showed that nano-drug was completely effective on H37Rv strain and inhibited



Figure 7 Sensitive strains of M.tb, treated with serial dilution (1/4, 1/8, 1/16, 1/32) of the nano-drug from the concentration of 2 mg/mL (No growth of bacteria was observed from the dilution of 1/8).
Abbreviation: (M)tb, *Mycobacterium tuberculosis*.



Figure 8 H37Rv strains of M.tb, treated with serial dilution (1/4, 1/8, 1/16, 1/32) of the nano-drug from the concentration of 2 mg/mL (No growth of bacteria was observed from the dilution of 1/32).
Abbreviation: (M)tb, *Mycobacterium tuberculosis*.

bacterial growth in the least dilution of 1/32 from the concentration of 2 mg/mL. The effect of the drug on the S strain is also noticeable since it has completely stopped the bacterial growth at dilution of 1/8 from the concentration of 2 mg/mL. As shown in Figures 7 and 8 the two repeated control samples of both S and H37Rv have been grown for untreated samples were considered as a control sample.

Conclusions and Future Perspective

In this investigation, a new formulation of the INH nano-drug was developed by using MWCNTs, which had a significant antibacterial effect in the low dosages, in comparison with INH alone. This nano-drug has more potential such as better penetration to the bacterial membrane, increased yields at the lower concentrations than the usual therapeutic doses, and decreased bacterial resistance toward the usual form of antibiotics. This study aimed to obtain the appropriate dose of the nano-drug, to increase the level of antibacterial function of INH. In this study, using INH nano-drug significant success in treatment was achieved at a lower concentration of nano-drug compared to the usual (1/16 for S and 1/32 for H37Rv). Finally, it was concluded that the functionalization of MWCNTs with INH would have

Table 2 Bacterial Growth Results in Different Dilutions of INH and INH Nano-Drug, Growth (+) and Non-Growth (-)

Concentrations of Drugs Complex and INH(From the Concentration of 2 mg/mL)	Bacterial Growth in S Strain in the Presence of Nano-Drug	Bacterial Growth of H37Rv Strain in the Presence of Nano-Drug
1	–	–
1:2	–	–
1:4	–	–
1:8	–	–
1:16	–	–
1:32	+	–
Control	+	+

Abbreviation: INH, isoniazid.

distinct advantages such as overcoming antibiotic resistance. Several studies demonstrated the possibility of using CNTs as a nanocarrier for TB drug delivery and were conducted to overcoming on antibacterial resistance of TB.[15,28] One study in 2019 reported that chitosan-functionalized CNTs could increase the drug permeability of INH in the treatment of TB in the bone and wound tissues.[33] Also, Barros et al,[34] demonstrated the efficacy of naphthoimidazoles together with INH and rifampin, as the main drugs for controlling tuberculosis. Also, success studies reported targeted delivery of rifampicin to TB-infected macrophages and also controlled delivery and tissue regeneration of TB. To date, this study has been performed to evaluate the efficacy of nano-drugs in comparison with the drug alone and also evaluation of drug delivery potential of MWCNTs. To use it effectively, more studies are needed, especially optimizing the method of drug conjugation, as well as more cellular and molecular studies to identify the mechanisms of its effects on bacterial growth.

Disclosure

The authors have no conflict of interest.

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