NTA2022

2nd International Conference on
Nanotechnology: Theory and Applications,
Cairo, 19 – 21 Dec., 2022

Ref. 051

Synthesis of Nystatin-mediated bismuth oxide nano-drug by using gamma radiation and evaluation of its *in vitro* antimicrobial activity

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KEYWORDS

Bismuth oxide, nanoparticle, nystatin, pathogens, antimicrobial, antifungal and antibacterial

SHORT SUMMARY

The novelty of recent study is the synthesis of bismuth oxide nanoparticles loaded with nystatin (an antifungal drug) via gamma rays to increase the synergistic antimicrobial potential against some clinical pathogenic bacteria and candida species. Full characterization of the synthesized Bi2O3 NPs-Nystatin was assessed in order to analyze the average crystal size, crystal distribution, crystallinity, chemical functional groups, morphology, and elemental structure. The antimicrobial activities of Bi2O3 NPs-Nystatin were examined against pathogenic bacteria and candida species, including the inhibition zone diameter, minimum inhibitory concentration, and antibiofilm activity. Additionally, SEM/EDX mapping technique was assessed to investigate its mode of action on Candida albicans. Results revealed that Bi2O3 NPs-Nystatin possessed a well crystallized semi-spherical shape with an average particle size of ≈27 nm with high level of purity. Interestingly, the synthesized Bi2O3 NPs -Nystatin encourages antibacterial behavior against almost all tested pathogenic bacteria with synergistic antifungal potential toward the investigated pathogenic fungi. Additionally, Bi2O3 NPs-Nystatin displayed promising antibiofilm agent, resulting in inhibition percentages of ≈94% and 85% against C. albicans and E. coli, respectively. The present research provides a revolutionary nano-drug to overcome the increasing global resistance of pathogenic microbes at low concentrations, eco-friendly, and working in an acceptable time frame.

EXTENDED ABSTRACT

The novelty of recent study is the synthesis of bismuth oxide nanoparticles loaded with nystatin (an antifungal drug) via gamma rays to increase the synergistic antimicrobial potential against some pathogenic bacteria and candida species. The full characterization of the synthesized Bi2O3 NPs-Nystatin was achieved by X-ray diffraction (XRD), dynamic light scattering (DLS), Fourier transform infrared spectroscopy (FTIR), and high-resolution transmission electron microscope (HR-TEM) techniques in order to analyze the average crystal size, crystal distribution, crystallinity, chemical functional groups, morphology, and elemental structure, respectively. The antimicrobial activities of Bi2O3 NPs-Nystatin were examined against pathogenic bacteria and candida species, including the inhibition zone diameter, minimum inhibitory concentration (MIC), and antibiofilm activity. Additionally, scanning electron microscope/ energy dispersive X-ray (SEM/EDX) mapping technique was performed to investigate the mode of action on the treated Candida albicans cells. Results revealed that Bi2O3 NPs-Nystatin possessed a well crystallized semi-spherical shape with an average particle size of ≈27 nm. EDX elemental study of the synthesized Bi2O3 NPs-Nystatin indicated a high level of purity. Interestingly, the synthesized Bi2O3 NPs -Nystatin displayed encouraging antibacterial behavior against almost all tested pathogenic bacteria, including Gram-positive (Bacillus cereus and Staphylococcus aureus; MRSA) and Gram-negative (Escherichia coli and Pseudomonas aeruginosa). As well as, a synergistic antifungal potential toward the investigated pathogenic unicellular fungi, 3 different isolates of each Candida albicans and Candida tropicalis.

Additionally, Bi2O3 NPs-Nystatin was found to be a promising antibiofilm agent, resulting in inhibition percentages of ≈94% and 85% against C. albicans and E. coli, respectively. The present research provides a revolutionary nano-drug-based solution to address the increasing global resistance of pathogenic microbes at low concentrations, thus donating a new treatment technique for infectious disease that is cost-effective, eco-friendly, and works in an acceptable time frame.

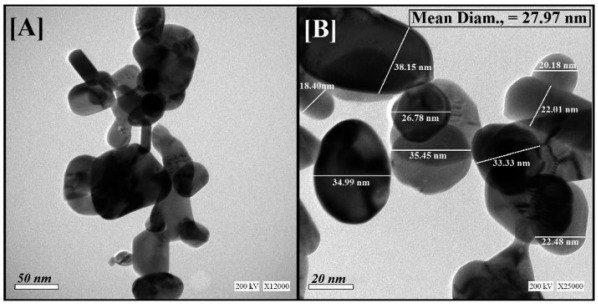

Fig. 1 Shape, nano-structure, and mean particle-size determination by HR-TEM for Bi2O3 NPs-Nystatin, where [A] presents the low magnification (50 nm) and [B] the high magnification (20 nm)image

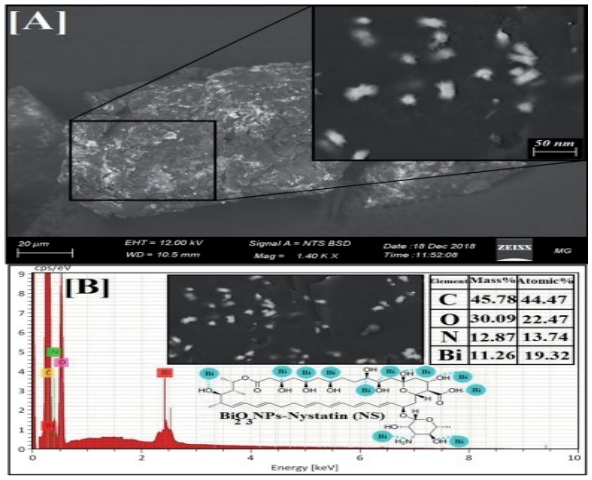

Fig. 3 Surface morphology and elemental analysis of the synthesized Bi2O3 NPs-Nystatin, where [A] SEM image, [B] EDX elemental analysis

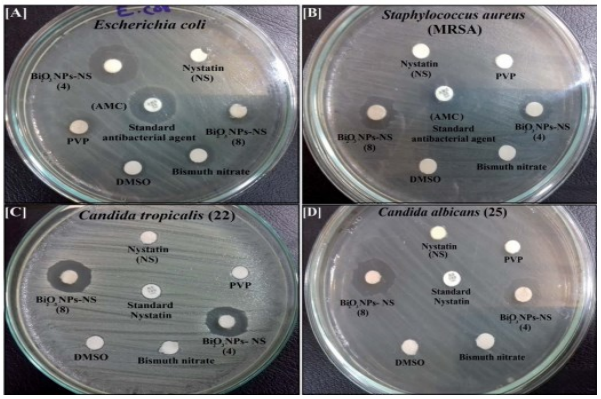

Fig. 5 Antimicrobial activity of the synthesized Bi2O3 NPs-Nystatin (two different samples; see Table 2), nystatin, bismuth nitrate, DMSO, and PVP against [A] Escherichia coli, [B] Staphylococcus aureus, [C] Candida tropicalis (22), and [D] Candida albicans (25) as IZD.

References

[1] Ahmed I. El-Batal, Hanady G. Nada, Reham R. El-Behery, Mohamed Gobara and Gharieb S. El-Sayyad (2020). Nystatin-mediated bismuth oxide nanoparticles synthesis using gamma rays for increasing the antimicrobial and antibiofilm activities against some pathogenic bacteria and Candida species. RSC Advances. 10:9274–9289.

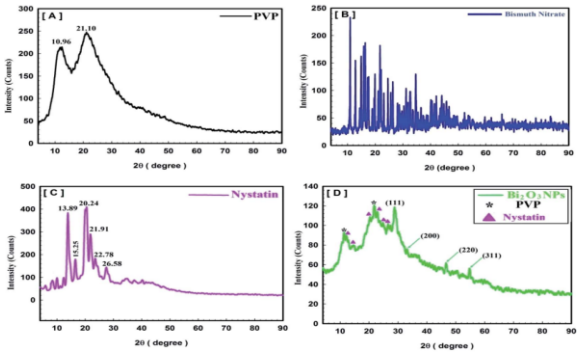

Fig. 2 Crystallinity and crystal-size determination using XRD analysis, where [A] polyvinylpyrrolidone (PVP), [B] bismuth nitrate, [C] nystatin drug (NS), and [D] the synthesized Bi2O3 NPs-Nystatin nano-drug

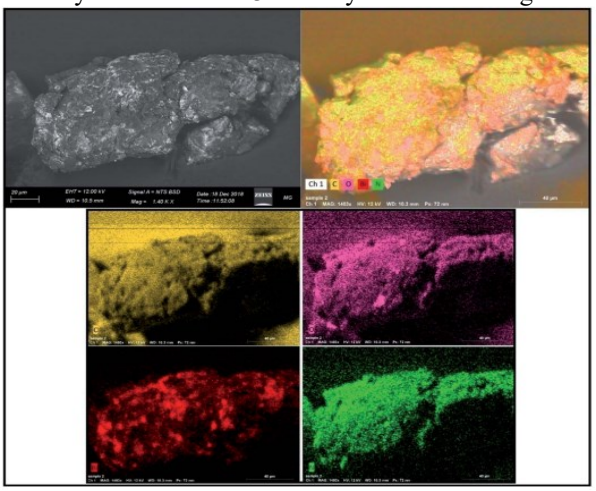

Fig. 4 SEM/EDX mapping images of the synthesized Bi2O3 NPs-Nystatin

Table 2 Antibacterial and antifungal activities of mono-dispersed Bi_2O_3 NPs-Nystatin, PVP, DMSO, and its precursors (bismuth nitrate and nystatin) against some multi-drug resistant (MDR) bacteria and pathogenic Candida species as ZOI (mm) and MIC (µg ml^{-1})

Pathogenic microbes	ZOI of Bi_2O_3 NPs-NS (run 4) (1 mg NS : 5 mg Bi) (mm)	MIC of Bi_2O_3 NPs-NS (run 4) (NS : Bi; µg ml^{-1})	ZOI of Bi_2O_3 NPs-NS (run 8) (0.5 mg NS : 5 mg Bi) (mm)	ZOI of bismuth nitrate (mm)	ZOI of nystatin (mm)	ZOI of PVP (mm)	ZOI of DMSO (mm)	•AMC or NS
Candida albicans (1)	$14.0^{ab} \pm 0.5773$	1.95 : 4.2	$13.0^{ab} \pm 0.5773$	Nil	Nil	Nil	Nil	Nil
Candida albicans (20)	$13.0^{c} \pm 0.5773$	0.24 : 0.52	$13.0^{bc} \pm 0.5773$	Nil	Nil	Nil	Nil	$7.0^{a} \pm 0.2000$
Candida albicans (30)	$14.0^{bc} \pm 0.5773$	0.48 : 1.05	$12.0^{bc} \pm 0.2886$	Nil	Nil	Nil	Nil	Nil
Candida tropicalis (1)	$13.0^{bc} \pm 0.5773$	0.24 : 0.52	$13.0^{cd} \pm 0.7637$	Nil	Nil	Nil	Nil	$7.0^{a} \pm 0.2886$
Candida tropicalis (12)	$13.0^{c} \pm 0.5773$	0.48 : 1.05	$14.0^{c} \pm 1.1547$	Nil	7.0	7.0	Nil	$7.0^{a} \pm 0.7637$
Escherichia coli	$17.0^{d} \pm 0.5773$	1.95 : 4.2	$12.0^{bc} \pm 0.5000$	8.0	Nil	Nil	7.0	$17.0^{c} \pm 0.1889$
Pseudomonas aeruginosa	•Nil	3.9 : 8.4	Nil	Nil	Nil	Nil	Nil	Nil
Staphylococcus aureus, MRSA	$13.0^{c} \pm 0.5773$	0.24 : 0.52	$12.0^{b} \pm 0.6110$	Nil	Nil	Nil	Nil	$15.0^{b} \pm 0.3000$
Bacillus cereus	$13.0^{c} \pm 0.5773$	0.24 : 0.52	$10.0^{a} \pm 0.4509$	Nil	Nil	Nil	Nil	$7.0^{a} \pm 0.4618$
LSD	1.00000	–	1.33333	–	–	–	–	1.83333

[1] Values are the mean ± SD ($n = 3$). Data within the groups were analyzed using one-way analysis of variance (ANOVA) followed by [a-e] Duncan's multiple range test (DMRT), LSD = least significant differences. •Nil means that no ZOI had been measured. •AMC = amoxicillin/clavulanic acid (antibacterial standard), NS = nystatin (antifungal standard).