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ORIGINAL ARTICLE

Efficacy Evaluation of Meropenem Against Resistant *Staphylococcus hominis* in Heart Failure Patients

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ABSTRACT

Objective: This study aimed to prepare nanohybrid from meropenem antibiotic and evaluation of its inhibitory effect against *Staphylococcus hominis* isolated from heart failure patients.

Methods: A nanohybrid antibiotic Meropenem-ZnO was prepared using direction exchange between antibiotic meropenem and zinc oxide layers (ZnO). The new nano antibiotic was identified by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), Atomic Force Microscope (AFM), and scanning electron microscopy (SEM). The antimicrobial activity of the nanohybrid meropenem was studied against *S. hominis* isolated from heart failure patients in the Care Center Unite (CCU) of Hospital of Imam Hussain Medical City in Karbala, that diagnosed of bacterial done by the devices Vitek.

Results: The results showed that FTIR spectroscopy results for the prepared antibiotics showed that the frequencies of some chemical groups shifted towards high and low frequencies. XRD also revealed the emergence of new diffraction planes in the spectrum of the nanohybrid antibiotic compared to the carrier spectrum Zinc oxide, which indicates that the prepared antibiotics understudy is nanohybrid antibiotics, Results of atomic force microscopy (AFM) showed that the mean dimensions of the nanoparticles diameters of the Meropenem-ZnO was 145.7 nanometers. The results of scanning electron microscopy (SEM) were converting irregular shapes of zink oxid into different geometric shapes interspersed with large spaces when forming the hybrid nanocomposite (Meropenem-ZnO) resulting from the direct interaction of the zinc oxide layers with the Meropenem antibiotic.

Conclusion: The efficacy of the nanohybrid Meropenem antibiotic in inhibition of isolated bacteria from heart failure patients.

INTRODUCTION

The challenge demanded the creation of a new/novel and efficient drug delivery method that improves the therapeutic index of currently used antimicrobial drugs while reducing local and systemic side effects and preventing the growth of microorganisms resistant to these antimicrobial agents. Antimicrobial medications placed in nanosized vehicles

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(nanomedicine) have the potential to alleviate the problems associated with traditional therapy and delivery systems.[1] Antimicrobial medication are loaded and carried using nanosized vehicles (NVs) of various sizes in nanomedicine. These novel NVs have unique properties, such as reduced chances of microorganisms developing resistance, significantly improved therapeutic efficacy, more soluble in serum than free drugs, increased systemic drug circulation times, prolonged therapeutic effects, reduced adverse side effects on healthy tissues/cells, and the ability to use combination therapy to deliver multiple drugs on same site-specific cell.[2] Vesicles or particles with at least one dimension between 1 and 100 nanometers are referred to as NVs.

In comparison to similar bulk materials, individual atoms, or molecules, NVs have some unique and advanced physicochemical properties. The main reasons for these characteristics are quantum effects and a significantly higher surface area to volume ratio. The National Institutes of Health established the National Nanotechnology Initiative in 2000 to support, coordinate, and advance nanoscale project research and development. "Nanotechnology is not simply working at ever smaller dimensions; rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale".[3] Because of their broad-spectrum activity against a variety of bacteria, metals such as zinc (Zn), copper (Cu), gold (Au), titanium (Ti), and silver (Ag) have been utilized for therapeutic purposes since prehistoric times.[4] Recent developments in nanotechnology have emphasized the significance of these metals, and antimicrobial nanoparticles (NPs) have received widespread scientific acknowledgment as potent inhibitory agents for the proliferation of infections. To prevent microorganism drug resistance, nanoparticles (NPs) have multiple functions, such as enhancing antimicrobial agent intracellular accumulation or inhibiting biofilm formation.[2,5] Various metal and metal oxide NPs have been studied for their antibacterial properties, including titanium dioxide (TiO2), silver oxide (Ag2O), copper oxide (CuO), zinc oxide (ZnO), gold (Au), silicon (Si), magnesium oxide (MgO), and calcium oxide (CaO).[6] The antibacterial efficacy of metal oxide NPS is due to their enormous surface area, which allows for a wide spectrum of bio-organic activities on the cell surface.[7] The larger the surface area to volume ratio of a particle, the better; hence, an increased area of contact between a metal and a microbe can improve its chemical and biological activity. The usage of nanoscale metals has resulted in a hundred-fold drop in concentration while simultaneously increasing antibacterial characteristics; particle size reduction from 10 m to 10 nm increases the surface area of contact by a factor of 109.[8]

Sepsis can be defined as the body responds to an infection generally bacteria, invading the body. It can be localized or widespread in the bloodstream, and is sometimes referred to as Septicemia. A total of 200 blood samples were collected from patients attending public hospitals and private hospitals in Erbil City during the period from September 2018 to February 2019. Questioner form was prepared for each patient, which includes: name, age, gender, and complaint. After blood collection, all the bacteria isolates were subjected to a series of confirming tests. The bacterial culture showed that among 200 blood samples, only 97(48.5%) showed positive culture. The prevalence of Septicemia was higher among the gram-positive bacteria were: *Staphylococcus aureus*, *Staphylococcus* epidermidis, and *Staphylococcus hominis*, *Micrococcus luteus*, *Enterococcus faecalis*, while the gram-negative bacteria were: *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Brucella melitensis*, *Salmonella typhi*, and *Proteus mirabilis* and antibiotic susceptibility profile showed that most of the isolated bacteria were resistant to more than one bacteria. Most of the isolated bacteria were gram-positive. Most of the bacteria isolated were resistant to most of the common antibiotics. However, varieties of pathogens are responsible for sepsis, and antimicrobial resistance has become a significant public health problem.[9] The accuracy and speed with which the newly redesigned colorimetric Vitek 2 compact system with an updated advanced expert system (AES) (bioMerieux, Marcy l'Etoile, France) identified clinical isolates and detected numerous antibiotic resistance were evaluated. The prevalence of Septicemia was higher among the gram-positive bacteria and particular *Staphylococcus hominis* because there were 17 (17.5%) of the bacterial isolates. The antimicrobial susceptibility for Staphylococcus hominis, they had the highest sensitivity to Ciprofloxacin 16(94.1%), followed by (Rifampicin, Erythromycin, Tetracyclin).[9] And they were highly resistant to Gentamicin13(76.3%) followed by (Amoxicillin, Meropenem, Vancomycin).[10]

Meropenem (mer" oh pen' em) is a broad-spectrum beta-lactam carbapenem antibiotic that disrupts bacterial cell wall integrity and synthesis by attaching to penicillin-binding proteins. Meropenem is active against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria, including *S. aureus*, *S. pyogenes*, *Streptococcus agalactiae*, *viridans* group *streptococci*, *E. faecalis*, *P. aeruginosa*, *E. coli*, *Proteus* mirabilis, *Bacteroides fragilis* and *Peptostreptococcus species*.[11] Meropenem was first approved in the United States in 1996, and it is now used to treat severe or severe skin, tissue, intraabdominal, and urogenital infections, as well as sepsis caused by susceptible organisms. It's usually only used in hospitalized patients with serious infections. A dose of 0.5 to 1-gram intravenous injection every 8 hours is recommended, with dose adjustments made for renal impairment. Meropenem is available as a generic and under the brand name Merrem as 500 mg or 1-gram lyophilized powder for injectable vials.[11]

METHODS AND MATERIALS

Preparation of Nanohyrbrid Meropenem.

Nanohybrid Meropenem

The nanohybrid antibiotic was prepared using the process defined by *Kolekar et al*.[12]

Zinc Oxide Solution

This solution was prepared by dissolving 1 gm of the Zinc Oxide in an amount of 50% ethanol. After completing the dissolution process, the volume was completed to 50 mL using ethanol.

Meropenem Solution

This solution was prepared by dissolving 0.5 gm of the meropenem in an amount of 50% ethanol. After completing the dissolution process, the volume was completed to 50 ml using ethanol.

Preparation of Nanohybrid from Zinc Oxide Layers with Meropenem Gel Solution Exchange Method

The techniques used previously published by Kolekar *et al.*[12] with the addition of 50 mL of the above-prepared ciprofloxacin solution (both at the same time) drop by drop into zinc oxide solution and stirrer magnetically at room temperature for two hours before putting the mixture in the incubator. The vibration was conducted at 37°C for 18 hours before being placed in a 40°C incubator for 24 hours. After an hour, centrifuge the precipitate at 5000 rpm for 20 minutes to separate it. Minutes then rinsed multiple times with distilled water before drying the precipitate at 40°C. It was then ground in a ceramic mortar before being kept.

Preparation of Concentrates and Petri Dishes

24 dishes were Prepared, 12 of them are nanomeropenem, and 12 of them are free meropenem. Each of the free and nano dishes was numbering and according to the concentrations (0, 25, 50, 100, 200, 400) with duplicate each concentration. 2 wells were made inside the media for all Petri dishes.[12] Tubes were Prepared, 6 of them are free-meropenem, and 6 are Nano-Meropenem.

Preparation of Stock Solution

The stock solutions of the free-Meropenem and the nano-Meropenem were prepared separately, with a weight of 0.8 gm of the drug and placed in a test tube, and 20 mL of distilled water was added to it to get a stock solution with a concentration of 400 mg/mL, which will be used in the subsequent steps to prepare the concentrations that used in this study.

Preparation of Antibiotic Concentrations

The concentrations used in this study were prepared for each of the free-Meropenem and nan-Meropenem, separately, according to the method shown in Table 1.

Table 1: Preparation of drug concentrates.

No. of tube	*Distal water (µL)*	*Stock Solution (µL)*	*Final volume (µL)*	*Final concentration (mg/mL)*
1	1000	0	1000	0
2	937.5	62.5	1000	25
3	875	125	1000	50
4	750	250	1000	100
5	500	500	1000	200
6	0	1000	1000	400

Characterization of the Nanohybrid Antibiotic

The nanohybrid antibiotic under study was characterized using several methods, including FTIR and XRD. Atomic Force Microscope (AFM), Scanning Electronic Microscope (SEM), and precise analysis of C, H, and N elements.

Measurement of antimicrobial activity of Free-Meropenem and Nano-Meropenem

The method described by Egorove in year (1985)[13] was followed to investigate about antimicrobial activity of free meropenem and nano meropenem as shown below:

Media

Muller Hinton ager media: was performed by weighing 38 gm of media and dissolved by 1 L distilled water, then autoclaved for 15 minutes. This media was used to investigate the antimicrobial activity of Free- Meropenem and Nano-Meropenem against *S. hominis.*

Activation of bacteria: *S. hominis* was activated on nutrient broth before one hour of culturing.

Antimicrobial Bioactivity Assay

After the activation of the bacteria, two wells were had been done (with diameter 8 mm) for each dish (Muller Hinton agar) and added 100 µL from concentration of antibiotic to each well, and 50 µL was spread from the suspension of activated bacteria on each petri dish and has been incubation at 37ºC for one day, and growth was seen. The diameter was observed for the inhibition zone around the well and ruler measured it.

Statistical Analysis

The results were statistically analyzed to determine the significant differences between the inhibition averages of the studied agents against bacteria isolated from heart failure with bacterial infections. These factors were: the antibiotics used in both free and nanohybrid; bacterial isolates; as well as the concentrations of antibiotics. Significant differences were determined at a probability level of 0.05.

RESULTS AND DISCUSSIONS

Infrared spectrum (FTIR) for Zinc Oxide (ZnO)

FT-IR spectrum of zinc oxide showed indistinct bands at 400-500 cm^{-1} which attributed to the metal bond ZnO vibration as shown in Figure 1.

Infrared Spectrum (FTIR) for Free Meropenem (Free-Meropenem)

FT-IR spectrum of free meropenem antibiotic: The absorption band at 3568 for phenolic (O-H) stretching. The two bands around 3477 and 3404 attributed to (O-H) stretching for carboxylic acid group. The band at 3203 due to (N-H) stretching. The band at 3020 assigned to carboxylic (O-H) which intermolecularly hydrogen bonded. The bands at 29787, 2935 and 2847 attributed to (C-H) aliphatic stretching. The strong band around1749 due to carboxylic (C=O) stretching. The medium band at 1653 for amidic (C=O) stretching.

The band at 1579 was assigned to olefinic (C=C) stretching. The band around 1452 was assigned to (CH3) bending. The band at 1390 for (C-N) stretching. The band at 1284 for (C-O) stretching of the carboxylic group. The band around 1147 for (C-O) stretching of phenol. The weak band at 665 is due to (C-S) stretching.

Infrared Spectrum (FTIR) for Nano Meropenem (Nano-Meropenem)

FT-IR spectrum of nano meropenem: The absorption band at 3373 attributed to phenolic (O-H) stretching, carboxylic (O-H) stretching and (N-H) stretching (overlapped). The band at 2918 is attributed to (C-H) aliphatic stretching. The band around 1635 due to carboxylic (C=O) stretching and amidic (C=O) stretching (overlapped). The olefinic (C=C) stretching band was shifted to lower frequency around 1550. The band of (N-H) bending appeared at 1510. The band for (CH3) bending was shifted to higher frequency around 1462. The (C-N) stretching band was shifted to higher frequency around 1400. The band for (C-O) stretching of carboxylic group was shifted to higher frequency at 1288. The band for (C-O) stretching of phenol was shifted to lower frequency around 1126. Infrared spectrum (FTIR) for nano Meropenem (Nano-Meropnem).

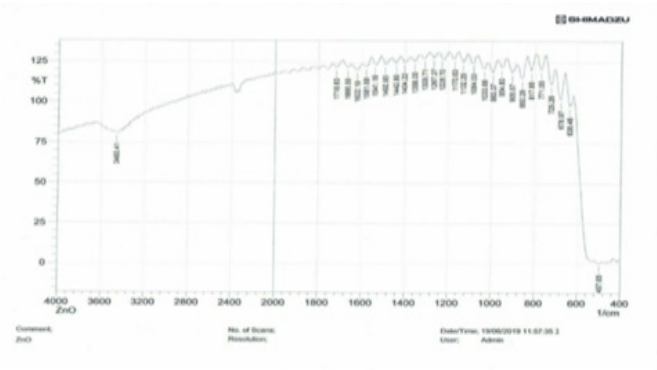

Figure 1: Infrared spectrum (FTIR) for zinc oxide (ZnO).

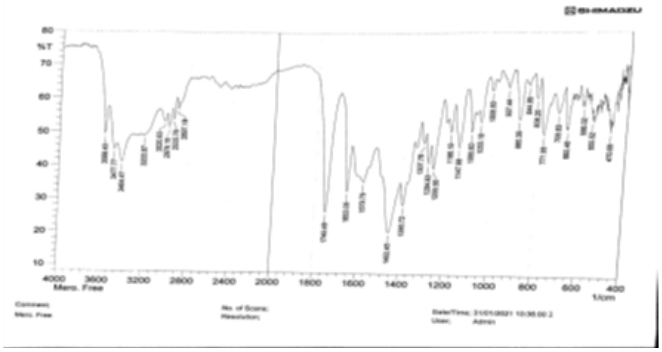

Figure 2: Infrared spectrum (FTIR) for free Meropnem antibiotic

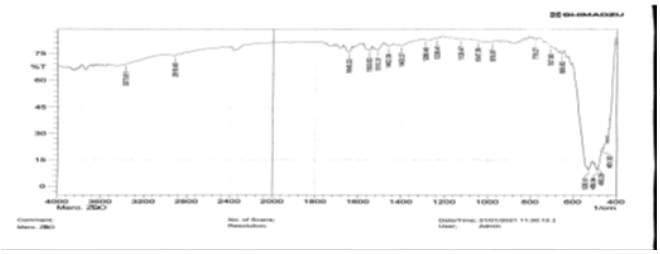

Figure 3: Infrared spectrum (FTIR) for nano meropenem

Characterization by using X-ray Diffraction Spectrum (XRD)

The XRD spectrum of zinc oxide (carrier) and the nanohybrid antibiotic (MERO-ZnO) were studied to find the difference in the thickness of the ZnO layers before and after the intercalation of meropenem between ZnO layers. Figure 4 illustrated XRD of free meropenem while Figure 5 showed the XRD spectrum of MERO-ZnO; results confirmed that meropenem was intercalated between ZnO layers.

Characterization by using Atomic Force Microscope (AFM)

AFM was used to study the outer surface of the nanohybrid meropenem meropenem-ZnO. Figure 6 showed semispherical forms of meropenem-ZnO in the two-dimensional image. Figure 6 showed

A three dimensional image of the surface section of the nanohybrid antibiotic indicating the successful preparation of nanohybrid antibiotic where the elevation of molecular assemblies of up to 145.7 nm.

Characterization by using Scanning Electronic Microscope (SEM)

Figure 7 shows the scanning electron microscope image of the layers of zinc oxide, where it is noticed that the clear-cut hexagonal shapes in which the oxide leaves appear

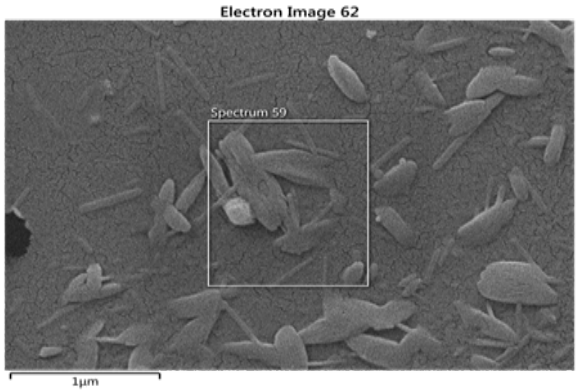

Figure 4: X-ray diffraction spectroscopy of free meropenem

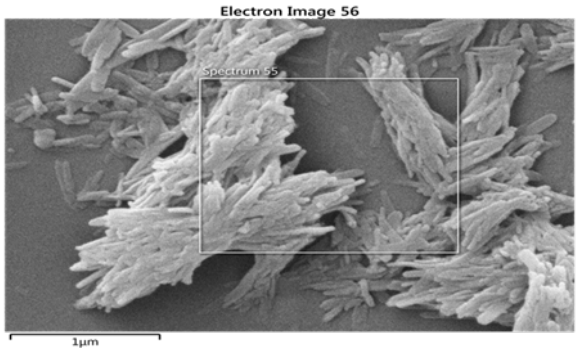

Figure 5: X-ray diffraction spectroscopy of nanohybrid meropenem.

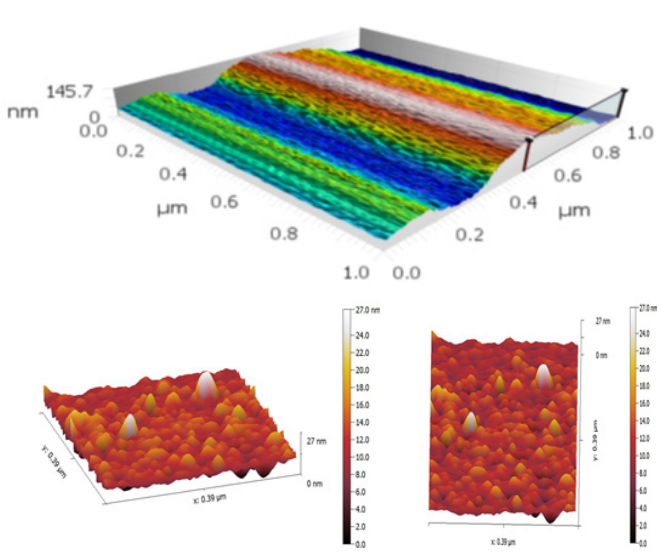

Figure 6: Two-dimensional and three-dimensional image of the MEM-Zn.

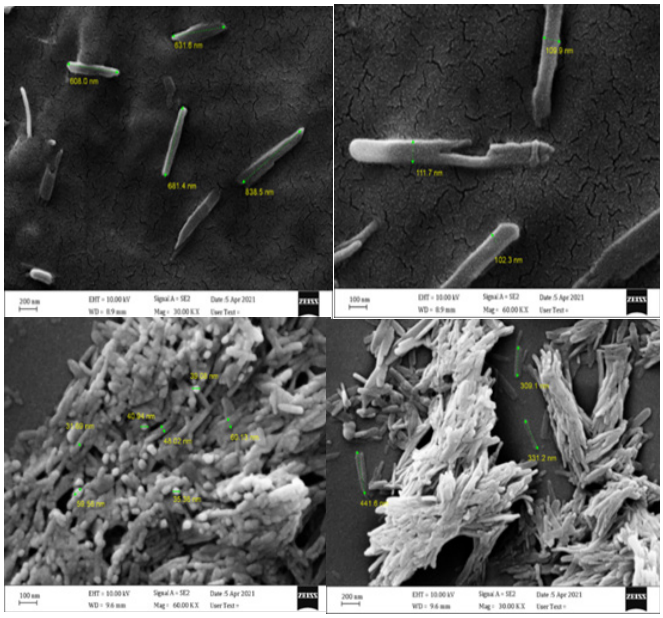

Figure 7: Scanning Electron Microscope (SEM) image of Zinc Oxide layers / with MERP-ZnO.

superimposed on top of each other in irregular shapes and sizes,[14] and that these irregular shapes convert into different geometric shapes interspersed with spaces when the hybrid nanocomposite (Mero-ZnO) is formed resulting from the direct interaction of the zinc oxide layers with the Mweopenem antibiotic, which indicates the success of the process of intercalation of the antibiotic into the zinc oxide the Figure 5.

Precise Analysis of Elements in the Nanohybrid Antibiotic

Elements chemical analysis showed that the percentages of Carbon, Hydrogen, Nitrogen, and Sulphur were 49.20, 5.92, and 9.1557 % for free.

Meropenem, while they were 17.74, 2.19, and 3.99 % for Nano-meropenem. These results indicate that the level of

Table 2: The components of Free Meropenem.

147.TXT
Eager 300 Summarize Results

Date : 2021/05/03 at 03:25:16
Method Name : Nitrogen/Carbon/Hydrogen/Sulphur
Method Filename : N C H S system.mth

Filename		AS Method		Vial
147(Z15)				
# Group	Sample Name	Type	Weig.	Pro.F
57 9	147	UNK	2.079	6.25

Component name	Element %
Nitrogen%	9.152077675
Carbon%	49.20296097
Hydrogen%	5.529557228
Sulphur%	0

1 Sample(s) in Group No : 9

Component Name	Average	Std. Dev.	% Rel. S. D.	Variance
Nitrogen%	9.152077675	0	0.0000	0.0000
Carbon%	49.20296097	0	0.0000	0.0000
Hydrogen%	5.529557228	0	0.0000	0.0000
Sulphur%	0	0	0.0000	0.0000

Table 3: The components of Nano Meropenem.

148.TXT
Eager 300 Summarize Results

Date : 2021/05/03 at 03:25:26
Method Name : Nitrogen/Carbon/Hydrogen/Sulphur
Method Filename : N C H S system.mth

Filename		AS Method		Vial
148Z15)				
# Group	Sample Name	Type	Weig.	Pro.F
58 10	148	UNK	2.532	6.25

Component name	Element %
Nitrogen%	3.39694047
Carbon%	17.74459457
Hydrogen%	2.192493677
Sulphur%	0

1 Sample(s) in Group No : 10

Component Name	Average	Std. Dev.	% Rel. S. D.	Variance
Nitrogen%	3.39694047	0	0.0000	0.0000
Carbon%	17.74459457	0	0.0000	0.0000
Hydrogen%	2.192493677	0	0.0000	0.0000
Sulphur%	0	0	0.0000	0.0000

meropenem loaded between the zinc oxide layers was 36 % (Tables 2 and 3).

Antimicrobial Activity of Meropenem

The results of the statistical analysis in Table 4 showed that there are high significant differences ($p \leq 0.001$) in the diameters of inhibition zone of the free ciprofloxacin against *S. hominis ssp hominis* at all concentrations that used compared with the control. In addition, there is an increase in the inhibition zone when the concentration was increased. The diameters of inhibition zone to Free-MEM were (9.5, 16.5, 18.5, 21.5, 23.5 and 27.5) mm of the following concentrations (5, 10, 20, 40, 80 and 160) mg/mL; respectively. When we used the Nano-MEM, there were significant differences ($p \leq 0.01$) in the diameters of the inhibition zone of the nano ciprofloxacin against *S. hominis ssp hominis* at all concentrations that used compared with the control. In addition, there are increasing in inhibition zone when the concentration was increased. The diameters of inhibition zone to Nano-MEM were (11, 17.25, 21, 23.5, and 23.5) mm of the following concentrations (25, 50, 100, 200, and 400) mg/mL; respectively. When we compare Free-MEM and Nano-MEM to each concentration, the results refer to high significance differences ($p \leq 0.001$) in the following all concentrations.

That agreement with Fadwa et al. who report the results found the antibiotics meropenem was found to be very effective on P. aeruginosa ATCC 2785 with MIC value 0.6 µg/mL with SD ± 0.2 and P. aeruginosa (MRO-17-29) the clinically isolated strain was found to be resistant with MIC value 16 µg/mL with SD ± 0. Whereas, the tested *P. aeruginosa*

Table 4: The inhibitory efficacy of (Meropenem) against (*S. hominis ssp hominis*) isolated from heart failure patient.

Concentration (µg/mL)	*Inhibition Zone (mm)*		
	Meropenem (Free)	*Meropenem (Nano)*	*P value*
O (Control)	0 ± 0.00	0 ± 0.00	1.0000
25	53.25 ± 1.25	11.00 ± 1.63	0.0000 **
50	56.00 ± 1.82	17.25 ± 2.75	0.0000 **
100	63.50 ± 1.29	21.00 ± 1.82	0.0000 **
200	75.00 ± 1.82	23.5 ± 1.91	0.0000 **
400	84.00 ± 1.82	23.5 ± 2.88	0.0000 **
p value	0.0000 **	0.0000 **	
LSD	1.93	2.83	

The numbers refer to mean ± Standard Deviation
* refers significance differences ($p \leq 0.05$)
** refers high significance differences ($p \leq 0.001$)

(MRO-17-3) strain isolated from urine sample was found to be intermediate susceptible to ciprofloxacin antibiotic with MIC value 3.33 µg/mL with SD ± 1.15.[15] Fosfomycin (FOS) is a unique mechanism-based inhibitor of bacterial wall formation. FOS interferes with the production of the peptidoglycan precursor uridine diphosphate N-acetylmuramic acid (UDP-MurNAc) by entering the bacterial cell through the L-alpha-glycerophosphate and hexose-6-phosphate transporter systems.[16] In most cases, FOS is used in conjunction with at least one other active substance. The association benefits from an increase in FOS's bactericidal activity and the avoidance of AMR and the reduction of side effects due to lower dosages. The following are some examples of commonly used empirical combination regimens that include FOS: FOS + Carbapenems.[17] Carbapenems Forty-four papers evaluating FOS in combination with carbapenems. Carbapenems are β-lactam antibiotics that work by attaching to penicillin-binding proteins to stop bacteria from making cell walls. Carbapenems are -lactams used intravenously to treat severe infections as a "last resort." The breakpoints for imipenem (IMI) are ≤ 2 µg/mL for Enterobacterales, *Acinetobacter* spp., *S. pneumoniae*, and ≤ 0.001 µg/mL for *Pseudomonas* spp. and *Staphylococcus* spp. Meropenem breakpoints are ≤2 µg/mL for *Enterobacterales*, *Acinetobacter* spp., *Pseudomonas* spp., *S. pneumoniae*, and ≤4 µg/mL for *Staphylococcus* spp. Ertapenem (ERT) breakpoints are ≤0.5 µg/mL for *Enterobacterales*, *S. pneumoniae*, and ≤4 µg/mL for *Staphylococcus* spp.[18]

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