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RESEARCH PAPER

Antibacterial Activity of Chitosan-Coated Mesoporous Silica Nanoparticles Loaded with Clindamycin and Azithromycin Against Staphylococcus aureus and Escherichia Coli

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ABSTRACT

Antibiotic-resistant Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli) nosocomial infections are a major public health issue that require alternate therapies. Chitosan-coated mesoporous silica nanoparticles (MSNs) can target and release antibiotics due to their large surface area, pore structure control, and pH responsiveness. Modified Stober technique produced azithromycin- and clindamycin-loaded chitosan-coated MSNs. FE-SEM, N2 adsorption-desorption, DLS, XRD, and FTIR examined morphology, surface area, pore size, particle size, zeta potential, and chemical structure. We tested loading efficiency and drug release in pH 5 and 7.4 phosphate buffers. Microbroth dilution and well diffusion for S. aureus and E. coli antibacterial activity were tested using one-way ANOVA and the Tukey test. These MSNs were spherical (50-100 nm), with broad surfaces, and equally scattered pores. roughly 100% of the two antibiotics were loaded, with roughly 20% capacity each. Compared to azithromycin-free, MSNs loaded with azithromycin demonstrated higher antibacterial activity, with a minimum inhibitory concentration of 0.125 µg/mL against S. aureus and E. coli, compared to 0.625 µg Clindamycin-loaded MSNs were inactive. Well diffusion measurements showed that MSN-carried azithromycin (8 mm, S. aureus; 13 mm, E. coli) had a minor inhibitory zone reduction compared to free azithromycin (17 mm, 12 mm). At pH 5, release was substantially higher, indicating pH-responsive release. Tukey test. Chitosan-functionalized MSNs boost azithromycin's S. aureus and E. coli lethality, making them a potential antibiotic resistance treatment for Gram-positive and Gram-negative pathogens and bacterial illnesses. Clindamycin-loaded MSNs' skewed efficacy accentuates antibiotic selection. These discoveries need more in vivo testing before medicinal use.

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INTRODUCTION

Nosocomial infections form part of health issues of great value as they occur as a result of medics care and cause a surge in morbidity, death and an increase in healthcare costs. They are mainly bacterial in origin, but are spread by medical procedures, including the use of ventilators and intravascular catheters, and *Staphylococcus aureus* (*S*. *aureus*) and *Escherichia coli* (*E. coli*) are among the main pathogens that cause urinary tract, respiratory, and blood infections [1]. This has been worsened by the spread of resistant strains of the organisms that have complicated treatment, making it hard and expensive [2]. Antibiotic resistance used to be restricted to the hospital environment, but nowadays it is prevalent in the community, and therefore, new treatment methods are required [3]. In the current study, the antibacterial performance of azithromycin and clindamycin-loaded chitosan (CH)-coated mesoporous silica nanoparticles (MSNs) interacted with *S. aureus* and *E. coli* will be assessed.

These are mentioned as some of the most virulent bacterial species in human pathology. The infections caused by *S. aureus*, the Gram-positive coccus, range from slight inflammation of the skin to severe diseases such as pneumonia and sepsis [4]. The virulence factors used by this bacterium are surface proteins and toxins that allow the organism to penetrate tissues and escape immune defences [5]. Such resistance, especially in methicillin-resistant varieties, has complicated its treatment [6]. About 20% of humans are permanent carriers; this percentage rises among hospitalised patients and people who are frequently exposed to antibiotics [7]. Such resistance mechanisms as those exerted by efflux pumps and enzymatic degradation require that new drugs be sought [8].

E. coli, a Gram-negative bacillus, has maintained the status of the principal gut flora member but can actually cause serious infections, including urinary tract infections and gastroenteritis [9]. Now, the clinical prognosis has actually been worsened with the increased emergence of antibiotic-resistant strains, especially those producing ESBLs, mainly in bloodstream infections [10]. Emergence of resistance against multiple classes of antibiotics due to production of beta-lactamases and low permeability of the membrane has compelled us to look for newer therapies [11].

Nanotechnology is shaping up to be one of the best solutions against antibiotic resistance. With its very large surface area, tunable pore volume, and good surface chemistry characteristics, MSN is an excellent material for drug delivery purposes, enhancing drug delivery and bioavailability [12]. Being a biocompatible polysaccharide, chitosan brings enhanced functionality to an MSN with its antimicrobial properties and pH-responsive drug release, allowing antibiotics to better penetrate bacterial cells [13]. Some studies have shown different results: some researchers claim nanoparticles carrying antibiotics have increased local concentrations and thus greater antibacterial activities [14], while others report that slower drug release envisaged for nanoparticles is likely a drop in antibiotic activity [15]. Such disparities necessitate further study into the design and testing parameters of nanoparticles.

The global rise in antibiotic resistance continues to increase, imparting an even greater urgent need for effective therapies [16]. MSNs coated with chitosan might enhance antibiotic efficiency, considering biofilm formation as a resistance mechanism [17]. This study investigates the antibacterial activity of chitosan-coated MSNs loaded with azithromycin and clindamycin against *S. aureus* and *E. coli* using microbroth dilution and well diffusion methods. This research intends to promote the strategies against antibiotic-resistant infections by fixing the literature gaps with respect to nanoparticle-based delivery efficacy and assay variability.

MATERIALS AND METHODS

Study Population

This experimental study was conducted at Shahrekord University of Medical Sciences, Iran, in the summer of 2024. The study population consisted of bacterial strains *S. aureus* and *E. coli*, obtained from clinical isolates at the Cellular and Molecular Research Centre. Inclusion criteria for the bacterial strains required confirmed identification of *S. aureus* and *E. coli* through standard microbiological techniques, including Gram staining, catalase, coagulase, and oxidase tests, as well as growth on selective media such as Mannitol Salt Agar for *S. aureus* and MacConkey Agar for *E. coli*. Exclusion criteria included contamination with other bacterial species or failure to meet identification standards. No human participants were involved in this study.

Synthesis and Characterization of Nanoparticles

MSNs were synthesized using a modified Stöber method. Cetyltrimethylammonium bromide (CTAB) was used as a template, which was later removed to create porous structures. Azithromycin and clindamycin were loaded into the MSNs, followed by coating with chitosan to enhance biocompatibility and pH-responsive drug release. The morphology of the prepared nanoparticles was evaluated using Field Emission Scanning Electron Microscopy (FE-SEM), confirming spherical particles with sizes ranging from 50 to 100 nm and uniform distribution [18]. Surface area, pore size, and pore size distribution were assessed using the N2 adsorption-desorption method, with results analyzed via Brunauer-Emmett-Teller (BET) and Barrett-Joyner-Halenda (BJH) models [19]. Particle size, distribution, and zeta potential were measured using dynamic light scattering (DLS) [20]. The crystalline structure was analyzed using X-ray diffraction (XRD) [21], while the chemical structure was characterized by Fourier Transform Infrared Spectroscopy (FTIR) [22]. Drug loading efficiency and capacity for azithromycin and clindamycin are presented in Table 1.

Drug release profiles were assessed in vitro in phosphate buffer solutions at pH 5 and pH 7.4 using a spectrophotometer to monitor the release kinetics of azithromycin and clindamycin over time [23].

Antibacterial Activity Assessment

The antibacterial activity of MSNs alone, MSNs loaded with azithromycin, and MSNs loaded with clindamycin was evaluated against *S. aureus* and *E. coli* using two standard methods: microbroth dilution and well diffusion. For the microbroth dilution method, serial dilutions of the test compounds were prepared in Mueller-Hinton broth, and bacterial suspensions were adjusted to a 0.5 McFarland standard (approximately 1.5×10^8 CFU/mL). The minimum inhibitory concentration (MIC) was determined as the lowest concentration preventing visible bacterial growth after 24 hours of incubation at 37°C [24]. The well diffusion method involved preparing Mueller-Hinton agar plates seeded with bacterial suspensions (0.5 McFarland standard). Wells were filled with test compounds at varying concentrations, and the diameter of the inhibition zone was measured after 24 hours of incubation at 37°C [15]. Both methods followed Clinical and Laboratory Standards Institute (CLSI) guidelines to ensure reproducibility.

Statistical Analysis

Data were analyzed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were reported as mean ± standard deviation for quantitative variables, such as nanoparticle size, loading efficiency, and inhibition zone diameters. The normality of data was assessed using the Kolmogorov-Smirnov test. Differences in antibacterial activity between groups (MSN alone, MSN with azithromycin, MSN with clindamycin, and free antibiotics) were evaluated using one-way ANOVA for continuous variables, followed by post-hoc Tukey's test for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Characteristics of Prepared Nanoparticles

Morphological Characteristics

The MSNs were successfully synthesized, and their morphology was assessed using FE-SEM. The FE-SEM images revealed that the nanoparticles were spherical, with sizes ranging from 50 to 100 nm and a uniform distribution (Fig. 1).

Surface Area, Pore Size, and Pore Size Distribution

The surface area, pore size, and pore size

Table 1. Loading Efficiency and Capacity of Nanoparticles

Nanoparticle Type	Loading Efficiency (%)	Loading Capacity (%)
Azithromycin-MSN	99.89±0.02	19.94±0.08
Azithromycin-MSN-Chitosan	99.88±0.01	18.13±0.07
Clindamycin-MSN	99.83±0.05	16.64±0.11
Clindamycin-MSN-Chitosan	99.73±0.24	16.63±0.14

distribution of the prepared MSNs were evaluated using the N2 adsorption-desorption method. The results, analyzed via BET and BJH models, are presented in Fig. 2. The BET plot confirmed a high surface area, while the isotherm plot and BJH plot indicated uniform pore size distribution.

Particle Size, Distribution, and Zeta Potential

Particle size, distribution, and zeta potential were measured using dynamic light scattering (DLS). The results for MSNs are shown in Fig. 3, indicating consistent particle size and surface charge. For azithromycin-loaded MSNs, the size

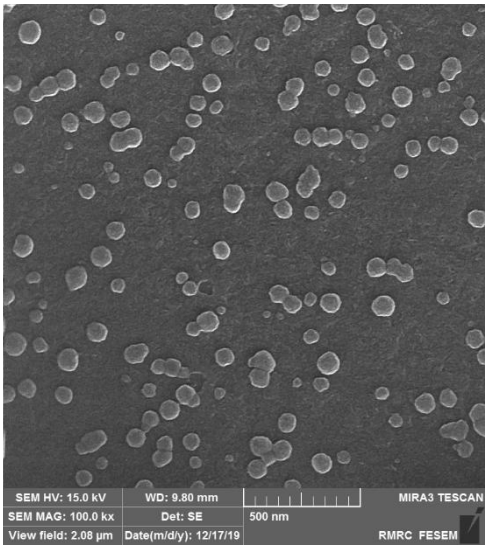


Fig. 1. FE-SEM Image of MSN.

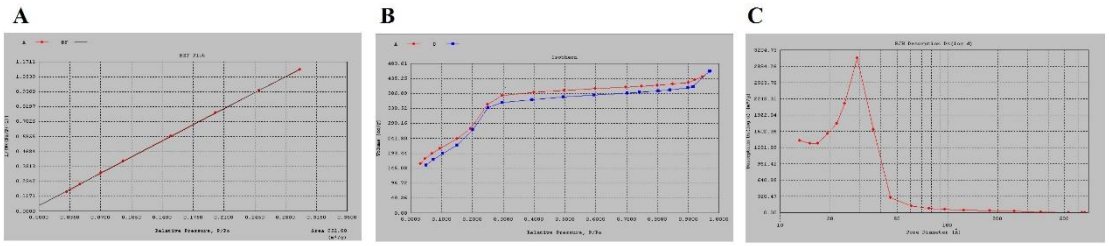


Fig. 2. A) BET Plot, B) Isotherm Plot, and C) BJH Plot of MSNs.

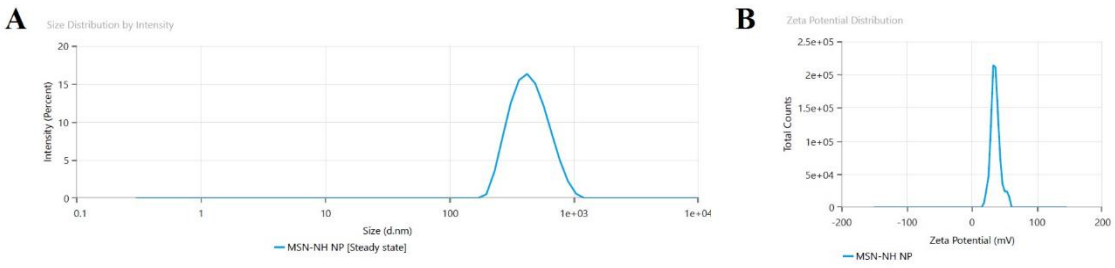


Fig. 3. Size and Zeta Potential of MSNs.

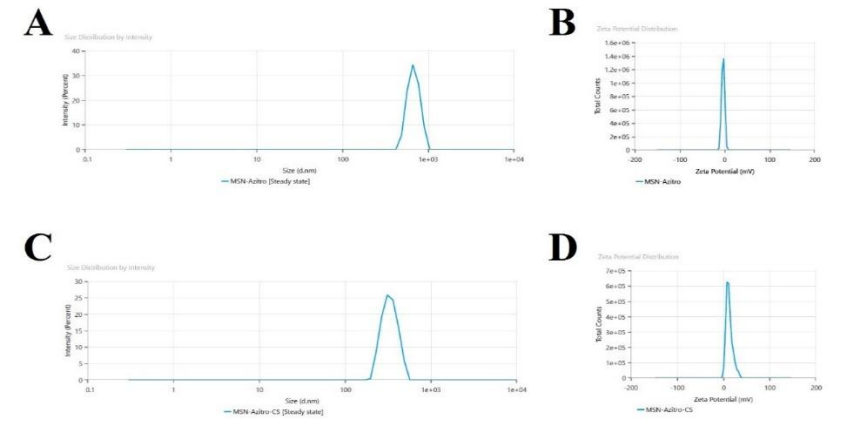
and zeta potential are presented in Figure 4, and for clindamycin-loaded MSNs, in Fig. 4.

Crystalline Structure

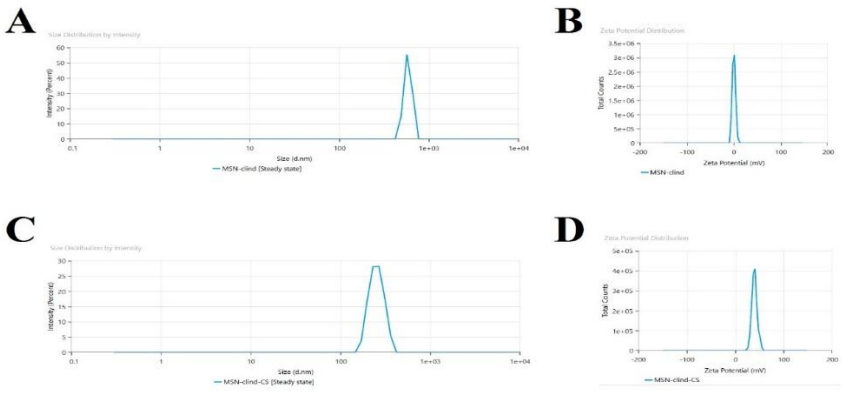
The crystalline structure of the prepared MSNs was analyzed using X-ray diffraction (XRD). The XRD patterns confirmed the amorphous nature of the nanoparticles, consistent with their mesoporous structure.

Chemical Structure

The chemical structure of the nanoparticles was evaluated using Fourier Transform Infrared Spectroscopy (FTIR). As shown in Fig. 5, the FTIR spectra were recorded for: (i) MSN, azithromycin-MSN, and pure azithromycin; (ii) azithromycin-MSN, azithromycin–chitosan-MSN, and chitosan; (iii) MSN, clindamycin-MSN, and pure clindamycin; and (iv) clindamycin-MSN, clindamycin–chitosan-



(i)



(ii)

Fig. 4. Size and surface zeta potential of MSNs loaded with antibiotics: i) Azithromycin-MSNs: A) Size, B) Surface zeta potential, C) Size of azithromycin-MSN-chitosan, D) Surface zeta potential of azithromycin-MSN-chitosan. ii) Clindamycin-MSNs: A) Size, B) Surface zeta potential, C) Size of clindamycin-MSN-chitosan, D) Surface zeta potential of clindamycin-MSN-chitosan.

MSN, and chitosan.

Drug Loading Efficiency and Capacity

The loading efficiency and capacity of azithromycin and clindamycin in MSNs were calculated. Additionally, cefazolin, ceftriaxone, and gentamicin were loaded onto MSNs, achieving a loading efficiency of nearly 100% and a loading capacity of approximately 20%. The results for azithromycin and clindamycin are summarized in Table 1. Calibration curves for azithromycin and clindamycin were established to quantify drug

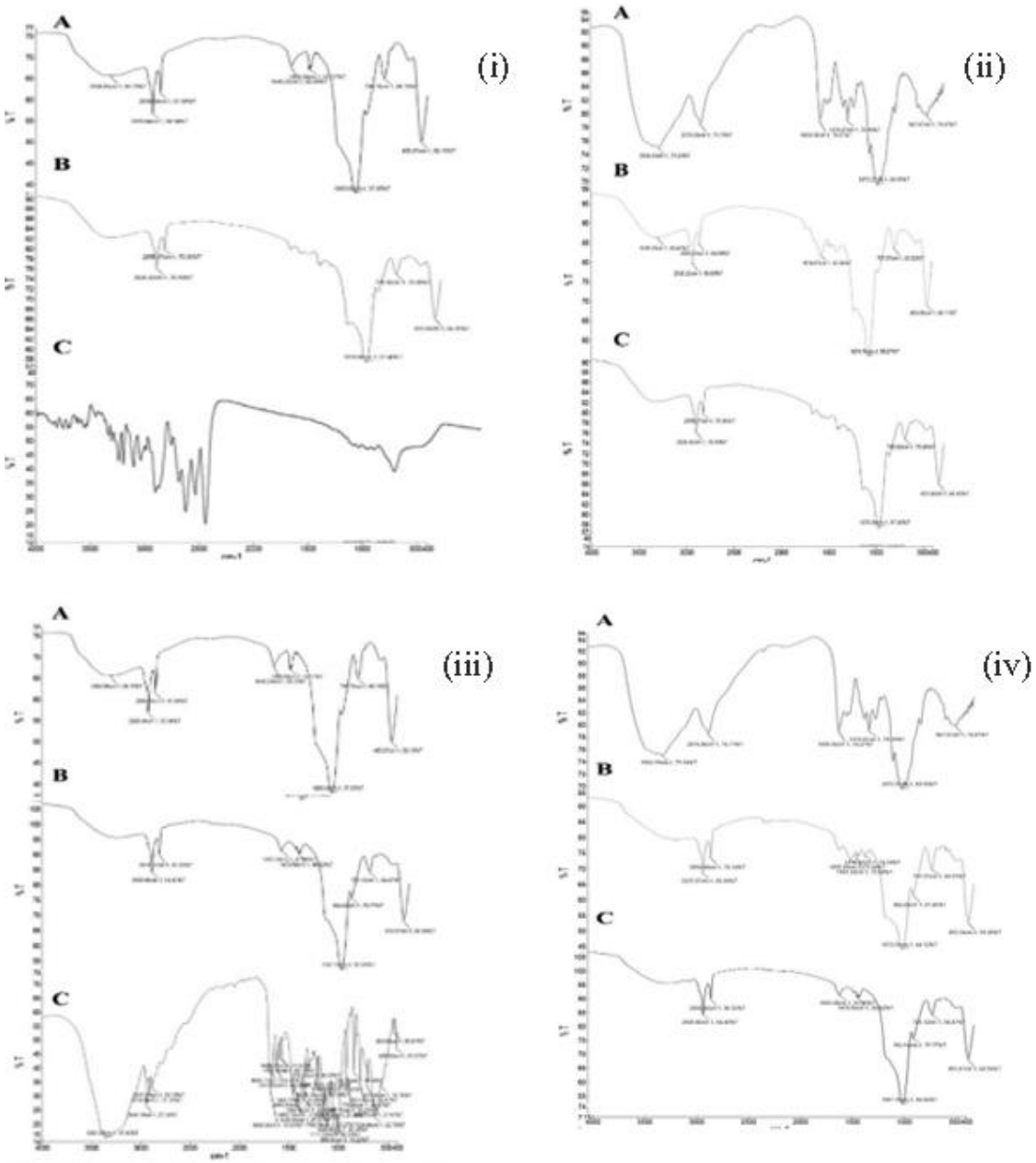


Fig. 5. FTIR spectra of different formulations. (i) MSN, Azithromycin-MSN, and Azithromycin. (ii) Azithromycin-MSN, Azithromycin-Chitosan-MSN, and Chitosan. (iii) MSN, Clindamycin-MSN, and Clindamycin. (iv) Clindamycin-MSN, Clindamycin-Chitosan-MSN, and Chitosan.

loading and release, as shown in Fig. 6.

Drug Release from Nanoparticles

The release profiles of clindamycin and azithromycin from MSNs were evaluated in phosphate buffer solutions at pH 5 and pH 7.4. The results, measured using a spectrophotometer, are presented in Fig. 7. Clindamycin release was higher at pH 5 compared to pH 7.4, indicating pH-dependent release behaviour. Similarly,

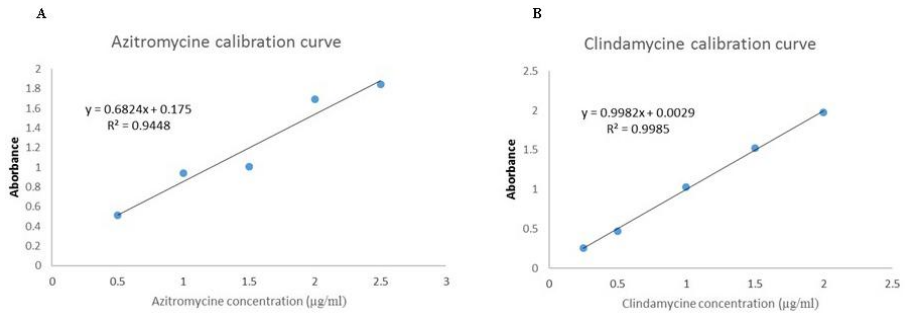


Fig. 6. (A) Calibration Curve for Azithromycin. (B) Calibration Curve for Clindamycin.

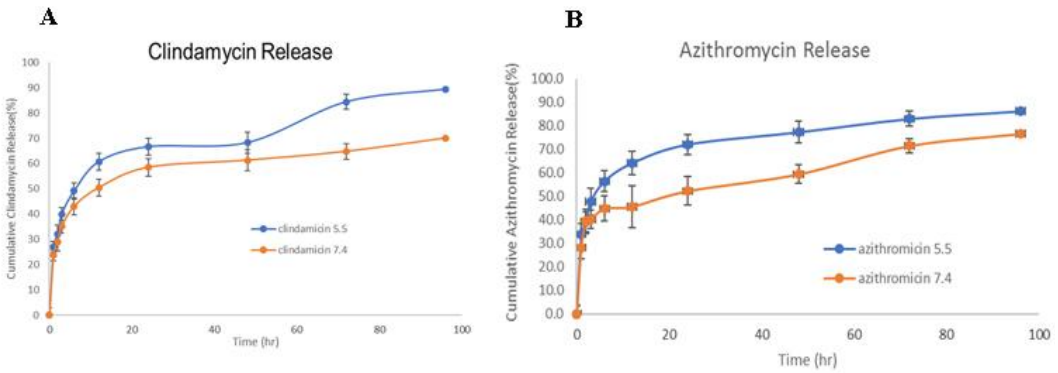


Fig. 7. (A) Clindamycin Release from Nanoparticles at pH 7.4 and 5.5. (B) Azithromycin Release from Nanoparticles at pH 7.4 and 5.5.

Table 2. MIC Results for Tested Drugs Against *E. coli* and *S. aureus*

Drug/Combination	MIC *S. aureus* (µg/mL)	MIC *E. coli* (µg/mL)
Azithromycin	0.625	0.625
MSN + Azithromycin	0.125	0.125
Clindamycin	No MIC	No MIC
MSN + Clindamycin	No MIC	No MIC
MSN	No MIC	No MIC
MSN–NH_2	No MIC	No MIC

azithromycin exhibited enhanced release at pH 5.

Antibacterial Activity

Microbroth Dilution Method

The antibacterial activity of MSNs alone, azithromycin-loaded MSNs, and clindamycin-loaded MSNs against *S. aureus* and *E. coli* was assessed using the microbroth dilution method. The minimum inhibitory concentrations (MICs) are presented in Table 2. Azithromycin alone and in combination with MSNs showed MIC values of 0.625 µg/mL and 0.125 µg/mL, respectively, for both *S. aureus* and *E. coli*. Clindamycin, both alone and with MSNs, showed no MIC against either bacterium.

The results for *S. aureus* and *E. coli* with azithromycin are shown in Fig. 8, respectively. Combined results for both antibiotics with MSNs are presented in Fig. 8.

Well Diffusion Method

The well diffusion method was used to evaluate the antibacterial activity, with results shown in Table 3. Azithromycin alone exhibited inhibition zones of 17 mm for *S. aureus* and 12 mm for *E. coli* at the highest concentration (1.25 µg/mL). Azithromycin-loaded MSNs showed reduced inhibition zones of 8 mm for *S. aureus* and 13 mm for *E. coli* at 0.3125 µg/mL. Clindamycin-loaded MSNs showed no significant antibacterial activity. Visual results for *S. aureus* and *E. coli* with azithromycin are shown in Fig. 9.

Results of this study provided deep insight into antibiotic-containing chitosan-coated mesoporous silica nanoparticles (MSNs) with potential for a novel drug delivery system able to fight antibiotic-resistant *Staphylococcus aureus* and *Escherichia coli*. Spherical MSNs with a uniform morphology, high surface area, and consistent pore size distribution were successfully synthesized, as evidenced by independent characterization—the findings confirming that MSNs are suitable as a drug delivery vehicle due to their tunable structural properties [21]. Drug molecules encapsulation is optimized by their high surface area and pore volume, and the suspension stability of nanoparticles creates avenues for biological utilization [19]. The chemical functionalization

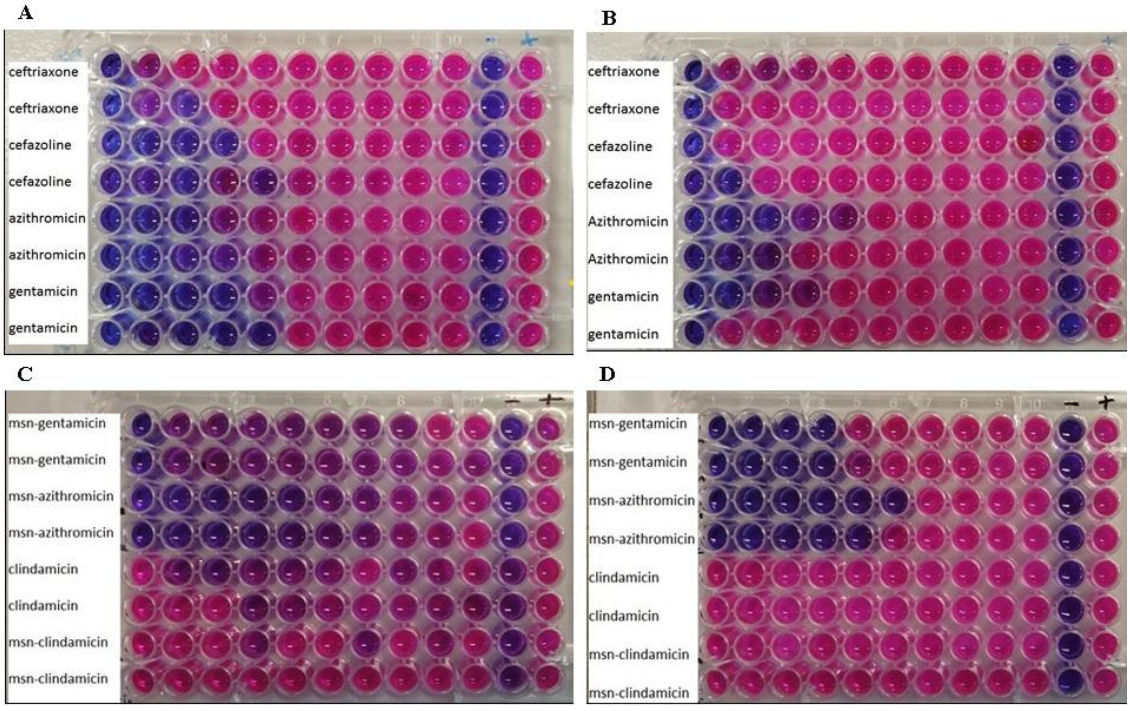


Fig. 8. (A) Microbroth Dilution Test Results for *S. aureus* with Azithromycin. (B) Microbroth Dilution Test Results for *E. coli* with Azithromycin. (C) Microbroth Dilution Test Results for *S. aureus* with Clindamycin and Azithromycin-Loaded Nanoparticles. (D) Microbroth Dilution Test Results for *E. coli* with Clindamycin and Azithromycin-Loaded Nanoparticles.

of the MSNs with chitosan and the antibiotics endorses their structural integrity and designs the framework responsible for assessing their antibacterial activity [20].

Near-complete drug loading efficiency (~100%) and constant ~20% loading capacity for both azithromycin and clindamycin are clear evidence of the encapsulation capability of MSNs, thus supporting the large pore volume theory of their use for antibiotic delivery [23]. The pH-dependent release profiles, owing to the enhanced release of drugs in acidic conditions, implicate the role of chitosan in controlled release, a notable feature for the treatment of bacterial infections in acidic

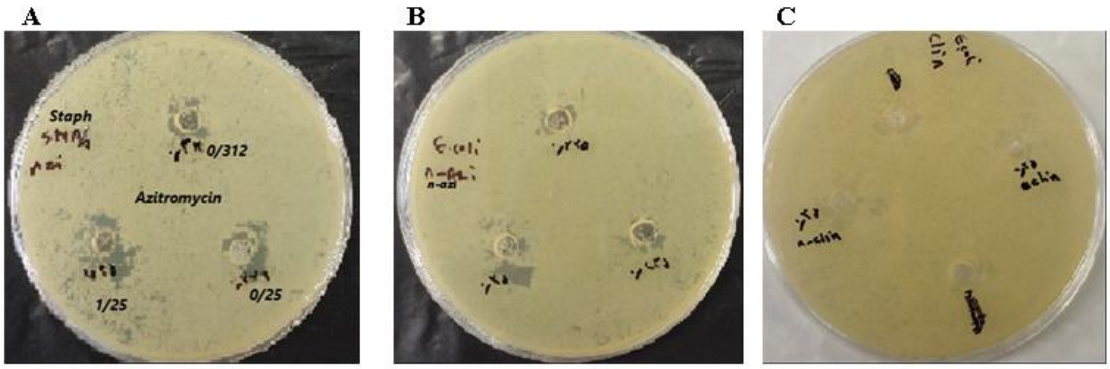


Fig. 9. (A) Inhibition Zone Diameter for *S. aureus* with Azithromycin. (B) Inhibition Zone Diameter for *E. coli* with Azithromycin. (C) Inhibition zone diameter for *Escherichia coli* bacteria with clindamycin antibiotic loaded with nanoparticles versus without nanoparticles.

Table 3. Well Diffusion Results for Tested Drugs Against *E. coli* and *S. aureus*

Drug Name	*S. aureus*		*E. coli*	
	Drug Dilution (µg/mL)	Inhibition Zone Diameter (mm)	Drug Dilution (µg/mL)	Inhibition Zone Diameter (mm)
Azithromycin	1.25	17	1.25	12
	0.625	12	0.625	10
	0.3125	8	0.3125	No inhibition zone
	–	–	–	–
Clindamycin	0.25	No inhibition zone	0.25	No inhibition zone
	–	–	–	–
Azithromycin + MSN	0.25	8	3.125	13
	0.125	7	1.565	No inhibition zone
	0.0625	No inhibition zone	0.07	No inhibition zone
	–	–	–	–
Clindamycin + MSN	–	–	–	–
	–	–	–	–

microenvironments such as biofilms or inflamed tissue [25]. Such pH-responsive behaviour could certainly enhance therapeutic effect and reduce systemic toxicity at a matter of paramount importance for clinical application [22].

The results for antibacterial activity show performance differences between MSN-based delivery of azithromycin and clindamycin. Azithromycin-loaded MSNs gave significantly lower MICs for both *S. aureus* and *E. coli* than free azithromycin, thus showing enhanced antibacterial activity. This enhancement in antibacterial activity could be attributed to quicker cellular uptake and increased local drug delivery imparted by the nanoparticles [26]. In contrast, clindamycin, either alone or loaded into MSNs, did not exhibit any significant antibacterial activity against the tested strains, probably due to resistance mechanisms such as efflux pumps or enzymatic inactivation [27]. The low efficacy of azithromycin when loaded into MSNs in the well diffusion assay, as compared to the microbroth dilution method, might be due to slower drug release in solid media, which limits diffusion [15]. These findings clearly indicate that azithromycin is a candidate more suitable for MSN delivery, while clindamycin showing ineffectiveness might be due to strain-specific resistance or inappropriate release kinetics [24].

The decreased MIC values registered by azithromycin-loaded MSNs denote a possibility of resistance mechanism permeation, especially in the case of *S. aureus*, where methicillin-resistant strains display heavy clinical burdens due to biofilm formation and multidrug resistance ability [28]. The pH-responsive release further contributes to this system being more applicable for infection targeting within acidic environments where regular antibiotics are less effective [29]. The lack of efficacy for clindamycin-loaded MSNs was unexpected-emphasizing its activity against Gram-positive bacteria-maybe due to erm-gene-mediated ribosomal inhibition, or possibly slower release kinetics from the MSNs [30]. These results emphasize an essential aspect: antibiotics must be selected such that they truly complement the nanoparticle delivery system for maximum therapeutic effect.

The microbroth dilution reports the continuous growth inhibition curve of bacteria over time in liquid media and thus is more appropriate for sustained release from MSNs [18]. The well diffusion assay, in contrast, is less appropriate since it depends on diffusion across agar; thus, encapsulated drugs may have underestimated efficacy for slow releases [15]. Such differences in methods parallel some observations in the literature in which factors specific to the assays may cause discrepancies and thus may require multiple approaches to test for safe conclusions [31]. The superiority observed in azithromycin-loaded MSNs in the microbroth dilution assay indicates favorability for situations in which sustained drug release, like treating chronic or biofilm-associated infections.

These results support the existing literature in that they confirm the effectiveness of chitosan-coated MSNs for the purpose of improving the antibacterial activity of azithromycin. Previously, the nanoparticle encapsulation has been proposed to enhance antibiotic delivery by enhancing local concentrations and bypassing resistance mechanisms [32]. Incorporation of chitosan departing somewhat from the traditional route because its antimicrobial activity and pH response augment the nanoparticle function [33]. The low antibacterial activity of clindamycin-loaded MSNs differs from some findings in the literature, suggesting that nanoparticle design and antibiotic choice are key factors influencing results [34]. The pH-responsive type of release supports the date for functionalized MSNs in the target drug delivery to acidic infection sites [35].

The importance of these findings includes their possibility to tackle the worldwide problem of antibiotic resistance, especially in *S. aureus*- and *E. coli*-mediated nosocomial infections. Resistant strains are major contributors to morbidity and mortality while elevating healthcare costs; hence, novel delivery systems, such as MSNs, are crucial to enhance antibiotic performance [36]. Azithromycin-loaded MSNs' ability to lower MIC values could translate into a lower antibiotic dose to limit toxicity and the possibilities of further resistance development [37]. The possibility of targeted drug release by the chitosan coating creates further opportunities, which is especially pertinent to biofilm-associated infections [38]. These findings, on the other hand, hold consequences for clinical applications, particularly in hospital settings where the resistant strains are dominant, and might lay the groundwork for nanoparticle-based therapies for multidrug-resistant infections.

The study has many problems. First, testing

only two bacterial strains limits the generalizability of the results, because clinical isolates have many resistance profiles. Second, since this was an in vitro study, some results may not have translated perfectly into in vivo conditions where immune responses and variations in pharmacokinetics might come into play. Third, it was concluded that further optimization of the nanoparticle design or of the antibiotic itself is needed due to the negative outcome obtained with clindamycin-loaded MSNs. And finally, a dose-dependent cytotoxicity assessment of the nanoparticles was not conducted, which is critical when considering clinical utility. Hence, these limitations necessitate a consideration of careful interpretation and further in-depth research.

Future studies could investigate more strains of bacteria, including multidrug-resistant bacteria, such as methicillin-resistant *S. aureus* and ESBL-producing *E. coli*, to further understand the nanoparticles' efficacy. In vivo studies on animal infection models should be performed to test performance and safety in biological environments. An optimization of clindamycin-loaded MSNs, possibly some optimization of the chitosan coating or the mesopore structure, might make these systems more efficient. Cytotoxicity studies on human cell lines would bring vital information concerning biocompatibility. Standardizing testing protocols, incorporating microbroth dilution and well diffusion methods, is going to help resolve said disparity and guarantee reproducibility. Then, the way could be paved for clinical translation of nanoparticle-based therapy of antibiotic-resistant infections.

CONCLUSION

In summary, this research has shown the ability of chitosan-coated MSNs to serve as promising drug-delivery systems for azithromycin and exhibit higher antibacterial activity against *S. aureus* and *E. coli*. pH-responsive release, enhanced loading efficiency, and lower MICs of the drug are the apparent benefits of employing this system to bypass resistance mechanisms. Nevertheless, the decreased efficacy of clindamycin-loaded MSNs calls for cautious antibiotic selection. These results contribute to the growing body of evidence that supports the use of nanotechnology as a tool to counter antibiotic resistance, thereby offering a promising avenue for the effective delivery of antibiotics. Consideration of the limitations identified and further investigation in the direction proposed may steer future research toward refining this methodology for the treatment of antibiotic-resistant infections.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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