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RESEARCH ARTICLE

Paclitaxel-Loaded PBCA Nanoparticles for Targeted Drug Delivery in Ovarian Cancer

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Abstract

Overview: Resistance to paclitaxel remains a critical barrier in the effective treatment of ovarian cancer, often resulting in reduced clinical responses and increased recurrence rates. Nanoparticle-mediated drug delivery has emerged as a promising strategy to overcome such resistance by enhancing drug bioavailability and targeting tumor cells more precisely. The present study focuses on the formulation of poly(butyl cyanoacrylate) (PBCA) nanoparticles to facilitate controlled paclitaxel delivery and improve its therapeutic efficacy against drug-resistant ovarian cancer cells. **Methods:** Paclitaxel-loaded PBCA nanoparticles were synthesized using a mini-emulsion polymerization technique. Physicochemical properties were assessed by measuring hydrodynamic size, polydispersity index (PDI), zeta potential, and in vitro drug release behavior. Morphological evaluation was conducted via Scanning Electron Microscopy (SEM) to confirm particle uniformity and surface characteristics. Cytotoxicity was examined against the A2780CIS ovarian cancer cell line following 48 hours of exposure to the nanoformulation and free paclitaxel. **Results:** The formulated nanoparticles displayed a spherical morphology with an average diameter of 355 nm, a PDI of 0.29, and a surface charge of –18.4 mV. Drug release profiling demonstrated a sustained and controlled release, with approximately 42% of paclitaxel released over 40 hours under physiological conditions. Cellular viability assays revealed that treatment with paclitaxel-loaded PBCA nanoparticles led to a 68% reduction in cell viability, significantly outperforming free paclitaxel, which showed a 41% decrease under identical conditions ($p < 0.01$). **Conclusion:** PBCA nanoparticles exhibited favorable physicochemical characteristics and enhanced anticancer activity in paclitaxel-resistant ovarian cancer cells. These findings support their potential application as a targeted and efficient nanocarrier system for improving the therapeutic index of chemotherapeutic agents in drug-refractory malignancies.

Keywords: Paclitaxel resistance- Poly(butyl cyanoacrylate) nanoparticles- Smart drug delivery system- Ovarian cancer

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Introduction

Recent technological and scientific breakthroughs in healthcare and industry have markedly improved the efficiency with which new methods and procedures are developed, contributing to stronger economic growth. Nevertheless, alongside these benefits, the rapid pace of innovation can generate additional stress in everyday life, highlighting the need to balance progress with well-being [1-11]. For instance, the integration of advanced computer systems into medical practice ranging from digital imaging and electronic health records to clinical decision-support tools has transformed patient care by enhancing diagnostic accuracy, streamlining workflows, and improving overall outcomes [12]. Cancer is a heterogeneous group of diseases characterized by uncontrolled cell proliferation and metastasis, posing a major global health challenge; recent research has explored its various forms, including

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breast cancer models such as MCF 7, oral squamous cell carcinoma, cervical cancer, other gynecologic malignancies, and lung cancer, each demanding tailored diagnostic and therapeutic strategies [13-23]. Cancer management strategies encompass both therapeutic interventions such as using radiopharmaceuticals for pain relief in metastatic disease and preventive measures to minimize iatrogenic risks, for example, shielding techniques during diagnostic imaging [24, 25]. In addition to genetic determinants implicated in diseases such as cancer, environmental factors like background radiation can influence the activity of key stress response genes, potentially altering disease susceptibility and progression [26]. Ovarian cancer remains one of the most lethal gynecologic malignancies worldwide, primarily due to its late diagnosis and frequent development of resistance to standard chemotherapeutic agents [27]. Among the first-line treatments, paclitaxel has shown considerable efficacy through its ability to stabilize microtubules and inhibit mitosis [28]. However, prolonged use often leads to the emergence of drug-resistant tumor cells, severely compromising clinical outcomes and limiting long-term survival [29-31]. The mechanisms underlying paclitaxel resistance are multifactorial, involving alterations in drug efflux, apoptosis pathways, and microtubule dynamics, which collectively demand the development of novel therapeutic strategies [32-34]. In many cases, pharmaceutical formulations must undergo preclinical evaluation in vitro on cell cultures or in vivo in animal models to assess their efficacy and safety before advancing to clinical trials [35, 36]. Nanotechnology stands out as a leading example of technological progress, having revolutionized targeted drug delivery in medicine and enabled novel chemical processes in industry by manipulating materials at the molecular and atomic scale [37-45]. Nanotechnology-based drug delivery systems have emerged as a promising avenue to overcome these limitations by improving drug solubility, stability, and tumor-specific accumulation [31]. Nanoparticles have been applied in diverse biomedical contexts, such as using nanoliposomes to transport DNAzymes across the blood–brain barrier [46] and employing 5 ALA–conjugated hollow gold nanoparticles to enhance radio and photosensitivity in KYSE esophageal cancer cells [47]. Recent advances in targeted delivery systems have demonstrated the potential for precision therapeutic approaches, including mRNA-encapsulated lipid nanoparticles that enable controlled modulation of specific cellular pathways, highlighting the broader applicability of nanoparticle-based platforms for achieving enhanced therapeutic specificity in cancer treatment [48]. Alginate based nano hybrid hydrogels have emerged as a promising drug delivery platform in oncology, leveraging their biocompatibility and tunable release kinetics to achieve targeted accumulation and sustained release of anticancer agents within tumor tissues [49]. Poly(butyl cyanoacrylate) (PBCA) nanoparticles, in particular, have garnered attention due to their biocompatibility, biodegradability, and ability to encapsulate hydrophobic chemotherapeutic agents such as paclitaxel [31]. These carriers can prolong systemic circulation time and provide controlled drug release, thereby enhancing cytotoxic effects at the tumor site while minimizing off-target toxicity [31]. In this study, paclitaxel-loaded PBCA nanoparticles were designed and evaluated as a targeted delivery platform for ovarian cancer therapy. The formulation was characterized in terms of hydrodynamic size, polydispersity index (PDI), surface charge, drug release kinetics, and morphological features. Furthermore, the cytotoxic potential of the nanoformulation was assessed against a drug-resistant ovarian cancer cell line (A2780CIS) to determine its therapeutic advantages over free paclitaxel. A schematic illustration of the synthesis and drug release mechanism of paclitaxel-loaded PBCA nanoparticles is presented in Figure 1.

Methods and Materials

Materials

Butyl cyanoacrylate monomer was purchased from Evobond® (TongShen Enterprise Co., Ltd., Taiwan). Polyethylene glycol (PEG400) and dextran (MW 40,000) were obtained from Sigma–Aldrich Co. (UK). Hydrochloric acid and sodium hydroxide were provided by Merck (Germany). Olive oil and honey were sourced from Farzan Rahbar Saba Co. and Sabalan Co. (Iran), respectively. The A2780CIS ovarian cancer cell line was obtained from the Iranian Pasteur Institute Cell Bank.

Preparation of Drug-Loaded PBCA Nanoparticles

Paclitaxel-loaded PBCA nanoparticles were prepared via a modified mini-emulsion polymerization technique under controlled laboratory conditions. Initially, a stabilizing aqueous phase was prepared by dissolving 40 mg of dextran (MW 40,000) in 0.01 N hydrochloric acid (200 µL), followed by the incorporation of 120 mg of natural honey and 30 µL of olive oil under gentle magnetic stirring (150 rpm). Once homogeneity was achieved, 250 µL of butyl cyanoacrylate monomer was added dropwise to the mixture, allowing pre-polymer dispersion.

Subsequently, 45 mg of paclitaxel was introduced into the formulation and mixed thoroughly. The entire mixture was subjected to stirring at 400 rpm for 10 minutes to form a pre-emulsion. To initiate emulsification, 20 mL of cold distilled water was gradually added in two equal steps while maintaining constant agitation. Probe sonication was then performed using a Bandelin Sonopuls HD 2070 (50 W) ultrasonic processor, with the sample vessel placed in an ice bath to prevent thermal degradation during sonication. The resulting emulsion was refrigerated at 4 °C for 24 hours to allow initial polymer network stabilization. Following this incubation period, the dispersion was returned to the magnetic stirrer and maintained at 150 rpm for 3.5 hours at ambient temperature to ensure complete polymerization of the monomer and proper drug entrapment. Finally, the pH of the colloidal suspension was carefully adjusted to physiological levels using 0.1 N sodium hydroxide.

Characterization of Nanoparticles

The physicochemical characteristics of the formulated nanoparticles, including hydrodynamic diameter, polydispersity index (PDI), and zeta potential, were evaluated using a Zetasizer Nano ZS3600 (Malvern Instruments, UK). For this purpose, the nanoparticle suspensions were diluted in phosphate-buffered saline (PBS, pH 7.2, 10 mM) at a ratio of 1:20 prior to measurement, ensuring optimal light scattering conditions. Drug loading (DL%) and encapsulation efficiency (EE%) were determined spectroscopically following nanoparticle purification. Both formulations were subjected to ultracentrifugation at 49,000 × g for 15 minutes at 4 °C to separate the unencapsulated paclitaxel from the nanoparticle pellet. The supernatant was carefully decanted, and a secondary ultracentrifugation cycle was performed to ensure the complete removal of loosely associated drug molecules. The concentration of unencapsulated paclitaxel in the final supernatant was quantitatively analyzed using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Encapsulation efficiency and drug loading were calculated using the following equations:

$$(1)\quad \text{Encapsulation Efficiency (\%)} = \frac{\text{Initial Paclitaxel (mg/mL)} - \text{Free Paclitaxel in Supernatant (mg/mL)}}{\text{Initial Paclitaxel (mg/mL)}} \times 100$$

$$(2)\quad \text{Drug Loading (\%)} = \frac{\text{Encapsulated Paclitaxel (mg/mL)}}{\text{Total Nanoparticle Mass (mg/mL)}} \times 100$$

To enable morphological analysis, the nanoparticle suspensions were lyophilized in the presence of 3% (w/v) mannitol as a cryoprotectant. The resulting dry powders were imaged using Scanning Electron Microscopy (SEM) (XL30, Philips, Netherlands) to assess surface topology and particle structure.

Drug Release Evaluation

To assess the release profile of paclitaxel from the nanoparticle formulation, a suspension containing 0.8 mg/mL of drug-loaded nanoparticles was prepared in human serum to mimic physiological conditions. The samples were incubated in a shaking incubator at 37°C, maintained at 130 rpm for 30 minutes to initiate interaction between serum components and the nanoparticles. Drug release was monitored over a 40-hour period by measuring the degradation-dependent release of paclitaxel into the surrounding medium. At predetermined time intervals, aliquots were withdrawn, and the absorbance of the supernatant was recorded at 220 nm using a UV-visible spectrophotometer. This wavelength corresponds to the characteristic absorbance of paclitaxel, allowing for quantitative tracking of its release. The release kinetics were calculated based on absorbance changes, representing cumulative drug release over time.

Cytotoxicity Assessment

The cytotoxic effects of the drug-loaded nanoparticles were investigated using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay on the A2780CIS ovarian cancer cell line, a model known for its resistance to paclitaxel. Cells were seeded in 96-well plates and treated with serial concentrations (0, 5, 10, 20, 40, 80, and 160 μM) of the nanoformulated drug, free paclitaxel, and control groups corresponding to both formulations. Following 48 hours of incubation under standard culture conditions (37°C, 5% CO_2), MTT solution was added to each well and incubated to allow mitochondrial dehydrogenases in viable cells to reduce MTT to insoluble formazan crystals. Subsequently, the formazan was solubilized using DMSO, and the absorbance was measured at 570 nm using a microplate reader. The resulting data were used to calculate cell viability and determine dose-dependent cytotoxicity profiles of the tested formulations.

Statistical Analysis

All quantitative data were analyzed using SPSS software version 15.0 (IBM Corp., USA). Results were expressed as mean ± standard deviation (SD) based on triplicate independent experiments (n = 3). Statistical significance was determined using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test to evaluate differences between experimental groups. A p-value of less than 0.05 was considered statistically significant throughout the analyses. The sample size was selected based on standard practices for preliminary in vitro assays to ensure reproducibility and minimize variability.

Results

Characterization of Nanoparticles

The polymerization of poly(butyl cyanoacrylate) was initiated by the gradual addition of cold distilled water under stirring. The reaction was followed by sonication, which facilitated polymer chain formation and particle dispersion. A visible change in the suspension's color to milky white indicated successful nanoparticle formation.

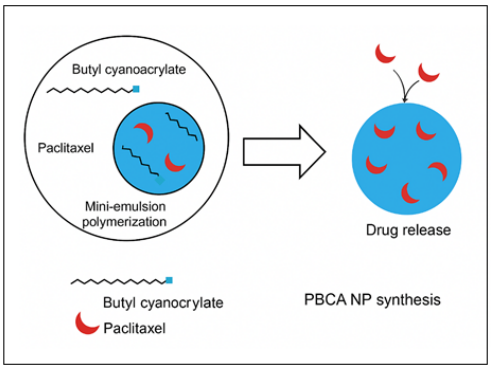

Figure 1. Schematic Illustration of the Synthesis and Drug Release Mechanism of Paclitaxel-loaded poly (butyl cyanoacrylate) (PBCA) Nanoparticles. In the mini-emulsion polymerization step, paclitaxel and butyl cyanoacrylate monomers are incorporated into a nanoscale matrix. The resulting spherical nanoparticles enable sustained drug release under physiological conditions, thereby improving the therapeutic index of paclitaxel in resistant ovarian cancer cells.

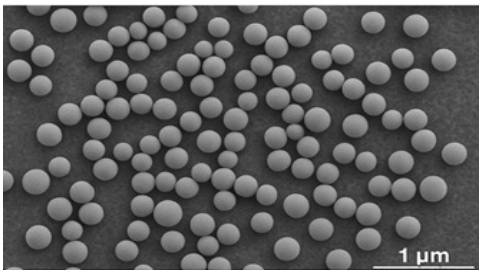

Figure 2. Scanning Electron Microscopy (SEM) Image of Paclitaxel-loaded PBCA Nanoparticles, Illustrating Uniform Spherical Morphology with Minimal aggregation. Scale bar = 1 µm

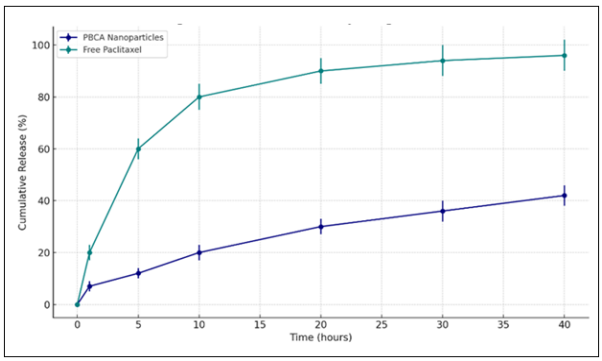

Figure 3. Drug Release Kinetics of Paclitaxel from PBCA Nanoparticles Versus Free Drug under Physiological Conditions. Data points represent mean ± SD (n = 3).

The synthesized paclitaxel-loaded PBCA nanoparticles were subjected to physicochemical characterization. Dynamic light scattering (DLS) analysis revealed that the nanoparticles had an average hydrodynamic diameter of 355 ± 12 nm, a polydispersity index (PDI) of 0.29, and a zeta potential of –18.4 ± 1.2 mV, suggesting moderately uniform distribution and good colloidal stability. SEM imaging (Figure 2) confirmed the spherical morphology and relatively smooth surfaces of the nanoparticles. Minor aggregation was observed in some areas, which could be attributed to partial drying during the sample preparation process a common artifact in SEM analysis of soft nanomaterials.

Drug Release

Drug release experiments demonstrated that the paclitaxel-loaded PBCA nanoparticles exhibited a controlled release profile: an initial burst of 7% within the first hour was followed by a gradual release, reaching a cumulative 42% release after 40 h under physiological conditions. In contrast, free paclitaxel displayed a rapid release pattern, with 96 ± 2.8% of the drug released into human serum over the same period (Figure 3).

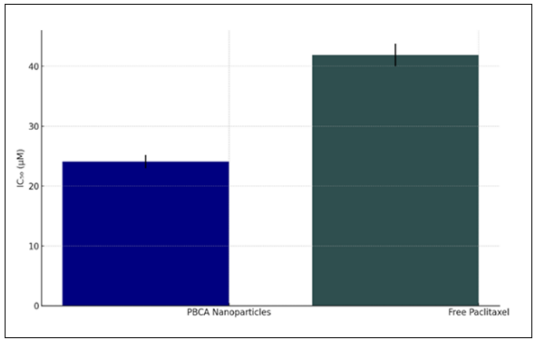

Figure 4. Values Represent Mean IC_{50} ± standard Deviation (n = 3) for Paclitaxel-loaded PBCA Nanoparticles and free Paclitaxel in A2780CIS cells.

Cytotoxicity of Nanoparticles

Initial tests confirmed that blank PBCA nanoparticles (48 µg/mL) exhibited no measurable cytotoxicity, indicating good biocompatibility. Over 48 h (Figure 4), paclitaxel-loaded PBCA nanoparticles demonstrated significantly greater cytotoxic effects than free paclitaxel. The half-maximal inhibitory concentration (IC_{50}) values were 24.1 ± 1.1 µM for the nanoparticle formulation and 41.9 ± 1.9 µM for free paclitaxel. Moreover, the nanoparticle system produced a 68% reduction in A2780CIS cell viability at the IC_{50} concentration, compared with a 41% decrease for the free drug ($p < 0.01$), indicating enhanced potency with increasing drug concentration.

Discussion

Targeted drug delivery systems are a cornerstone in the advancement of modern oncology, aiming to maximize therapeutic efficacy while minimizing systemic toxicity [50]. In conventional chemotherapy, nonspecific distribution of drugs like paclitaxel often leads to off-target effects, low bioavailability, and the development of multidrug resistance (MDR) mechanisms, particularly in aggressive cancers such as ovarian carcinoma [51, 52]. The emergence of nanotechnology-based platforms has provided a viable solution to these challenges by enabling enhanced permeability, controlled release, and selective accumulation of chemotherapeutics at the tumor site [50, 51]. Among various nanocarriers, poly (butyl cyanoacrylate) (PBCA) nanoparticles have garnered attention due to their biocompatibility, biodegradability, and capacity to encapsulate hydrophobic drugs like paclitaxel [51]. The current study demonstrates that paclitaxel-loaded PBCA nanoparticles not only improve the physicochemical stability of the drug but also exhibit enhanced cytotoxicity against the A2780CIS ovarian cancer cell line, which is known for its resistance to taxane-based therapies [51]. Our findings indicate that the PBCA nanoparticles had a hydrodynamic diameter of ~355 nm, a negative surface charge, and a moderate PDI, all indicative of a stable colloidal formulation. The drug release profile revealed a sustained pattern, with approximately 42% of paclitaxel released over 40 hours, compared to the 96% burst release of free paclitaxel [51]. This controlled release is advantageous for maintaining therapeutic drug levels over prolonged periods while avoiding toxic peaks [50]. The MTT cytotoxicity assays further validated the therapeutic superiority of the nanoformulation. The nanoparticle group induced a 68% reduction in cell viability, significantly outperforming free paclitaxel (41%, $p < 0.01$). These findings align with previous reports emphasizing the enhanced uptake

and intracellular retention of nanoparticle-bound drugs in resistant tumors through mechanisms like endocytosis and reduced drug efflux via P-glycoprotein (51,53). Notably, blank PBCA nanoparticles demonstrated no detectable cytotoxicity, reaffirming the carrier's safety profile for biomedical applications. When benchmarked against other nanocarriers such as liposomes or PEGylated micelles, PBCA nanoparticles offer several advantages, including rapid and reproducible formulation, controlled release without burst kinetics, and efficient cellular uptake [54-56]. Furthermore, the use of excipients such as dextran and natural honey introduces additional biocompatibility benefits [57]. However, their biological variability and potential microbial load raise regulatory concerns unless highly purified and standardized [57]. Future studies should focus on refining formulation components, introducing surface PEGylation to prolong circulation, and developing lyophilization techniques for enhanced stability [58, 59]. From a translational perspective, scalability and compliance with Good Manufacturing Practice (GMP) regulations are critical [59]. The mini-emulsion polymerization method employed here is cost-effective and adaptable to scale-up, using readily available reagents and mild reaction conditions. Nevertheless, GMP implementation will require stringent validation, including batch reproducibility, endotoxin testing, and long-term stability evaluations [59]. These results are consistent with prior PBCA research. Researchers demonstrated that doxorubicin-loaded PBCA nanoparticles achieved sustained release and tumor suppression in murine models [54, 55]. while researchers successfully used polysorbate-80-coated PBCA nanoparticles for brain-targeted delivery of paclitaxel in glioblastoma [57]. Compared to FDA-approved poly(lactic-co-glycolic acid) (PLGA) carriers, which often suffer from burst release and suboptimal encapsulation of hydrophobic drugs, the PBCA system in our study achieved a more desirable balance between drug retention and cytotoxicity [54, 56].

Future Research and Conclusion

Cutting-edge technological developments have profoundly reshaped medicine, dentistry, and biomedical engineering, revolutionizing approaches to diagnosis and treatment. Innovations like deep learning, convolutional neural networks, and advanced imaging methods have improved diagnostic accuracy for conditions ranging from neurological disorders to dental implants and acute medical issues. These advancements have facilitated enhanced classification systems, better biomarker detection, and systematic analyses, leading to improved patient outcomes across various medical fields. This progress highlights the power of integrating state-of-the-art computational tools with clinical practice to tackle complex health challenges effectively [60-73]. In this regard, technology has made significant strides in the treatment of various cancers, particularly in the field of drug delivery. Innovations such as targeted drug delivery systems, nanoparticle-based therapies, and precision medicine have revolutionized cancer treatment by enhancing the efficacy and specificity of therapeutic agents. These advancements allow for more precise targeting of cancer cells, minimizing damage to healthy tissues and reducing side effects [74-83]. Deep learning and imaging innovations have improved cancer detection, with breakthroughs in brain tumor classification [84] and lung cancer segmentation [85]. AI enhances diagnosis and patient care across medical fields [86]. In cancer therapy, targeted drug delivery using nanoparticles improves precision and outcomes. Environmental management benefits from genetic studies of insects [87] and strategies for mass milk disposal [88]. This study underscores the promising potential of PBCA nanoparticles as smart nanocarriers for paclitaxel delivery in drug-resistant ovarian cancer. The nanoformulation exhibited favorable physicochemical properties, sustained drug release, and enhanced cytotoxicity in vitro compared to the free drug. These results suggest that PBCA-based delivery systems can overcome chemoresistance barriers and may contribute to more effective and safer cancer therapies. Further in vivo studies and clinical validation are warranted to fully explore their therapeutic potential.

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Data availability

Not applicable as we used information from previously published articles.

Ethical issue and approval

Not applicable as we used information from previously published articles.

Consent for publication

All authors have given consent for publication.

Conflict of interest

The authors declare no potential conflict of interest.

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