DOI:10.31557/APJCB.2024.9.2.209

REVIEW

The Application of Polybutyl Cyanoacrylate (PBCA) Nanoparticles in Delivering Cancer Drugs

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Abstract

Overview: Cancer remains a significant global health challenge, accounting for one in eight deaths worldwide. Chemotherapy, the primary cancer treatment, is often limited by drug resistance. Optimizing therapy procedures has been suggested to improve survival and quality of life for cancer patients, including those with drug resistance. In recent years, nanotechnology has garnered significant attention for its potential in cancer treatment. Nanoparticles (NPs) are widely utilized to enhance therapeutic outcomes by improving drug bioavailability, solubility, and retention time. NPs offer essential conditions for targeted drug delivery through various delivery systems, including microcapsules or NPs. Polybutyl cyanoacrylate (PBCA) is among the most commonly used carriers for drug delivery in cancer treatment, with several studies investigating its efficacy. **Methods:** This article aims to review the effectiveness of PBCA as a drug delivery system in the treatment of various cancers. **Results:** Several studies have utilized PBCA for drug delivery in cancer treatment, indicating its potential efficacy in this regard. **Conclusion:** The review highlights the potential of PBCA as a promising drug delivery system for the treatment of different types of cancer.

Keywords: Drug resistance- Drug delivery- Cancer, Nanoparticle- Poly butyl cyanoacrylate

Asian Pac J Cancer Biol, **9 (2)**, 209-218

Submission Date: 03/10/2024 Acceptance Date: 04/28/2024

Introduction

Advances in technology and knowledge across diverse industries are fueling initiatives to improve operational excellence and product performance. Service-oriented businesses are working to enhance their delivery and performance standards while manufacturing sectors are prioritizing the enhancement of product quality. In the electronics industry, substantial resources are being allocated to prolong product lifespans, leading to the development of more dependable and capable devices. Likewise, significant strides are being made in the healthcare, dentistry and medical sectors to refine treatments and uncover cures for various diseases [1-23]. Today, cancer remains a significant health challenge, contributing to a high number of fatalities [24]. According to the World Economic Forum in 2011, approximately 13.3 million new cancer cases were projected for the year 2010, amounting to an estimated cost of US$ 290 billion. However, these costs are anticipated to rise and reach a staggering US$ 458 billion by 2030 [25]. Cancer refers to the uncontrolled multiplication and proliferation of irregular cells within the body [25]. More than 200 distinct types of cancer are known to affect humans [25]. More than 200 distinct types of cancer are known to affect humans [26]. Environmental elements have been implicated in contributing to 80-90% of cancer cases [27]. In contrast, hereditary factors have been linked to merely 3-10% of cancer instances [26]. Chemotherapy is recognized as a primary method for treating cancer; however, its efficacy is constrained by drug resistance [28]. This issue is particularly prevalent in patients with metastatic tumors. Lu et al., (2016) categorized chemotherapy resistance into two groups - inherent and acquired. The researchers suggest that innate resistance may stem from intratumoral heterogeneity [28]. Acquired resistance arises due to

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genetic and epigenetic modifications, leading to alterations in drug sensitivity [29]. Traditional chemotherapeutic drugs are indiscriminately distributed throughout the body, affecting both malignant and healthy cells alike, thereby restricting their usage owing to heightened toxicity levels [30]. Despite advancements in chemotherapy extending patient survival over the past 25 years, alternative methods are necessary given its limitations. Consequently, research fields have progressed to develop novel approaches like targeting blood vessels that supply tumors and utilizing targeted therapeutics [31]. Currently, nanotechnology is widely implemented across various uses, notably in medical therapeutics [32]. With respect to nanotechnology, nanoparticles (NPs) are increasingly utilized to enhance therapeutic effectiveness by increasing bioavailability, solubility, and duration in the system [33]. By employing nanoparticle-drug formulations, there is potential to decrease healthcare expenses for patients and lessen associated toxicities [34]. Tracing back to the 1980s, nano-medicine emerged as a promising field, with nano-encapsulation being instrumental in enhancing drug efficacy, specificity, safety, and overall potency [35].Nano-medicinal interventions offer multiple benefits, encompassing heightened interactions with the biological milieu, elevated uptake into designated tissues, boosted absorbance rates, prolonged retention periods, and augmented intracellular permeability [36]. The design of nano-medicinal formulations heavily depends on selecting appropriate polymeric frameworks that provide optimal encapsulation capabilities, enhanced bioavailability, and extended retention durations [37]. The dimensions and distribution patterns of nanoparticles (NPs) play significant roles in determining their impact on cell membranes and penetrative abilities in physiological drug obstacles. Investigations indicate that tailoring the particle size based on the intended tissue or target site and considerations regarding circulatory conditions yields favorable results [31]. Polybutylcyanoacrylate (PBCA) nanocarriers boast desirable attributes such as diminutive sizing, straightforward manufacturing, scalability, effortless purification processes, excellent in vitro stability, and swift removal from the body [38]. PBCA NPs demonstrate capacity to mitigate cisplatin's instability issues, indicating their potential role in facilitating cancer treatments [39]. Ebrahimi Shahmabadi et al. [40] highlighted PBCA's advantageous traits for delivering cisplatin in glioblastoma, namely enhanced stability and gradual release. These nanoparticles can be fabricated using either anionic polymerization reactions or miniemulsion polymerization techniques. Additional investigations conducted in controlled environments revealed that the miniemulsion polymerization approach proved effective for producing Cisplatin-loaded PBCA nanoparticles specifically designed for treating ovarian cancer [41]. Previous research findings indicated that emulsion polymerization might not be an ideal solution for incorporating medications into PBCA NPs, instead recommending alternatives such as miniemulsion polymerization for this purpose [42].

Which PBCA production technique is best suited for pharmaceutical transport? How proficient is chosen PBCA modality at addressing certain forms of cancer? Hence, this investigation aims to assess the performance of selected nanoparticles against diverse neoplastic diseases.

Overview of techniques employed for generating polymer-based nanoparticles

The most common method for creating drug-containing poly(butyl cyanoacrylate) nanoparticles (PBCA NPs) is to introduce the drug during the emulsification process or when it adheres to the surface of the NPs. This approach is often utilized due to its simplicity and effectiveness in loading drugs onto PBCA NPs [43-44]. The carrier's capacity can be enhanced through certain production elements such as using a stabilizer, regulating the pH of the mixture, and controlling the quantity and duration of drug addiction. Additionally, modifying the compatibility between the drug and the nano-particle material using adjustable water-loving (hydrophilic) or water-repelling (hydrophobic) qualities of poly(BCAco-OCA) can promote drug loading and encapsulation effectiveness [45]. Most of the trapped medication's mass by PBCA NPs is constrained due to the drug's solubility in the reaction medium [46-48]. Over recent years, there has been significant growth in the application scope of polymer NP surface areas, which have become increasingly important across numerous industries, ranging from medicine and biotechnology to pollution management and environmental science. Presenting an explanation for what NPs stand for is essential. In essence, NPs refer to tiny, particulate substances measuring between 10 and 1000 nanometers in diameter, characterized by their solid state and colloidal nature [49]. Initially, NP manufacturing techniques originated from the discipline of latex engineering established by polymer chemists. This was based upon in situ polymerization of monomers across varying media types. Early pioneers synthesized initial NPs utilized for medicinal purposes via polymerization processes back in the 1970s. Known as vesicular structures called "nanocapsules," they functioned similarly to reservoirs where enclosed materials were confined within fluid cores - either oily or aquatic - encircled by robust outer layers made up of solid materials [50]. A schematic imagine of polymer NPs is presented in Figure 1.

Two widely recognized polymerization approaches include dispersion polymerization and emulsion polymerization. With regard to dispersion polymerization, this technique utilizes three primary components: an initiator, monomer, and solvent. Herein, the freshly formed polymer functions as its own dispersant or stabilizing

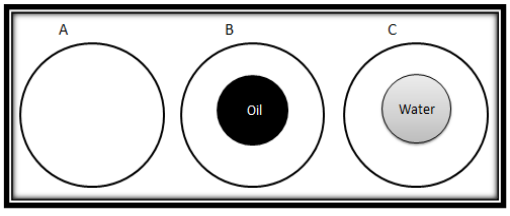

Figure 1. A Schematic of Polymer NPs (a), Nanocapsules Having Oil (b) and Nanocapsules Having Water (c).

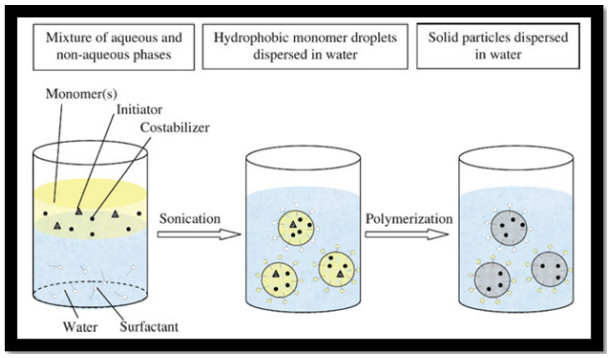

Figure 2. The Process of Direct (oil-in-water) Miniemulsion Polymerization, Adopted from Landfester and Musyanovych, (2010)

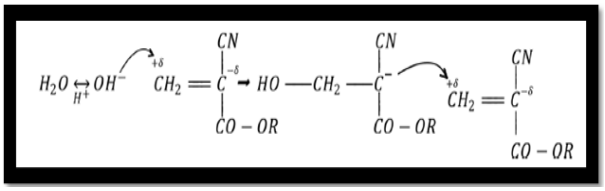

Figure 3. Anionic Polymerization of Alkyl Cyanoacrylate Monomers Forming of NPs. Hydroxyl ions in water are starting the reaction.

agent during the process [51]. Through the course of dispersion polymerization, polymers come into existence within the uninterrupted stage before subsequently crystallizing out right into novel separate particle phases. These emergent entities get steadied thanks to the presence of polymeric agents acting as stabilizers [51]. Dispersion polymerization hinges on the concept wherein the monomer is diffused or dissolved in an aquatic setting. Emulsion polymerization constitutes another approach whereby the monomer becomes suspended in a non-solvent containing surfactants mixture leading towards formation of swelled microscopic particles plus stable monomer drops. Such reactions proceed given presence of catalysts. Emulsion Polymerizations fall under two categories, namely those occurring organically within a constant medium versus other instances taking place aqueously likewise [51]. Given that PBCA is customarily formulated employing miniemulsion and anionic polymerization tactics, the focus shall rest solely on said strategies. Research efforts recounting the conception of taxane-imbued PBCA NPs leveraging mini-emulsion protocols or anionic polymerization have indeed emerged previously [52-53].

Miniemulsion commonly acknowledged strategy to generate diminutive, enduring particles nested in an unbroken surrounding medium via high sheer force implementation [54]. Droplet dimensions predominantly depend on specific emulsifiers' identity and employed quantities in respective configurations. Mini-emulsion polymerization triggers polymerization initiation inside tinier, secured droplets instead - essentially meaning that polymerization events occur within diminutive nanoscale capsules. To facilitate direct miniemulsions, researchers often incorporate long-chain alkanes functioning as auxiliary stabilizers during oil-in-water settings. Figure 2 provides schematic overview covering direct mode of miniemulsion polymerization sequence embracing dispersement of oil portions through water-based platforms [55]. Contrasting emulsion polymerization, this tactic doesn't mandate migration of monomers nor additional hydrophobic molecules from original tanks into designated sites meant for polymerization responses [56]. Owing to this, miniemulsion polymerization might reasonably merit recognition as some sort of single-stage nano-encasement operation, especially tailored towards effective sequestration of hydrophobic substances [57]. Nearly all poly (alkylcyanoacrylate) nanoassemblages originate fruitful results after capitalizing on anionic polymerization techniques [58]. Cyanoacrylic acid derivatives undergo in-situ synthesis while steeped in aqueous environments through means of anionic polymerization. One notable example includes suspending butyl cyanoacrylate monomer within aquatic domains, consequently generating discrete particles [41]. Depiction of anionic polymerization response featured in Figure 3. Demonstrated capability exists regarding encasement of double-stranded DNA filaments into PBCA nanostructures enabled via anionic polymerization, implicating active engagement between miniemulsion droplets plus neighboring steady domain [59].

Utilizing Poly(butyl cyanoacrylate) (PBCA) as a drug carrier system for cancer treatment

In this study, we explore the use of Poly(butyl cyanoacrylate) (PBCA) as a delivery vehicle for diverse medications via multiple techniques. We will delve into each method's mechanics and examine the pharmaceuticals being transported.

Using PBCA in ovarian cancer

Paclitaxel proves to be an effective antineoplastic agent against several forms of cancer, most notably demonstrating remarkable success in treating ovarian cancer [60]. The commercial version of this product encounters significant difficulties due to its inadequate solubility in water [61]. Furthermore, research indicates that one possible outcome of overcoming multi-drug resistance (MDR) could be the absorption of nanoparticles (NPs) onto the surface of cells [62]. Earlier investigations have disclosed techniques for producing paclitaxel-infused PBCA nanoparticles either via miniemulsion processes or anionic polymerization methods [52]. According to a study by Ren and colleagues in 2011 [63], paclitaxel-filled PBCA nanoparticles were developed using the interfacial polymerization technique to examine their potential in mitigating MDR in human ovarian resistant cells (A2780/T) and explore their underlying mechanisms. The resulting NPs had a spherical shape with an average size of 224.5±5.7 nm. The findings suggested that these NPs enhanced cytotoxicity and relieved MDR by hindering the activity of P-glycoprotein induced by the NP system. Additionally, they found that interfacial polymerization resulted in higher encapsulation and drug loading efficiency than emulsion polymerization, attributed to the inclusion

of surfactants like lecithin and dextran 70. Another investigation explored the toxic impact of Cisplatin-filled PBCA NPs on the Cisplatin-resistant ovarian cancer cell line A2780cp [41]. Cisplatin is a primary medication for treating ovarian cancer due to its mechanism of attaching to DNA and triggering apoptosis. Researchers created nanoparticles (NPs) via the miniemulsion polymerization technique. The NPs' dimensions, size distribution, and zeta potential were measured at 489 nanometers, 0.429, and -20 millivolts, respectively. This research proposes enhanced effectiveness of Cisplatin-PBCA NPs and recommends further examination with in vivo experiments related to ovarian cancer. Kanaani et al. (2017) recently examined the fundamental attributes and cytotoxic consequences of nano-poly (butyl cyanoacrylate) containing carboplatin on ovarian cancer cells. They developed non-PEGylated and PEGylated NPs utilizing the mini-emulsion polymerization method for PBCA NPs. Both formulation's cytotoxicity was tested on the A2780CIS ovarian cancer cell line following various time intervals of 24, 48, and 72 hours. According to the cytotoxicity outcomes, both forms of nano-drugs demonstrated higher toxicity compared to the unbound drug. Furthermore, this study suggests that PBCA NPs could serve as promising options for nano-drug development in chemotherapy. Conclusively, these scientists determined that both PEGylated and non-PEGylated PBCA NPs function well as carriers for delivering carboplatin to the ovarian cancer cell line A2780CIS [56].

Using PBCA in gastric cancer

Magnetic targeting medication is considered the latest type of targeted treatments, offering advantages over other types of medications due to its reduced absorption by the reticuloendothelial system (also known as RES). This unique feature sets it apart from previous generations of targeted therapies [64]. The widely recognized challenge in treating solid tumors involves the creation and delivery of magnetic-responsive carriers capable of being administered via intravenous injection and reaching any desired location within the body's systems. Successful implementation of such a method could significantly improve cancer therapy outcomes [65]. Past investigations examined the impact of aclacinomycin A-infused magnetic polybutylcyanoacrylate NPs on stomach tumor progression using both in vivo and in vitro methods. To do this, they created magnetic PBCA spheres containing aclacinomycin A via interface polymerization. Before starting treatment, magnets (with strength of 2.5 Tesla) were positioned inside the tumor tissues for each mouse. Encapsulation of aclacinomycin A within these magnetic PBCA spheres resulted in a content level of 12.0% and an average particle size of 210 nanometers. Inhibition rates of free aclacinomycin A (at dose of 8mg per kilogram of body mass), high-dose magnetic PBCA spheres loaded with aclacinomycin A (8mg/kg bm), low-dose magnetic PBCA spheres carrying aclacinomycin A (1.6mg/kg bm) and plain magnetic PBCA spheres on human stomach cancer in nude mice were measured at 22.63%, 52.55%, 30.66% and 10.22%, respectively. Researchers determined that magnetic-guided chemotherapy utilizing aclacinomycin A-laden magnetic PBCA spheres exhibited enhanced tumor targeting, improved effectiveness, and decreased toxicity compared to conventional approaches.

Applying PBCA in breast cancer

According to Li et al. (2015), there is a notable impact of Cisplatin, when enclosed in dextran Nanoparticles (NPs), on suppressing breast cancer. Research has indicated that the effectiveness of Cisplatin can be enhanced through its combination with different types of NPs [66]. In their study, Farhat et al., (2009) evaluated the potential of Lipoplatin as a therapy for HER2/neu negative metastatic breast cancer and concluded that using liposomal Cisplatin alongside vinorelbine may result in promising activity and well-tolerated outcomes as an initial treatment option for this particular form of cancer [67]. Koohi Moftakhari Esfahani et al. (2016) investigated the usefulness of Cisplatin-infused PBCA NPs in managing breast cancer utilizing an orthotopic model of the disease. The researchers created these Cisplatin-laden PBCA NPs via a miniemulsion polymerization technique. Their findings suggested that employing Cisplatin-loaded PBCA NPs might improve the drug's efficiency while simultaneously reducing its adverse effects [38]. Cabeza et al. (2015) examined the anti-tumor properties of doxorubicin in treating breast cancer by incorporating it into PBCA-NPs. These NPs were fabricated using the emulsion/polymerization method. Based on their results, they proposed that the heightened anti-tumor activity of doxorubicin-loaded PBCA-NPs could allow for a reduced dosage of doxorubicin necessary to produce an adequate therapeutic response while minimizing toxic side effects [68].

Applying PBCA in prostate cancer

A research project was carried out to examine how prostate cancer cells absorb and distribute PBCA-encapsulated Nile Red or free Nile Red in the culture media [69]. The researchers used flow cytometry and confocal laser scanning microscopy to analyze the uptake and intracellular localization. According to their findings, direct delivery of anticancer medicines to intracellular target molecules via a contact-mediated approach was not successful. However, they suggested that using a contact-based transfer method and higher uptake of encapsulated medications over non-encapsulated ones may aid in delivering hydrophobic anticancer treatments, improving cancer therapy.

Applying PBCA in glioblastoma cancer

Glioblastoma is identified as one of the most invasive forms of cancer in humans. Due to its location within the brain, it's challenging to treat this type of cancer because drugs need to cross the blood-brain barrier (BBB) first. A research team led by Ebrahimi Shahmabadi et al. [40] carried out a study to evaluate how well cisplatin-loaded Polybutylcyanoacrylate nanoparticles (PBCA NPs)

perform against glioblastoma. They synthesized these nanoparticles using the miniemulsion polymerization technique and added a layer of polysorbate 80 to help them penetrate the BBB in rats with glioblastomas. Their results showed that while nanodrugs had lower effectiveness compared to free drugs, they also reduced harmful side effects associated with traditional treatments, suggesting potential benefits when applied to different types of tumors. However, modifications like adjusting particle size or altering their surfaces could improve successful penetration through the BBB.

Applying PBCA in brain cancer

Considers have combined PBCA with the nonionic surfactant polysorbate-80 and found fitting conveyance of an assortment of little polar drugs into the central apprehensive framework (CNS) in numerous considers [70, 71]. Drugs including doxorubicin, loperamide, tubocurarine, and dalargin were adsorbed onto PBCA-NPs and targeted to the CNS, where their pharmacological effects were found [72]. PBCA-NP did not produce nonspecific disruption of the BBB. Studies have proposed an alternative to the uptake of PBCA-NPs in the brain, whereby NPs induce nonspecific permeation of the BBB [73]. PBCA-NPs have been reported to be capable of delivering drugs as BBB-impermeable fluorophores of various sizes, from 500 Da target polar molecules to 150,000 Da tagged immunoglobulins in live mouse brains [74]. However, high doses of PBCA-NP with polysorbate-80 may damage the BBB. Studies have reported that PBCA-NP only has pharmacological effects after drug administration. It has been shown that polysorbate 80 can adsorb plasma apolipoprotein E (Apo-E) and Apo-E coated NPs through the LDL uptake system [75]. Research involving rat subjects examined polysorbate 80-covered poly-lactic-co-glycolic acid nanoparticles that contained methotrexate-transferrin. The findings suggested improved tissue entry, reduced organ harmfulness, and enhanced tumor-fighting abilities compared to untargeted NPs [76]. According to Kreuter and Gelperina (2008), NPs covered with polysorbate 80 or poloxamer 188 demonstrated successful transportation of doxorubicin past the blood-brain barrier (BBB) and decreased medication toxicity [77]. In contrast, magnetic NPs were noted by Laurent et al. (2012) and Mahmoudi et al. (2011) as particularly effective for enhancing BBB permeability due to heightened sensitivity among brain cells relative to those found in the liver and heart. This suggests that magnetic NPs may be an optimal choice for drug delivery within the central nervous system [78, 79]. Reimold et al. [80] assessed NP distribution to the brain using fluorescence microscopy. They employed a novel miniemulsion technique to create PBCA particles, which exhibited high yields and consistent production. These NPs encapsulated either FITC-dextran, rhodamine-123, or doxorubicin at varying concentrations and were then coated with polysorbate 80 prior to injection into rats. Results revealed that surface-modified PBCA-NPs successfully crossed the BBB and functioned as a vehicle for drug administration to the central nervous system (CNS). Consequently, it was determined that colloidal polymeric structures offered a promising method for overcoming the BBB challenge. Tian et al. [81] investigated the efficacy of polysorbate-80-covered PBCA-NPs for administering medications to animal brains. Utilizing emulsion polymerization techniques, they synthesized these NPs containing temozolomide and observed elevated levels within the brain when utilizing polysorbate-80-coated PBCA-NPs versus unbound medication. Thus, their research supports the potential use of polysorbate-80-coated PBCA-NPs as a suitable carrier for temozolomide delivery to the brain.

In conclusion, mankind has made remarkable progress in several disciplines by leveraging insights from both physical and mental health conditions. This interdisciplinary approach has led to advancements in areas like medicine, dentistry, chemistry, biochemistry, psychology, electrical engineering, environmental science, nanotechnology, nutrition, and many others. Consequently, our understanding and capabilities in these domains have improved significantly, leading to enhanced productivity and better quality of life [82-93] [82, 95-112]. The objective of this review paper was to examine research investigating the use of the PBCA technique in drug delivery across various types of cancer. While the PBCA process has been extensively implemented in certain malignancies, it is currently being studied in others. Therefore, drawing definitive conclusions about the efficacy of the PBCA approach for drug delivery is challenging. Nevertheless, many studies have indicated positive outcomes associated with using the PBCA method for effective drug delivery. Concerning the preparation method, it appears that miniemulsion is well-suited for this purpose. Furthermore, there is evidence suggesting that the PBCA technique may be particularly useful in treating brain cancer. Further investigation is recommended to fully establish the effectiveness of the PBCA procedure.

Acknowledgments

Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute .

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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