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Original Article

EVALUATION THE EFFECT OF NANOTECHNOLOGY ON PHARMACEUTICAL AND BIOLOGICAL PROPERTIES OF METRONIDAZOLE

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ABSTRACT

Objective: This study aimed to evaluate the application of nanotechnology in improving the solubility and biologic activity as the antibacterial and antifungal drug of metronidazole (MTZ).

Methods: Nanoparticles of bismuth sulfide (Bi_2S_3) were used as the nanocarriers for metronidazole (MTZ) and they were synthesized by chemical co-precipitation method. Drug loading on Bi_2S_3 nanoparticles, lattice property alteration and average particles sizes were evaluated using fourier transform infrared (FTIR) spectroscopy, atomic force microscopy (AFM), and powder X-ray diffraction (PXRD). The evaluation of the release of MTZ from Bi_2S_3 nanoparticles was carried out using USP type II rotating paddle apparatus. The antimicrobial activity of MTZ before and after loading was carried out by disc diffusion method against two aerobic gram+ve and one aerobic gram–ve bacteria, in addition to two fungi.

Results: This study showed successful loading process as well as particles size reduction of MTZ after loading on Bi_2S_3 nanoparticles. *In vitro* release study showed a significant* increase in solubility and dissolution of MTZ after loading on Bi_2S_3 nanoparticles. MTZ showed a significant* increase in antibacterial (against gram+ve aerobic *staphylococcus aureus* and *bacillus subtilis*) and antifungal (*Candida glabrata* and *Candida tropicalis*) activities after loading process.

Conclusion: Nanotechnology was applied successfully to improve both, solubility and biologic activity of the model drug used, metronidazole (MTZ).

Keywords: Nanotechnology, Nanocarriers, Metronidazole (MTZ), Bismuth sulfide (Bi_2S_3) nanoparticles

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INTRODUCTION

Nanotechnology is the control of a matter at dimensions of roughly 1 to 100 nm, providing unique properties of the matter because of its small size [1]. Nanotechnology offers many benefits in medicine such as protecting drugs from degradation [2], enhancing solubility of water insoluble or poorly soluble drugs [3] as well as increasing efficacy of active ingredient. These benefits help to reduce drug doses which in turn decrease the risk of its side effect and toxicity[4]. Nanocarriers are nano materials being used as a vehicle for another substance, such as drugs [5], with a diameter range from 1-100 nm [6]. They are taken up by target cells more easily than larger molecules, so they can be successfully used as delivery tools for bioactive compounds [7]. Ideal nanocarriers properties include blood stability, no activation of neutrophils, non-inflammatory, non-immunogenic, non-toxic, non-thrombogenic, readily biodegradable, reticulo-endothelial system avoidance, applicable to different molecules (such as small molecules, peptides, proteins and nucleic acids), inexpensive manufacturing process and scalable [8].

Among nanoparticles with biomedical advantages are inorganic nanoparticles which include metals (gold, copper, silver, magnesium and iron), metal oxides (iron oxide, zinc oxide, titanium dioxide and cerium oxide) and quantum dots (cadmium selenide and cadmium sulfide)[9]. Metal are unique with various biomedical applications involving drug and gene delivery, highly sensitive diagnostic assays, radiotherapy enhancement and thermal ablation [10]. Metal nanoparticles such as bismuth sulfate (Bi_2S_3) have displayed a wide potential in applications including optics, public health products and catalysis [11]. Metronidazole (MTZ) was the designed drug used in this study, is a nitroimidazole antimicrobial agent that is widely used in the treatment of protozoal and anaerobic infections [12] including *Bacterial vaginosis*, *Giardiasis*, *Clostridium difficile* and *Trichomonasis.* MTZ cause bacterial cell death by disruption of DNA's helical structure resulting in bacterial nucleic acid synthesis inhibiting [13]. It has limited or absent antibacterial activity against aerobic bacteria. MTZ belongs to a biopharmaceutical classification system (BCS) class IV drug with an extremely poor water solubility (1 mg/ml) and low permeability. The low solubility of drug lead low absorption and bioavailability [14]. Nanotechnology was here utilised as an attractive approach to overcome the low solubility and bioavailability problems [15, 16] by the reduction in particle size of MTZ and thereby alteration in the concomitant physical and to some extent chemical properties [17]. This study was designed to evaluate the effect of nanotechnology as a novel drug delivery approach using metal nanocarrier (Bi_2S_3 nanoparticles) on the solubility and biological activity of MTZ as a model drug. Additionally, MTZ have certain biologic spectrum, thereby improving its biological activity by the use of nanotechnology is a promising approach to reduce their dosing frequency as well as to reduce the amount of drug per each dose to decrease undesirable side effect and to widen their spectrum against different types of microbes that was already had no antimicrobial activity against.

MATERIALS AND METHODS

Materials

Metronidazole (JIANGSU YEW PHARMACEUTICAL Co. Limited, China), disodium sulfide (Na_2S10H_2O) (THOMAS BAKER Co. Limited, India), bismuth nitrate Bi $(NO_3)_3.6H_2O$ (Qualikems Fine Chem Co. Ltd., India), ethanol C_2H_6O (Sigma Chemical Co. Limited, USA) and dimethyl sulfoxide (DMSO) (Loba Chemie Pvt. Ltd, India) were used in this study.

Methods

Synthesis of bismuth sulfide (Bi_2S_3) nanoparticles

Bi_2S_3 nanoparticles were prepared by chemical co-precipitation technique as described in0.1 M aqueous solution Na_2S10H_2O was added at a rate of 10 drops/min onto 0.1 M aqueous solution $Bi(NO_3)_3.6H_2O$ with vigorous stirring (1100 rpm) at 80 °C by a magnetic stirrer (Dragon Lab, USA). The stirring (1100 rpm) was continued after titration at 80 °C for 3 h. Then the black sticky

product (final product) was filtered, washed with deionized water, desiccated in a desiccator containing silica gel for 3 d and collected to be evaluated [18, 19].

Loading of metronidazole on Bi_2S_3 nanoparticles

MTZ was loaded to Bi_2S_3 nanoparticles using incorporation method as described in [20]. This method involved the addition of the drug in the last step of nanoparticles synthesis, where 0.1 M of MTZ in ethanol solvent was added by fast dropping to the mixture of bismuth nitrate and sodium sulfide while it is vigorously stirred (1100 rpm) at 80 °C. The final product was filtered, washed with deionized water and desiccated for 3 d in a desiccator containing silica gel to be collected and evaluated [21].

Characterization of metronidazole-loaded Bi_2S_3 nanoparticles

Fourier transform infra-red spectroscopy (FTIR)

To determine the nature of functional groups and the purity of unloaded MTZ as well as loaded MTZ with Bi_2S_3 nanoparticles, samples were evaluated by using fourier transform infrared spectroscopy (FTIR) instrument (Shimadzu Japan) with spectroscopy (4000-500 cm^{-1}) using potassium bromide disc [22].

Powder x-ray diffraction (PXRD)

The crystallinity of unloaded MTZ and after loading with Bi_2S_3 nanoparticles was determined by PXRD instrument (Shimadzu, Japan). This was equipped with Cu-Ka radiation (λ = 1.54060 Å), voltage (40 Kv) and current (30 mA). The samples were analyzed in scanning speed of (5°/min) and axis θ-2θ with a range of 0 to 60 degrees [23].

Atomic force microscopy

Atomic force microscopy (AFM) (Augestrom advance Inc., USA) was used to determine the particle size, size distribution and shape of nanoparticles by resolving individual particles and groups of particles in three dimensions analysis [24]. It was performed for unloaded, loaded MTZ and blank Bi_2S_3 nanoparticles. Powder samples were dissolved in methanol, and few drops of each sample were dropped separately on a silica glass plate and allowed to dry at room temperature to be deposited on the plate, then the deposited film was scanned with AFM instrument [25].

The drug loading, drug yield and drug entrapment efficiency percentages

The drug loading percent was calculated as a percentage ratio of the drug weight alone in nanoparticles to the weight of drug loaded with nanoparticles and as follow:

$$\text{Drug loading percent} = \frac{\text{weight of drug in nanoparticles}}{\text{weight of nanoparticles loaded with the drug}} \times 100\%$$

The percent of the drug yield was calculated as a percentage ratio of the nanoparticles weight after drug incorporation with nanoparticles to the weight of nanoparticles and drug fed initially in the reaction before incorporation and as follows [26]:

$$\text{Drug yield percent} = \frac{\text{weight of nanoparticles after drug incorporation (actual)}}{\text{weight of nanoparticles and drug before incorporation (theoretical)}} \times 100\%$$

The entrapment efficiency percent (% E. E) of the drug was calculated as a percentage ratio of the drug weight in nanoparticles after incorporation to the weight of drug that initially fed in the reaction before incorporation and as follows [27]:

$$\text{E. E percent} = \frac{\text{weight of drug in nanoparticles after incorporation (actual)}}{\text{weight of drug before incorporation (theoretical)}} \times 100\%$$

***In vitro* release study**

The release of MTZ from Bi_2S_3 nanoparticles was performed using USP type II rotating paddle apparatus (Copley, UK) at 37+0.5 °C with rotating speed of 100 rpm. An equivalent 10 mg of MTZ loaded Bi_2S_3 nanoparticles, as well as 10 mg of unloaded MTZ (as control), were dispersed separately in 500 ml of phosphate buffer solution (pH 7.4). Then 5 ml samples were withdrawn at predetermined time intervals and replaced with the same volume of fresh media after each withdrawal. The withdrawn samples were filtered and the content of MTZ was determined by using UV-visible spectrophotometer (Shimadzu, Japan) at 278 nm, each experiment was analyzed in triplicate [28, 29].

Biological susceptibility test of MTZ loaded on Bi_2S_3 nanoparticles

The susceptibility test was performed using disc diffusion method to evaluate the biologic activity of MTZ loaded Bi_2S_3nanoparticles in comparison with unloaded MTZ as well as with blank Bi_2S_3nanoparticles. Each sample was tested against two types of gram+ve bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and one type of gram–ve bacteria (*Escherichia coli*) using serial diluted concentrations of 250, 125, 62.5 and 32.25 µg/ml of unloaded MTZ and an equivalent concentrations of MTZ loaded with Bi_2S_3 nanoparticles as well as an equivalent fraction of blank Bi_2S_3 nanoparticles present in each concentration of loaded MTZ. The same concentrations were used to evaluate the antifungal activity against two candida fungi species, *Candida glabrata* and *Candida tropicalis.*

The samples were dissolved using dimethyl sulfoxide (DMSO) as a solvent. All bacteria species used were cultured in Muller Hinton agar for 24 h at 37 °C for antibacterial susceptibility test [30, 31], while the two fungi species were cultured in Sabouraud Dextrose agar at 37 °C for 48 h [32].

Statistical analysis

SPSS for windows (version 13, SPSS Inc., Chicago, IL, USA) was the package used for statistical analysis. Statistical significance for each test (*P* value) of less than 0.05 was dependent. All the experiments were carried out in triplicates and the comparisons of quantitative data obtained from the biologic activity of metronidazole (MTZ) were analyzed using one-way and two-way ANOVA tests, as well as Student t-test, was used for comparison of quantitative data for *in vitro* release, the results were expressed as mean±standard deviation.

RESULTS

Characterization of metronidazole-loaded Bi_2S_3 nanoparticles

Fourier transform infra-red spectroscopy (FTIR)

FTIR spectrum of pure unloaded MTZ (fig. 1 A) showed bands at 2954 cm^{-1}and2837 cm^{-1}attributed to C-H stretching of a methyl group, while the band at 3089 cm^{-1}represent C-H stretching of alkene mono substituted (=CH-). The band at 3211 cm^{-1} is related to the O-H stretching due to intra molecular hydrogen bonding. For loaded MTZ on Bi_2S_3 nanoparticles FTIR spectra (fig. 1 B), same functional groups of unloaded MTZ are presented with small shifting [33].

Powder x-ray diffraction (PXRD)

For pure unloaded MTZ, x-ray diffraction peaks (fig. 2 A) were appeared in high multiplicity with narrow sharp intense peaks, indicating the highly crystalline property of MTZ molecules lattice. While the diffracted peaks after a loading process of MTZ on Bi_2S_3 nanoparticles (fig. 2 B) showed nor intense neither sharp peaks. In addition, the multiplicity of diffracted peaks was largely decreased or diminished.

Atomic force microscopy (AFM)

Images from AFM microscope showed smooth surfaces with fine particle size distribution. Two (2D) and three (3D) dimensions particle size images of MTZ determined by AFM device before (fig. 3 A) and after (fig. 3 B) loading on Bi_2S_3 nanoparticles were 112.99 nm (representing MTZ only) and 113.23 nm (representing MTZ+Bi_2S_3 nanoparticles as one particle) respectively. The average particle size of blank Bi_2S_3 nanoparticles (fig. 3 C) was found 114.55 nm. Particle size distribution was also measured using AFM microscope and displayed almost more pyramidal shaped and more fine distribution of MTZ particles after loading on Bi_2S_3 nanoparticles (fig. 4 B) than that of pure drug (fig. 4 A). Particle size distribution was measured for blank Bi_2S_3 nanoparticles too (fig. 4 C).

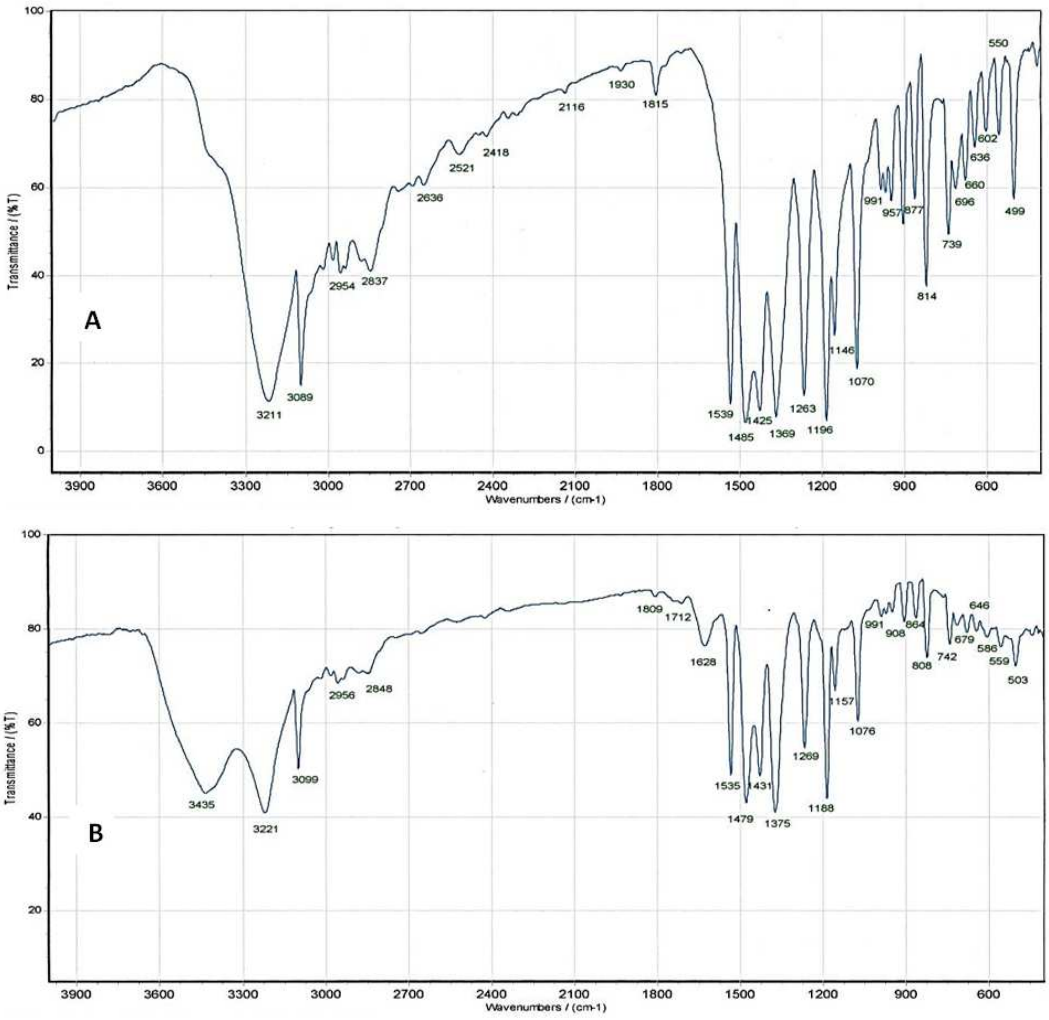

Fig. 1: FTIR of (A) unloaded metronidazole (MTZ) and (B) metronidazole (MTZ) loaded Bi_2S_3 nanoparticles

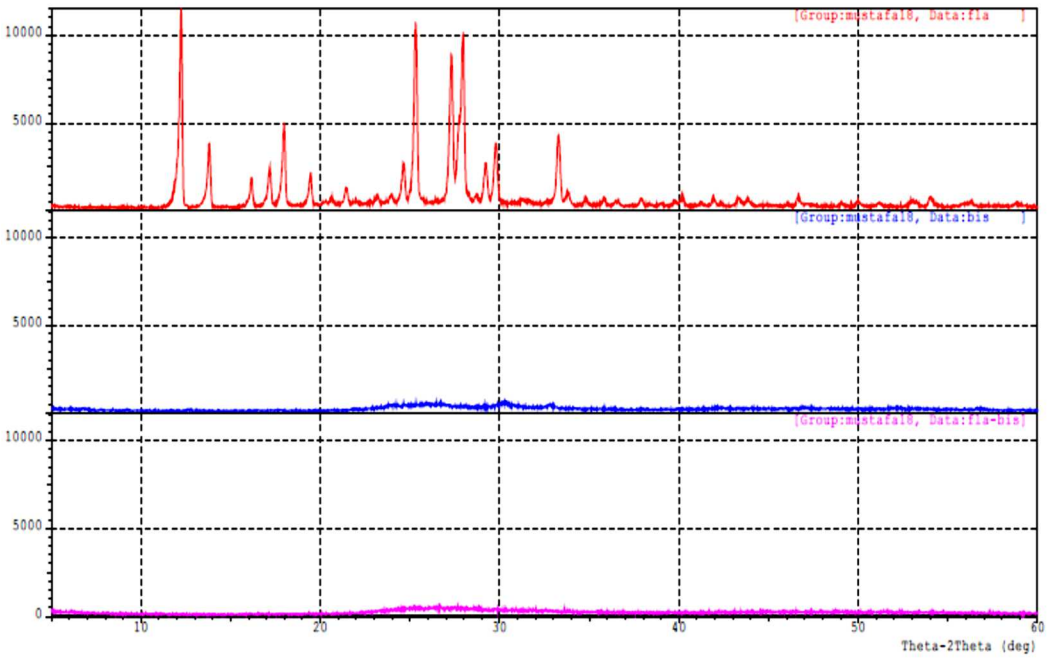

Fig. 2: XRD of (A) unloaded metronidazole (MTZ), (B) metronidazole (MTZ) loaded Bi_2S_3 nanoparticles and (C) blank Bi_2S_3 nanoparticles

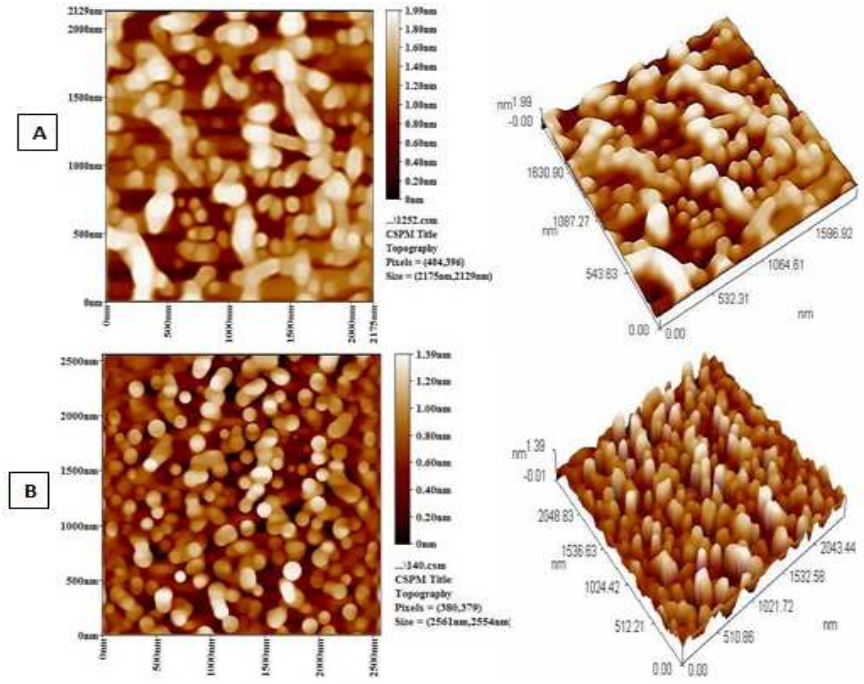

Fig. 3: AFM 2D and 3D images of (A) unloaded metronidazole (MTZ), (B) metronidazole (MTZ) loaded Bi_2S_3 nanoparticles and (C) blank Bi_2S_3 nanoparticles

The drug loading, drug yield and drug entrapment efficiency percentages

Loaded drug percentage for MTZ on Bi_2S_3 nanoparticles was found 62.72%, while the yield MTZ percentage on Bi_2S_3 nanoparticles was found 68.53%. The entrapped MTZ percentage for was found 93.83%.

***In vitro* drugs release study**

MTZ *in vitro* release from Bi_2S_3 nanoparticles (fig. 5) in phosphate buffer solution (pH 7.4) showed significantly* enhanced dissolution of drugs after loading on Bi_2S_3 nanoparticles in comparison with the dissolution of pure unloaded MTZ before loading process. Where MTZ was completely released (100%) from Bi_2S_3 nanoparticles after 45 min, while unloaded MTZ showed 60% dissolution after the same time of 45 min.

Biological susceptibility test of MTZ loaded on Bi_2S_3 nanoparticles

Antibacterial activity evaluation of MTZ (table 1) before and after loading process with Bi_2S_3 nanoparticles was performed against gram+ve bacteria *Staphylococcus aureus* and *Bacillus subtilis* using different concentrations as mentioned previously.

The antibacterial activity of MTZ loaded on Bi_2S_3 nanoparticles showed significant* antibacterial activity against gram+ve bacteria *Staphylococcus aureus* at concentration 125 and 250 µg/ml, which was absent at all concentrations used of pure unloaded MTZ. Significant*enhancement in the antibacterial activity of MTZ loaded on Bi_2S_3 nanoparticles against gram+ve bacteria *Bacillus subtilis* was found at all concentrations used, in contrast to pure unloaded MTZ which had no antibacterial activity at the concentrations (32.25 and 62.5 µg/ml) and significant* improvement in the activity at concentrations 125 and 250 µg/ml after loading process.

All tested samples in all concentrations used showed no activity on *Escherichia coli.* Antifungal activity of MTZ loaded Bi_2S_3 nanoparticles (table 2) was also evaluated against *Candida glabrata* and *Candida tropicalis* and showed significantly* increased activity at all tested concentrations 32.25,62.5, 125 and 250 µg/ml in comparison with same concentrations of the unloaded drug.

DISCUSSION

Fourier transformed infrared (FTIR) spectrum (fig. 1) of unloaded metronidazole (MTZ) indicated that the loading of MTZ on Bi_2S_3 nanoparticles was achieved physically without any chemical reaction or degradation of the drug, where the main functional groups of unloaded MTZ (fig. 1 A) were found in loaded MTZ on Bi_2S_3 nanoparticles (fig. 1 B) with small shifting[34]. The *in vitro* release and dissolution profile of MTZ (fig. 5) was found to be improved significantly* after loading process with the complete release of MTZ from Bi_2S_3 nanoparticles after 45 min. On the other hand, the unloaded MTZ showed 60% dissolution after the same time. This might be attributed to the lattice transformation, as indicated by powder x-ray diffraction (PXRD), of unloaded MTZ (fig. 2 A) from crystalline into the amorphous structure (fig. 2 B) after loading process that may induce an alteration in physical and pharmaceutical properties of the drug [35, 36]. In the *in vitro* release study(fig. 5), the dissolution medium used was phosphate buffer solution (pH 7.4), same pH of plasma, since MTZ-Bi_2S_3 nanoparticles complex was prepared as final active materials and not as a dosage form. Two and three dimensions images (fig. 3) of MTZ particle sizes before and after loading with Bi_2S_3 nanoparticles using AFM device indicated successful loading process with reduction in particle size of the drug, whereas the sum of average particle sizes of unloaded MTZ (112.99 nm) and blank Bi_2S_3 nanoparticles (114.55 nm) was found much lower than that of loaded drug (113.23 nm)[37]. This reduction in particle size of MTZ after loading process also contribute to the increased solubility and dissolution profile of MTZ [38, 39].

In this study, AFM particle size distribution diagram (fig. 4) indicates more even and effective particle size distribution of MTZ loaded Bi_2S_3 nanoparticles than that of the unloaded drug. This even distribution of MTZ particles after loading process might contribute to the improved and effective release profile of MTZ from the carrying nanocarrier, Bi_2S_3 nanoparticles. High loading and high yield percentages of MTZ indicate effective and reproducible loading process without losing a large fraction of MTZ during loading preparation. The excellent entrapped drug percentage also indicates successful loading process as well as efficient therapeutic response, since the metal nanocarrier (Bi_2S_3 nanoparticles) entrapped and carried enough MTZ to produce the desired antimicrobial effect [40].

Both antibacterial (against *S. aureus* and *B. subtilis*) and antifungal (against *C. glabrata* and *C. tropicalis*) activities were improved significantly* after loading of MTZ on Bi_2S_3 nanoparticles (as displayed in table 1 and table 2). The improved biologic activity of MTZ after loading process could be a result of reduced particle size as confirmed by AFM measurement that lead to increase effective surface area of exposure, where the particle size reduction into nano-size (100 nm) facilitate penetration of drug particles into microbial cell membrane and into targeted organelles thereby providing targeted nanotechnology delivery system of MTZ toward microbial pathogens [41, 42]. The significant* enhancement in the solubility as well as dissolution profile of MTZ might also contribute to the improved biological activity, since the enhanced dissolution of the drug after loading process allowed drug to be released effectively out of Bi_2S_3 nanocarrier that provides more available MTZ in solution to be transported or diffused into the target pathogenic bacteria and fungi [43, 44]. The significant* increase in the solubility of MTZ would expect to improve absorption and hence bioavailability of the prepared MTZ loaded Bi_2S_3 nanoparticles [45, 46].

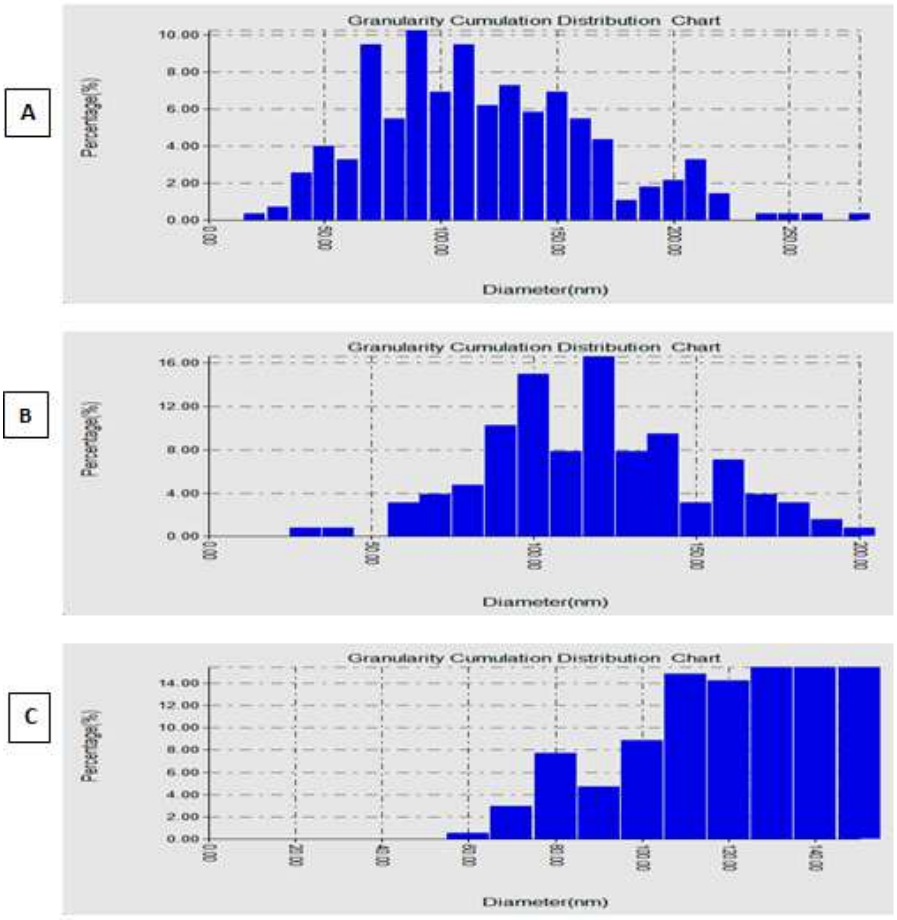

Fig. 4: AFM particle size distribution of (A) unloaded metronidazole (MTZ), (B) metronidazole (MTZ) loaded Bi_2S_3 nanoparticles and (C) blank Bi_2S_3 nanoparticles

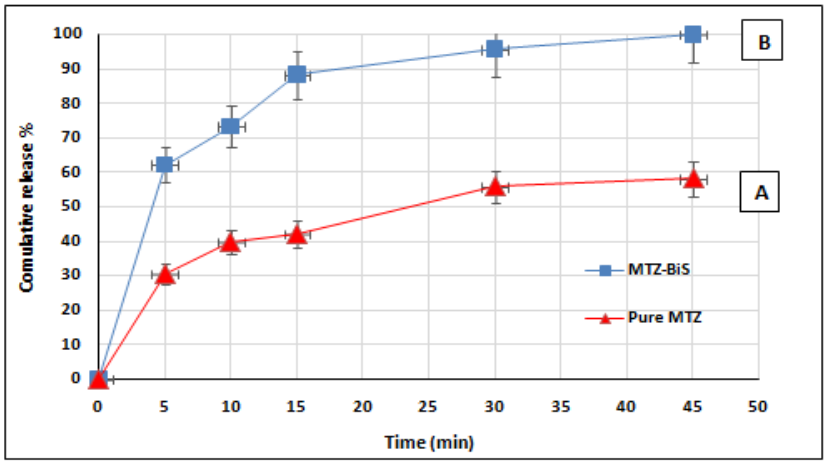

Fig. 5: *In vitro* profile of (A) unloaded metronidazole (MTZ) and (B) metronidazole (MTZ) loaded Bi_2S_3 nanoparticles. Data represent mean (n=3)+SD

Table 1: Antibacterial activity of unloaded MTZ, MTZ loaded Bi_2S_3 nanoparticles and blank Bi_2S_3 nanoparticles represented as inhibition zone in millilitre (mm)

Sample	*Staphylococcus aurous*				*Bacillus subtilis*				*Escherichia coli*			
	Concentration µg/ml											
	32.25	62.5	125	250	32.25	62.5	125	250	32.25	62.5	125	250
DMSO	_	_	_	_	_	_	_	_	_	_	_	_
Bi_2S_3nanoparticles	_	_	_	_	_	_	_	_	_	_	_	_
Pure MTZ	_	_	_	_	_	_	10	10	_	_	_	_
MTZloadedBi_2S_3nanoparticles	_	_	11	13	13	15	19	21	_	_	_	_

Note: MTZ (metronidazole); Bi_2S_3 (bismuth sulfide nanoparticles)

Table 2: Antifungal activity of unloaded MTZ, MTZ loaded Bi_2S_3 nanoparticles and blank Bi_2S_3 nanoparticles represented as inhibition zone in milliliter (mm)

Sample	*Candida glabrata*				*Candida tropicalis*			
	Concentration µg/ml							
	32.25	62.5	125	250	32.25	62.5	125	250
DMSO	_	_	_	_	_	_	_	_
Bi_2S_3 nanoparticles	_	_	7	11	_	_	4	6
Pure MTZ	9	10	11	17	11	12	13	13
MTZ loaded Bi_2S_3nanoparticles	13	14	40	45	12	17	21	28

Note: MTZ (metronidazole); Bi_2S_3 (bismuth sulfide nanoparticles).

CONCLUSION

This study concluded that the use of nanotechnology may offer many benefits in the pharmaceutical field. It may enhance the solubility of water insoluble or poorly soluble drugs such as MTZ, as well as increasing the efficacy of its active ingredient. This significant* improvement in pharmaceutical and biological properties by the utilization of nanotechnology permit further future applications using other drugs, such as anticancer drugs that possess serious side and toxic effects on human body and therefore improving drug properties help to reduce drug doses which in turn decrease the risk of its side effects and toxicity.

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AUTHOR CONTRIBUTION

This study was self-funded and was written, achieve experimental and analytical work and revised by the author.

CONFLICT OF INTERESTS

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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