RESEARCH ARTICLE

Utilizing Niosome Nanoparticles for the Combined Treatment of Curcumin and Cisplatin in Oral Cancer

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Abstract

Overview: Oral cancer remains a significant health challenge due to its aggressive nature and limited treatment options. This study investigates the use of niosome nanoparticles to deliver a combination of curcumin and cisplatin, a natural anti-inflammatory and anti-cancer agent and a widely used chemotherapeutic drug, respectively. **Methods:** Niosome nanoparticles were formulated and optimized for encapsulation efficiency and stability. The physicochemical properties of the nanoparticles were characterized, including particle size, zeta potential, and polydispersity index (PDI). In vitro cytotoxicity assays were conducted using oral cancer cell lines to evaluate the efficacy of the combined treatment. **Results:** The niosome formulations with a mean particle size of approximately 150 nm, a favorable zeta potential of 24.6 ± 3.2 mV, and a low PDI of 0.23 ± 0.05. The release profile showed a controlled and sustained release of both curcumin and cisplatin over 48 hours, with a cumulative release of 51% for curcumin and 48% for cisplatin. In vitro studies revealed that the combined treatment significantly reduced cell viability compared to individual treatments, with a synergistic effect observed at specific concentrations. **Conclusion:** The findings suggest that niosome nanoparticles can effectively deliver a combination of curcumin and cisplatin, enhancing the therapeutic potential against oral cancer. This innovative approach may pave the way for more effective treatment strategies, ultimately improving patient outcomes in oral cancer therapy.

Keywords: Curcumin- Cisplatin- nanoparticles- Oral cancer

Introduction

Oral cancer is a devastating disease that affects millions of people worldwide, with a high mortality rate due to its aggressive nature and limited treatment options [1-3]. Cisplatin, a widely used chemotherapeutic agent, has been the cornerstone of oral cancer treatment for decades. However, its use is often hampered by severe side effects, including nephrotoxicity, neurotoxicity, and ototoxicity, which can significantly impact patients' quality of life. Furthermore, the development of resistance to cisplatin is a major concern, reducing its effectiveness and necessitating the exploration of alternative treatment strategies [4-7]. Curcumin, a natural anti-inflammatory and anti-cancer agent, has been shown to have synergistic effects when combined with chemotherapeutic agents, including cisplatin [8]. Curcumin's anti-cancer properties are attributed to its ability to inhibit cell proliferation, induce apoptosis, and modulate various signaling pathways. However, its poor water solubility and limited

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bioavailability hinder its therapeutic potential [9-10]. Recent advances in nanotechnology have led to the development of novel drug delivery systems, such as niosome nanoparticles, which can enhance the therapeutic efficacy of both cisplatin and curcumin [11-13]. Niosome nanoparticles are non-ionic surfactant-based vesicles that can encapsulate both hydrophilic and lipophilic compounds, improving their solubility and bioavailability [14-15]. The combination of curcumin and cisplatin in niosome nanoparticles offers a promising approach to the treatment of oral cancer. By encapsulating both agents in a single nanocarrier, we can potentially reduce the side effects associated with cisplatin while enhancing its therapeutic efficacy. Moreover, the synergistic effects of curcumin and cisplatin may lead to improved anti-cancer activity, reduced drug resistance, and enhanced patient outcomes [16].

In this study, we investigate the use of niosome nanoparticles for the combined treatment of curcumin and cisplatin in oral cancer. By exploring the physicochemical properties of niosome nanoparticles, their ability to encapsulate and release both agents, and their anti-cancer effects in vitro, we aim to shed light on the potential of this innovative approach for improving oral cancer treatment. The use of niosome nanoparticles to deliver a combination of curcumin and cisplatin offers several advantages. These benefits include enhanced bioavailability and solubility of both agents, reduced side effects associated with cisplatin, improved therapeutic efficacy and anti-cancer activity, potential to overcome drug resistance, and enhanced patient outcomes. By harnessing the potential of niosome nanoparticles, we may be able to develop a more effective and safer treatment strategy for oral cancer, ultimately improving the quality of life for patients affected by this devastating disease. Considering these benefits, using niosome nanoparticles can be a significant step forward in developing more effective treatments for oral cancer. This innovative technology can help us provide more personalized and targeted treatments for patients with oral cancer, ultimately improving their quality of life.

Materials and Methods

Materials

Acquired from the Sigma Corporation Were cisplatin, curcumin, Span 60, Cholesterol, Polyethylene Glycol 200, culture solution RPMI 16-40, Ethanol. Additionally, the CAL 27 cell line was supplied courtesy of the Cell Bank affiliated with the Iranian Pasteur Institute.

Synergistic effect of cisplatin and curcumin in CAL 27 cells

The sensitivity of CAL 27 cells to individual drugs and the drug combination was determined using a cytotoxicity assay. Briefly, cells were plated in 96-well at a density of 1×10^4 cells per well, each well with 100 μL medium, and incubated for 24 h in a CO_2 incubator, followed by the addition of Cisplatin, curcumin, or Cisplatin: curcumin (1:4, 1:8). Following a 24 h incubation, the relative effect on the presence of viable cells was determined

by MTT assay. The median-effect algorithm analysed a synergy of the two drugs over a range of drug ratios and concentrations.

Preparation of nanoparticles containing drugs

In summary, to form a mixture, $AgNO_3$ (100 mg, 0.45 mmol) was added to a suspension of cisplatin in double-distilled water. This mixture was then heated at 45 °C for 2 hours and stirred overnight in a flask, kept in the dark with aluminum foil covering. Afterwards, the mixture was centrifuged at 10,000 g for 10 minutes to remove the AgCl precipitate. The solution was subsequently filtered through a 0.2 μm syringe filter. The concentration of cisplatin was determined using a SpectrAA-24OFS Atomic Absorption Spectrometer (Varian, USA) and adjusted to 100 mM. In the next step, a cisplatin solution (100 μL, 150 mM) was mixed into a cyclohexane/Igepal CO-520 (75, 33 V: V, 8 mL) and cyclohexane/triton-X100/ hexanol blend to create a well-dispersed water-in-oil reverse micro-emulsion. Tween 20 (40 μL, 12 mM) was added to the Cisplatin-containing microemulsion and stirred for 15 min. Separately, another reverse micro-emulsion containing KCl was prepared by adding a KCl solution into a similar reverse micro-emulsion. The two emulsions were combined, and the reaction proceeded for 30 minutes. Afterwards, ethanol (15 mL) was added to the mixture and vortexed, followed by centrifugation at 10,000 g for at least 10 minutes to remove the cyclohexane. The resulting pellets were washed with ethanol 2 times, then re-dispersed in chloroform (3.0 mL). To prepare cisplatin niosomes, span 60 (8 mg), cholesterol (14 mg), PEG200 (14 mg), and NPC nanoparticle cores solution (1.5 mL, 1 μg/mL) were dispersed in ethanol, and the ethanol was removed by rotary evaporation. The remaining niosomes were then dispersed in water. For curcumin niosome preparation, span 60 (8 mg), cholesterol (14 mg), PEG200 (14 mg), and a curcumin solution (1.5 mg/mL, 1.5 mL) were mixed in ethanol. Once the ethanol was evaporated, the residual niosomes were dispersed in PBS (3 mL). To create liposomes co-loaded with cisplatin and curcumin (Cis/CUR-NPs), span 60 (8 mg), cholesterol (14 mg), and PEG200 (11 mg) were combined with NPC nanoparticle core solution (1.5 mL at 1 μg/mL) and a curcumin solution (1.5 mL at 1.5 mg/mL) in 20 mL of ethanol. This mixture was then subjected to rotary evaporation to remove the chloroform. The remaining lipids were subsequently suspended in 3.0 mL of PBS at pH 7.

Characterization of Niosomes

The particle size and zeta potential, PDI of the niosomal formulations were analyzed using a Zeta PALS analyzer from Brookhaven Instruments Corporation (Austin, TX). Measurements were performed at room temperature, with each parameter recorded three times. The average values and standard deviations were then calculated. Niosomal Cisplatin and Curcumin concentrations were quantified using an atomic absorption spectrometer and an F-4500 fluorescence spectrophotometer (Hitachi, Japan).

In Vitro drug release

The in vitro release of Cisplatin and Curcumin from cisplatin/curcumin nanoparticles was evaluated using the dynamic dialysis method. A 2 mL sample of cisplatin/curcumin nanoparticles was placed into a pre-treated dialysis bag (MWCO: 10 kDa). The bag was then submerged in a brown bottle containing 200 mL of dialysis solution, which consisted of 25% (v/v) ethanol in PBS. The solution was stirred at 140 rpm at 37 °C. At specific time intervals (1 h, 2 h, 4 h, 6 h, 9 h, 12 h, 24 h, and 48 h), two 10 μL samples were withdrawn from the dialysis bag. HPLC analyzed curcumin concentration after demulsification with methanol, and Cisplatin concentration was measured after digesting the sample with concentrated nitric acid.

In vitro cell cytotoxicity

The cytotoxicity of Cisplatin-Sol (free cisplatin), Cisplatin-niosomes, Curcumin-Sol (free curcumin), Curcumin-niosomes, Cisplatin/Curcumin-Sol (a solution of free cisplatin and curcumin at a 1:4 ratio), and Cisplatin/Curcumin nanoparticles were assessed using the MTT assay. In brief, cells were seeded into 96-well plates at a density of 1×10^4 cells per well, each well containing 100 μL of medium, and incubated for 24 hours in a CO_2 incubator. Different formulations were then added at varying concentrations. After an additional 48-hour incubation, the viability of the cells was measured using the MTT assay, following the instructions in the user manual. Cell viability for each group was expressed as a percentage relative to the untreated control cells. Based on the viability data, the IC_{50} was calculated.

Statistics analysis

Data values were expressed as mean ± S.D. Unless otherwise specified, statistical analyses were performed using analysis of variance (ANOVA) followed by Dunnett's multiple comparison test, utilizing GraphPad Prism Version 5 software (San Diego, CA, USA). P-values.

Results

In vitro synergistic effect of cisplatin and curcumin combinations

To identify the optimal combination ratio, an MTT assay was conducted to assess the viability of CAL 27 cells after 24 hours of treatment with Cisplatin and Curcumin, either individually or in combination at various molar ratios. The median-effect method and combination index (CI) were employed to evaluate the synergistic inhibitory effects (Figure 1). The combination index (CI) was plotted as a function of the fraction affected (fa) in CAL 27cells, where fa values corresponded to growth inhibition. The CI values indicated synergism (CI < 1), additivity (CI = 1), or antagonism (CI > 1). As shown in Figure 1, synergistic activity was observed at higher levels of growth inhibition with the combinations of Cisplatin at ratios of 1:4. However, when the Curcumin proportion increased to a Cisplatin ratio of 1:8, the combination exhibited an

Table 1. The IC_{50} Values for Six Groups Against the CAL 27 Cell Line During a 24-hour Incubation Period

Compounds	IC_{50} (μM)
Cis-Sol	178±10.4
Cis-NPs	79±6.6
CUR-Sol	114±8.8
CUR-NPs	98±7.2
Cis-CUR-Sol	66±2.9
Cis-CUR-NPs	32±1.9

antagonistic effect (CI > 1), with the antagonism becoming more pronounced at higher levels of growth inhibition. Figure 1 demonstrates that at a Cisplatin ratio of 1:4, the synergistic effect became significant when inhibition exceeded 50% (fa = 0.5) and continued to increase in the higher inhibitory range (fa = 0.9), indicating that this ratio provides a more effective anti-tumor synergy compared to other ratios. Therefore, this combination ratio was selected for further study in the preparation and evaluation of co-loaded nano-niosomes.

Preparation and characterization of Nanoparticles

Niosomes co-loaded with Cisplatin and Curcumin, as well as separate niosomes for each drug, were formulated using a mixture of Span 60, Chol, and PEG200 in the ratio 60:20:4. Dynamic Light Scattering (DLS) measurements revealed that the average particle size of these Cisplatin/Curcumin nanoparticles was 150.9 nm, with a zeta potential of 24.6 ± 3.2 mV. The polydispersity index was 0.23, indicating the particles' uniform size and good dispersion. Release profiles, detailed in Figure 2, showed a two-phase release for both drugs: an initial burst within the first 4 hours, followed by a sustained release over the next 24 hours, with cumulative releases of 48% for Cisplatin and 51% for Curcumin at 48 hours. The release rates throughout the period were consistent, suggesting that the encapsulation allowed for a sustained and simultaneous release of both drugs, supporting their synergistic potential.

In vitro cytotoxicity and synergistic effect of Nanoparticles in CAL 27 cells

An MTT assay was utilized to assess the cytotoxic effects of various formulations on CAL 27 cells. Cis-NPs exhibited notably higher cytotoxicity against CAL 27 cells compared to Cis-Sol at equivalent concentrations, with Cis-Sol displaying a higher IC_{50} than Cis-NPs, suggesting that niosomal encapsulation of Cisplatin might facilitate greater uptake by cancer cells, thereby enhancing its cytotoxic impact. The cytotoxic effects of CUR-Sol and CUR-NPs were comparable, with no significant differences noted (p < 0.05) at the tested concentrations. Both Cis/CUR-Sol and Cis/CUR-NPs showed the most significant cytotoxic effects on CAL 27 cells. When compared to the single-drug formulations of Cis-Sol and Cis-NPs, the combination of Cis and CUR in a niosomal carrier significantly increased the anticancer efficacy synergistically. Consequently, the co-loaded liposomes

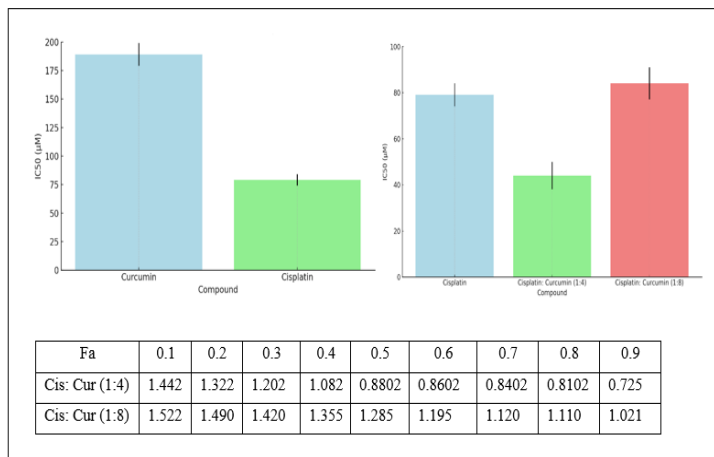| Fa	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Cis: Cur (1:4)	1.442	1.322	1.202	1.082	0.8802	0.8602	0.8402	0.8102	0.725
Cis: Cur (1:8)	1.522	1.490	1.420	1.355	1.285	1.195	1.120	1.110	1.021

Figure 1. Screening of the Optimal Combination Ratio of Cisplatin and Curcumin in CAL-27 Cells
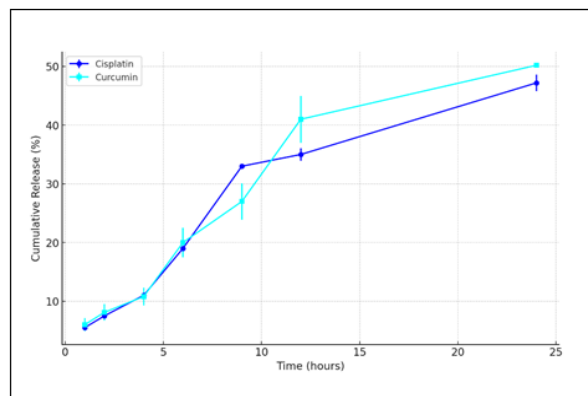

Figure 2. Preparation and Characterization of Cis/CUR- nanoparticles. In vitro release of Cisplatin and CUR in 48h

demonstrated enhanced cytotoxicity compared to their respective free drug solutions (Table 1).

Discussion

Oral cancer poses a significant health challenge globally due to its aggressive nature and limited treatment options. Traditional therapies, including surgery, radiation, and chemotherapy, often fall short in terms of efficacy and patient tolerance. The development of innovative drug delivery systems is essential to improve therapeutic outcomes [17]. Niosome nanoparticles have emerged as a promising carrier system for delivering hydrophobic drugs, enhancing bioavailability, and providing targeted delivery [18]. This study investigates the combined use of curcumin, a natural anti-inflammatory and anti-cancer agent, with cisplatin, a widely used chemotherapeutic drug, utilizing niosome nanoparticles for effective treatment against oral cancer [19-23]. In this research, niosome nanoparticles were formulated and optimized. The characterization of these nanoparticles showed a mean particle size of approximately 150 nm, a zeta potential of 24.6 ± 3.2 mV, and a low polydispersity index (PDI) of 0.23 ± 0.05. These characteristics are crucial for ensuring the stability of the niosomes in biological fluids and enhancing their uptake by cancer cells. Smaller particles with a favorable zeta potential tend to have improved dispersion and reduced aggregation, allowing for better penetration into tissues [24-27]. The controlled release profile of curcumin and cisplatin over 48 hours demonstrated the potential of niosomes to deliver these drugs effectively. A cumulative release of $51\% \pm 5.2\%$ for curcumin and $48\% \pm 4.5\%$ for cisplatin indicates that the niosome formulation can maintain drug availability at the target site over an extended period. This sustained release is advantageous in minimizing the frequency of dosing and enhancing patient compliance, ultimately contributing to better treatment outcomes [8, 28-29]. The combination of curcumin and cisplatin presents a powerful therapeutic strategy against oral cancer. Curcumin possesses anti-inflammatory, antioxidant, and anti-cancer properties, which can enhance the effectiveness of cisplatin. Studies have shown that curcumin can sensitize cancer cells to cisplatin by inhibiting survival pathways and enhancing apoptosis. This synergistic effect is particularly important in the context of oral cancer, where resistance to chemotherapy is a significant concern. The findings from in vitro cytotoxicity assays revealed that the combined treatment significantly reduced cell viability compared to individual treatments, further underscoring the potential of this combination in enhancing therapeutic efficacy [19-20, 23, 30] While both niosomes and liposomes serve as effective drug delivery systems, they have distinct characteristics that influence their performance. Liposomes are composed of phospholipid bilayers and can encapsulate both hydrophilic and hydrophobic drugs, providing flexibility in formulation. However, their stability can be compromised by

environmental factors such as temperature and pH, leading to premature drug release. Niosomes, on the other hand, are formed from non-ionic surfactants, offering greater stability in biological environments and potentially lower production costs [15, 31-36]. Furthermore, niosomes can be engineered to achieve specific targeting, enhancing the accumulation of drugs in tumor tissues. The smaller size and modified surface characteristics of niosomes may facilitate better penetration through biological barriers compared to liposomes. This is particularly relevant in the treatment of solid tumors, such as oral cancer, where effective drug delivery to the tumor site is crucial for therapeutic success [31-39]. Despite their advantages, the use of niosome nanoparticles in drug delivery is not without limitations. One significant concern is the biodistribution and pharmacokinetics of niosomes. They can be rapidly eliminated from the bloodstream by the reticuloendothelial system (RES), reducing their circulation time and therapeutic concentration at the tumor site. Additionally, niosomes may face challenges related to tissue penetration, as their size and surface properties can impact their ability to reach and accumulate in tumor tissues effectively [40-44].

The human body's complex structure encompassing biology, mechanisms, chemistry, and more continuously interacts with technological advancements. With the increasing prevalence of various diseases, including cancers, heart conditions, mental disorders, and others that have persistently impacted human life, innovative solutions like artificial intelligence, advanced pharmaceutical formulations, and expert psychological support are proving invaluable. These advancements offer significant potential to enhance disease management and treatment, fostering a better quality of life [45-72]. We examine important diseases and health issues. Drug delivery systems have significantly improved transporting of essential biological materials [73]. Cancer is one of the leading causes of death globally, and chemotherapy has been extensively used as a treatment method over the past few decades [74]. Oral squamous cell carcinoma (OSCC) is a common and impactful form of oral cancer with widespread health consequences globally [75]. Apart from cancer, the COVID-19 pandemic can be mentioned as it endangered the lives of people worldwide [76]. For example, the coronavirus has created numerous challenges for healthcare teams, especially for nurses [77]. Among the health issues that threaten human life, stroke can be mentioned, and research has been conducted in this area [78]. One of the diseases that becomes more prevalent with ageing in society is Alzheimer's [79]. Recent advancements include medical modeling, which has become an important innovation in the field [80]. Technology holds a special place in today's diagnostics and treatment; for example, artificial intelligence provides significant assistance in achieving these goals [81]. Among technological advancements, vaccine development stands out as it has effectively contributed to improving quality of life [82]. Individual and environmental factors significantly influence a person's growth and skill development [83].

In conclusion, the findings of this study suggest that niosome nanoparticles can effectively deliver a combination of curcumin and cisplatin, significantly enhancing their therapeutic potential against oral cancer. The synergistic effects of curcumin and cisplatin represent a promising approach to overcoming resistance and improving treatment outcomes. While niosomes offer several advantages over traditional liposomes, addressing the limitations related to drug clearance, stability, and tissue penetration is essential for translating this technology into clinical practice. Future research should focus on optimizing niosome formulations and exploring advanced targeting strategies to maximize the clinical benefits of niosome-mediated drug delivery systems in oral cancer therapy.

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