Mini Review

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International Journal of Drug Development and Research
0975-9344

2022
Vol. 14 No. 12: 986

Optimized Antifungal and Antibiotic Activities of Nanoparticles Entrapped in Antibody Octominin

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Citation: Raksha T (2022) Optimized Antifungal and Antibiotic Activities of Nanoparticles Entrapped in Antibody Octominin. Int J Drug Dev Res J, Vol. 14 No. 12: 986.

Abstract

The nanoencapsulation of antimicrobial peptides (AMPs) has been utilized as a strategy to overcome obstacles such as poor stability, adverse interactions, and toxicity. Antimicrobial peptides (AMPs) have emerged as an essential solution for controlling multi-drug-resistant (MDR) pathogens. Octominin's potent antimicrobial activity against Candida albicans and Acinetobacter baumannii has been demonstrated in previous research. The ionotropic gelation method is the focus of this study, which focuses on the nanoencapsulation of Octominin using chitosan (CS) and carboxymethyl chitosan (CMC) as drug delivery systems. Octominin-encapsulated CS nanoparticles (Octominin-CNPs) had a zeta potential of +51.23 0.38 mV and an average diameter of 372.80 2.31 nm, respectively. Encapsulation efficiency was 96.49 percent, and loading capacity was 40.20 percent. Furthermore, transmission electron microscopy data revealed the irregular shape of the Octominin-CNPs with aggregations, as well as a rapid initial release followed by a sustained biphasic release profile for up to 88.26 3.26% of the total Octominin release for 96 h. Octominin-CNPs had significantly lower toxicity in vitro and in vivo than Octominin at higher concentrations. In the time-kill kinetic and microbial viability assays against C. albicans and A. baumannii, respectively, Octominin-CNPs' antifungal and antibacterial activities were slightly higher than Octominin's. At the tested concentrations, Octominin-CNPs produced morphological alterations, changes in cell membrane permeability, and slightly higher levels of reactive oxygen species than Octominin did against both C. albicans and A. baumannii, according to mode of action evaluations. Octominin-CNPs had slightly higher biofilm inhibition and eradication activities in antibiofilm activity assays than Octominin. Octominin was successfully encapsulated in CS, and Octominin-CNPs outperformed Octominin in terms of antimicrobial activity and toxicity against C. albicans and A. baumannii.

Keywords: Acinetobacter Baumannii; Biofilm; Candida Albicans; Chitosan; Encapsulation; Octominin; Octominin-Cnps; Octopus Minor

Received: 02-Dec-2022, Manuscript No. IJDDR-22-13315; **Editor assigned:** 05-Dec-2022, Preqc No. PQ-IJDDR-22-13315; **Reviewed:** 15-Dec-2022, QC No. IJDDR-22-13315; **Revised:** 23-Dec-2022, Manuscript No. IJDDR-22-13315 (R); **Published:** 30-Dec-2022, **DOI:** 10.36648-0975-9344-14.12-986

Introduction

The rapid development of antibiotic resistance is reducing the effectiveness of antibiotics that are available for purchase. As a outcome, scientists are concentrating on antibiotic-free alternatives. Antimicrobial peptides (AMPs) are a gathering of host guard particles and have been demonstrated to be solid in controlling a great many pathogenic microscopic organisms, growths, and infections [1]. A brief sequence of amino acids with a cationic charge, greater hydrophobicity, and amphipathic nature makes up AMPs. The induction of morphological changes, modification of membrane permeability, generation of reactive oxygen species (ROS), DNA damage, and inhibition of protein synthesis are just a few of the many antimicrobial activities that these properties facilitate for AMPs. Due to their poor in vivo stability, potential toxicity development, and adverse interactions

with the immune system of the host, AMPs have limited clinical use despite their potential antimicrobial activity. Cyclization, terminal adjustment, and surprising amino corrosive presentation are normal alterations that can be acquainted with AMPs to conquer these restrictions before restorative applications. The encapsulation of AMPs into nanoparticles (NPs) is now a major method for reducing toxicity through pharmacokinetics modifications, improving stability by preventing proteolytic degradation, and delivering AMPs specifically to the site of infection [2-5].

Nanotechnology's applications have collaborated in the biomedical and microbiological fields for advanced therapeutic applications due to its rapid development. The potential for drug delivery and effective and synergistic drug action at the targeted site has been demonstrated by drug encapsulation into NPs. A lot of nanoencapsulation has been done with chitosan (CS), a linear polysaccharide made of D-glucosamine and N-acetyl-D-glucosamine units that are randomly distributed. As an excipient for drug formulation, CS has been demonstrated to be biocompatible, biodegradable, and non-toxic. Additionally, CS's inherent multiple antimicrobial modes of action against a wide range of organisms, including multidrug-resistant (MDR) microorganisms, have proven successful as biomaterials. As a outcome, AMPs can be encapsulated into chitosan nanoparticles (CNPs) to circumvent their therapeutic limitations. Encapsulation of AMPs with CNPs has been the subject of numerous studies. Examples include Zhu et al. demonstrated CS quaternary ammonium salt-induced antibacterial activity against Escherichia coli for AMP encapsulation [6-8].

Based on the defense protein of Octopus minor, which has 23 amino acids, a total net charge of +5, a hydrophobic ratio of 43%, and a Boman index of 1.86 kcal/mol, octominin is a novel synthetic AMP. Octominin's anticandidal and antibacterial properties against Candida albicans and Acinetobacter baumannii were previously demonstrated in our research. Encapsulating Octominin into the core–shell structure of CNPs to increase their antimicrobial activity against C. albicans and A. baumannii was the primary focus of this study. Based on their size, zeta potential, morphology, encapsulation efficiency (EE), loading capacity (LC), and AMP release profiles, we evaluated the Octominin encapsulated CNPs (Octominin-CNPs). Using a time-kill kinetic assay and viability test, we then confirmed its antimicrobial activity against C. albicans and A. baumannii. To confirm the efficacy and mode of action of Octominin-CNPs in comparison to unencapsulated Octominin, morphological changes, membrane permeability changes, ROS generation, and antibiofilm activity were also examined [9,10].

Octominin-CNPs' Encapsulation Optimization

The best ratio of Octominin: CMC: Octominin was used in varying proportions in the CS encapsulation reaction, with the other two components (CMC and CS) remaining constant. Mixture 4 from reaction (CS: CMC: The EE of Octominin-0.4:2:1 was the highest. Even though mixture 5 of reaction (CS: CMC: Octominin-0.4:2:1.5) had a lower EE and a higher LC (48.85%) than reaction mixture 4 (40.20%). A CS, taking into account the EE and average particle size: CMC: The optimal ratio for future encapsulation experiments was chosen to be 0.4:2:1.

Octominin-Cnp Preparation, Characterization, and Release

Octominin-CNPs were gotten utilizing the ionotropic gelation strategy with CS: CMC: octaminin in a ratio of 0.4 to 2 to 1. There was no particle aggregation in the opalescent Octominin-CNPs suspension. The Octominin-CNPs were initially observed to be fully dispersed in the suspension with no visible aggregates after a small amount of sonication. Octominin-CNPs' diameter was found to be slightly greater than that of CNPs in the outcomes of the laser diffraction particle size analysis; Octominin-CNPs and CNPs had particle diameters of 246.81 nm and 372.8 2.3 nm, respectively. The cationic idea of CS delivered positive zeta possibilities of +51.23 ± 0.38 and +59.33 ± 3.63 mV for Octominin-CNPs and CNPs, separately, in PBS at pH 7.4.

After the NPs were isolated, the amount of Octominin that remained in the supernatant was measured to determine the EE and LC. Octominin-CNPs had a LC of 40.20 percent and an EE of 96.49 percent. Peptide discharge energy of Octominin-CNPs were seen in PBS at pH 7.4 for 96 h. The peptide discharge profile showed a biphasic discharge design with an underlying fast straight arrival of up to 56.2% until 24 h, and a later supported discharge rate to arrive at the most extreme combined arrival of 88.26% at 96 h. Transmission electron microscopy (TEM) investigation was led to notice the morphology of the Octominin-CNPs versus CNPs. Both NPs' TEM micrographs revealed excessive aggregation and round-shaped particles. Octominin-CNP aggregation was significantly lower than that of CNPs.

Antifungal and Antibacterial Activities of Octominin-CNPs vs. Octominin

Octominin was found to have antifungal activity against C. albicans at minimum inhibitory concentrations (MIC) and minimum fungicidal concentrations (MFC) of 50 and 200 g/mL, respectively, as well as antibacterial activity against A. baumannii at MIC and MBC of 5 and 10 g/mL, respectively, in previous research. At peptide concentrations of MICs and MBC/MFC, the antimicrobial properties of Octominin-CNPs and Octominin were compared to those of C. albicans and A. baumannii. shows how Octominin-CNPs and Octominin treatment affects time-kill kinetics and fungal and bacterial viability. CNPs treated samples showed minor antifungal and antibacterial activities against C. albicans and A. baumannii, respectively, in time-kill kinetic assays, growing slightly below negative controls. Octominin was more effective against fungi and bacteria in the early hours than Octominin-CNPs. Nonetheless, in the late hours (6 h post treatment; hpt), the antifungal and antibacterial activities of Octominin-CNPs were slightly higher than those of free Octominin.

Comparing the Morphological Effects of Octominin-CNPs

After treating C. albicans and A. baumannii with Octominin-CNPs,

Octominin, and CNPs, field emission electron microscopy (FE-SEM) was used to assess the severity of the morphological changes. CNPs treatment had the same morphological structure as the negative control in C. albicans and did not alter the fungal cells' surface. Comparing Octominin-CNPs and Octominin's antifungal effects on C. albicans revealed that encapsulated peptides were more effective because they caused more damage to the fungal surface. In particular, Octominin-CNPs caused significant damage with substantial pore formation and cell shrinkage, whereas Octominin-MIC (50 g/mL) caused minor damage with small pore formation. Octominin caused cell shrinkage and cell disruption in a few cells at MFC (200 g/mL), whereas Octominin-CNPs caused total cell disruption, causing the greatest damage to fungal cells. The morphological alterations in the A. baumannii samples followed a similar pattern. However, when compared to the negative control, CNPs only caused surface shrinkage in bacterial cells. At the MIC (5 g/mL) and MBC (10 g/mL) levels, Octominin-CNPs outperformed Octominin at all concentrations against A. baumannii. At the MIC level, the Octominin-CNPs treated cells had a higher number of cells with bacterial cell shrinkage than Octominin alone. Both groups demonstrated bacterial cell damage with the formation of holes at the MBC level; However, in the Octominin-CNPs-treated group, the severity was higher.

Discussion

Octominin's characteristic physiochemical properties, release kinetics, in vitro and in vivo toxicity, and antifungal and antibacterial efficiencies were determined when it was encapsulated into CNPs in order to examine the therapeutic effects and targeted drug delivery capacities of CS-based nano-encapsulated AMPs. Encapsulation is limited by the attraction of CS to cationic AMPs. An excellent approach to overcome this repulsion is to incorporate anionic compounds as a crosslinker into the ionotropic gelation. In this regard, demonstrated the hydrophobic and cationic encapsulation of renin substrate I into CNPs using sodium tripolyphosphate (TPP) as the anionic crosslinker. Octominin and CS were successfully crosslinked using CMC, a negatively charged, water-soluble polymer, in this study. The Octominin-CMC mixture began to form microaggregates after 40 minutes of stirring, and the addition of CS made it easier to form dense, peptide-rich NPs that covered the CS layer.

Previously, AMPs LL37 was encapsulated in polylactic-co-glycolic acid (PLGA) and synthesized NPs with a particle diameter of less than 300 nm, a 70% EE, and a lower LC (0.10%). Additionally, AMPs CM11 was encapsulated in CNPs coated with hyaluronic acid with a particle diameter of 190 nm and a 60% EE. Octominin-CNPs had an average particle diameter of 372.80 2.31 nm and higher EE (96.49%) and LC (40.60%) than these AMP encapsulation studies, indicating that Octominin was effectively encapsulated by CNPs. Octominin caused conformational and charge rearrangements in CS during the encapsulation process, which outcomeed in Octominin-CNPs having a larger particle diameter and lower zeta-potential values than CNPs. Likewise, showed that CS-embodied temporin B had a higher measurement and lower zeta potential than clear CNPs. Additionally, the NPs' TEM analyses revealed that the particle textures of the two samples were comparable. Octominin-CNPs, on the other hand, exhibited a lower level of aggregation. After Octominin-ionotropic gelation, confirmational and zeta-potential deviations in CS may also be to blame for this effect. The Octominin discharge profile from the Octominin-CNPs followed a biphasic design with an underlying burst (up to 24 h) trailed by a sluggish and supported discharge. The LL37 poly (lactic-co-glycolic acid) NPs benefited from a biphasic release profile with a similar pattern. It did this by first releasing a large amount of LL37 quickly at the wound site to start the therapeutic effect, and then it did a sustained release to keep the LL37 concentration there for a long time after the nanoparticle was given to the patient. The biphasic introductory fast and later supported discharge example of Octominin-CNPs was valuable for the quick fungicidal and bactericidal activity to destroy microorganisms, forestall the regrowth of organisms, and foster obstruction improvement against Octominin.

In HEK 293 cells, Octominin reduced cell viability in a concentration-dependent manner, despite its low cytotoxicity level (up to 100 g/mL). However, the Octominin-CNPs' excellent ability to reduce Octominin's cytotoxicity, even at concentrations above 200 g/mL, was demonstrated by an in vitro cytocompatibility test. This outcome demonstrated that Octominin's encapsulation into CNPs may enhance its use capability at high doses with minimal toxicity and enhanced therapeutic activities with sustained drug release patterns. demonstrated a similar effect when gedunin was encapsulated into CNPs, increasing its anticancer activity against NCI-H292 cells and decreasing its cytotoxicity toward MRC-5 lung fibroblast cells. Octominin-CNPs' non-toxic nature up to 50 g/mL and low ROS generation at high doses (100 g/mL) were confirmed in this study using zebrafish larvae, ensuring the possibility of Octominin-CNPs application in animal models at higher concentrations as a therapeutic agent. Previously, Octominin applications were limited in the zebrafish larvae model due to its toxicity above 25 g/mL.

Aside from being an embodying specialist, the most explored property of CS is its antimicrobial impact against an extensive variety of target organic entities, like green growth, microbes, yeasts, and parasites. 2,6-diamino chitosan (also known as 2,6-DAC) is a CS-derived cationic polymer that has excellent synergistic antimicrobial effects when used in conjunction with various antibiotics to combat methicillin-resistant Streptococcus aureus and multidrug-resistant (MDR) A. baumannii. Due to the synergistic action of CS and its encapsulated AMP, Octominin-CNPs exhibited higher antifungal and antibacterial activities than Octominin. Even though Octominin-CNPs' antimicrobial activity against C. albicans and A. baumannii was marginally comparable to that of Octominin in the time-kill kinetics assay and the fungal/bacterial viability assay, mode of action outcomes demonstrated that Octominin-CNPs had superior antifungal and antibacterial capabilities. Because nutrient depletion causes spontaneous microbial death, prolonged fungi and bacteria incubation times in culture media present experimental challenges. In this study, Octominin-CNPs' antimicrobial activities against Octominin were measured using 24-hour antimicrobial activity assays. In any case, we anticipated that Octominin-CNPs would have outperformed Octominin in time-kill kinetics by inhibiting fungal and bacterial growth for a longer period of time against C. albicans and A. baumannii.

Octominin's multiple modes of action against C. albicans and A. baumannii were demonstrated in previous research. However, when Octominin-CNPs treatments were compared to Octominin treatments in this study, we observed an increase in the intensity of these modes of action. Few studies have proposed that the physiochemical properties of CS may increase the microbial membrane's osmotic pressure-induced disruption and shrinkage, despite the fact that the precise mode of action of CS for its antimicrobial activity has not been extensively discussed. CS's conjugated cationic AMP's ability to bind to the membrane components of both gram-positive and gram-negative bacteria and fungi can be enhanced by its electrostatic interactions. Both C. albicans and A. baumannii showed significantly higher levels of cell membrane permeability alterations in the Octominin-CNPs-treated groups than in the Octominin-treated groups in the FE-SEM analysis and in the PI uptake assay, respectively. The synergistic effect of CS and Octominin on membrane disruption can be defined as this. According to the findings of other studies, CS may act as a barrier on the surface of bacterial or fungal cells, restricting their ability to absorb nutrients into their cells. Fungi and bacteria can eventually self-destruct thanks to ROS-mediated stress caused by a lack of nutrients. In this study, further enhanced permeabilization outcomeed in the internalization of high levels of Octominin and CS to induce metabolic stress, synergistically triggering ROS generation in C. albicans and A. baumannii, and ultimately outcomeing in fungal/bacterial cell death.

It is anticipated that the positive charge of CS will interact with electrostatically negatively charged microbes that settle on the surfaces to prevent the formation of biofilms. Additionally, CS has the ability to bind with components of biofilms, such as extracellular polymeric substances, proteins, and DNA, thereby eliminating preformed biofilms.

Conclusion

In conclusion, our findings emphasize that Octominin delivery into C. albicans and A. baumannii biofilms via CNP encapsulation is an effective Trojan horse strategy. Additionally, Octominin-CNPs' biphasic release profile was advantageous for both rapid and sustained antimicrobial activity. Octominin's antibacterial and antifungal activities were enhanced synergistically by the physicochemical properties of CS. In the time kill kinetics assay, Octominin-CNPs outperformed Octominin-CNPs in terms of antimicrobial activity, morphological changes, membrane permeability, ROS generation, and antibiofilm activity in both C. albicans and A. baumannii. Octominin's development as a final dosage form to overcome inherent limitations in therapeutic use to combat MDR pathogens may be facilitated by this novel strategy.

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