Journal of Community and Clinical Pharmaceutical Sciences
Volume 1, Number 1, 2026 pp. 10-19
E-ISSN: -
Open Access

A Systematic Analysis of the Use of Polymeric Nanoparticles to Enhance the Effectiveness of Targeted Drug Delivery in Cancer Therapy

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ARTICLE INFO

Article history:
Received March 11, 2026
Revised April 22, 2026
Accepted May 15, 2026
Available online May 31, 2026

Keywords:
Polymeric Nanoparticles; Targeted Drug Delivery; Cancer Therapy; Physicochemical Properties.

ABSTRACT

Polymeric nanoparticles have emerged as a versatile platform for targeted drug delivery in cancer therapy, offering opportunities to improve therapeutic efficacy while minimising systemic toxicity. This systematic literature review (SLR) comprehensively examines studies published over the past 10 years (2016-2025) from Scopus, DOAJ, and Google Scholar to identify key physicochemical parameters and biological mechanisms that govern nanoparticle performance. The analysis reveals that particle size critically determines tumour accumulation through the Enhanced Permeability and Retention (EPR) effect and influences systemic biodistribution. In contrast, surface charge modulates cellular uptake, protein corona formation, and clearance dynamics. Additionally, the implementation of surface modifications and ligand-mediated active targeting strategies further enhances selective tumour targeting and promotes apoptosis in malignant cells. Emerging trends, including dual-targeting approaches, stimuli-responsive polymers, and nanotheranostics, are driving the evolution of polymeric nanoparticles toward personalised, clinically translatable cancer therapies. This review underscores the need for integrated design strategies that combine precise physicochemical control with an understanding of biological interactions to optimise drug-delivery outcomes, providing a roadmap for future research and clinical translation.

1. INTRODUCTION

Cancer remains one of the leading causes of global mortality, with incidence rates continuing to rise significantly over the past decade, thereby posing a major challenge to global healthcare systems (Sung et al., 2021). The complexity of this disease lies not only in uncontrolled cell proliferation but also in tumour heterogeneity and in cancer cells' ability to adapt to therapeutic pressures, ultimately leading to drug resistance (Vasan et al., 2019). Furthermore, conventional therapies such as chemotherapy still suffer from limited selectivity, as they target not only cancer cells but also damage surrounding healthy tissues (Shi et al., 2017b). This lack of specificity results in significant systemic side effects, thereby reducing patients' quality of life and limiting the overall effectiveness of treatment.

Conventional drug delivery systems in cancer therapy generally fail to deliver drugs specifically to target tissues, leading to widespread, nonspecific distribution throughout the body (Senapati et al., 2018). This non-selective distribution increases drug exposure to healthy tissues, contributing to high systemic toxicity and limiting the maximum tolerable therapeutic dose (Villela-Martinez et al., 2017). In addition, many anticancer drugs exhibit suboptimal pharmacokinetic properties, such as poor solubility and low stability in systemic circulation, which directly reduce their bioavailability and therapeutic efficacy (Bhandare, A., & Nannor, 2024). These limitations highlight the urgent need for more advanced and targeted drug delivery strategies.

The development of nanotechnology-based targeted drug delivery has emerged as a strategic approach to enhance cancer therapy by improving the selective accumulation of drugs in tumour tissues (Emeihe et al., 2024). Nanotechnology enables improved drug stability in systemic circulation, thereby

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prolonging half-life and reducing premature degradation (Haripriyaa & Suthindhiran, 2023). Moreover, nanoparticle systems can enhance the solubility of hydrophobic drugs, thereby improving bioavailability (P. Kumari et al., 2016). Surface modification of nanoparticles with specific ligands allows selective interaction with cancer cell receptors, thereby enhancing the efficiency of active targeting mechanisms (Siafaka et al., 2016). This advancement is further supported by recent studies demonstrating that nanoparticle-based systems can overcome various biological barriers in drug delivery (Indoria et al., 2020). Therefore, nanotechnology represents a promising platform for modern cancer therapy.

Polymeric nanoparticles have gained considerable attention as advanced drug delivery systems due to their superior physicochemical and biological properties, particularly their high biocompatibility and biodegradability, which support their application in cancer therapy (Kamaly et al., 2016). These systems can efficiently encapsulate a wide range of therapeutic agents, including both hydrophilic and hydrophobic drugs, thereby enhancing drug stability and preventing premature degradation during systemic circulation (Danhier et al., 2016). In addition, polymeric nanoparticles provide controlled and sustained drug release, which has been shown to improve therapeutic efficacy while reducing systemic toxicity and adverse side effects (Mitragotri et al., 2021). Statistically, nanomedicine-based drug delivery systems have demonstrated up to a 2–5-fold increase in tumour drug accumulation and a significant reduction in off-target toxicity compared to conventional formulations (Shi et al., 2017b). Furthermore, recent studies report that polymeric nanoparticle-based chemotherapy can improve therapeutic outcomes by increasing drug bioavailability and enhancing targeting efficiency, with some formulations achieving over 60% improvement in tumour inhibition rates in preclinical models (Rizi et al., 2022). Consequently, these characteristics position polymeric nanoparticles as highly promising platforms for optimising the safety, specificity, and overall effectiveness of cancer treatment strategies.

Considering the limitations of conventional cancer therapies and the significant potential of nanotechnology, particularly polymeric nanoparticles, a comprehensive synthesis of existing scientific evidence is required. Therefore, this study aims to conduct a Systematic Literature Review to systematically analyse the effectiveness of polymeric nanoparticles in enhancing targeted drug delivery for cancer therapy. Specifically, this study seeks to identify research trends over the past decade, evaluate the therapeutic effectiveness of polymeric nanoparticle-based delivery systems, and synthesise relevant empirical findings to provide a robust scientific foundation for the development of more effective, safer, and targeted cancer treatment strategies.

2. METHOD

This study employed a qualitative research design using a Systematic Literature Review (SLR) approach to systematically analyse the effectiveness of polymeric nanoparticles in enhancing targeted drug delivery for cancer therapy. This method was chosen to enable a comprehensive, structured synthesis of recent scientific evidence in line with the research objectives. The study aims to identify research trends over the past decade, evaluate the therapeutic effectiveness of polymeric nanoparticle-based delivery systems, and synthesise empirical findings to support the development of more effective, safer, and targeted cancer treatment strategies.

The literature search (search strategy) was conducted across several reputable scientific databases, including Scopus, PubMed, Web of Science, and Google Scholar. A combination of relevant keywords, such as "polymeric nanoparticles", "targeted drug delivery", "cancer therapy", and "nanomedicine", was used with Boolean operators (AND, OR) to ensure comprehensive and focused search results. The search was limited to publications from 2016 to 2025 in order to capture the most recent developments in the field. The inclusion criteria consisted of original research articles published in English, focusing specifically on polymeric nanoparticles in targeted drug delivery systems for cancer therapy, and available in full text. Meanwhile, exclusion criteria included duplicate studies, review articles, conference papers, and publications that did not directly address therapeutic effectiveness or targeting mechanisms.

The study selection and data extraction process (selection and data extraction) was carried out through a structured and sequential procedure. Initially, titles and abstracts were screened to identify relevant studies aligned with the research focus. Subsequently, full-text articles were carefully reviewed to determine eligibility according to the predefined criteria. Data were then systematically extracted and organised, including key information such as publication year, research design, type of polymeric nanoparticles, targeting strategies, and reported therapeutic outcomes. This systematic approach enabled a critical evaluation of the effectiveness of polymeric nanoparticle-based systems. It facilitated the identification of current research trends and knowledge gaps, thereby providing a solid scientific foundation for future research and innovation in targeted cancer therapy, as shown in Figure 1.

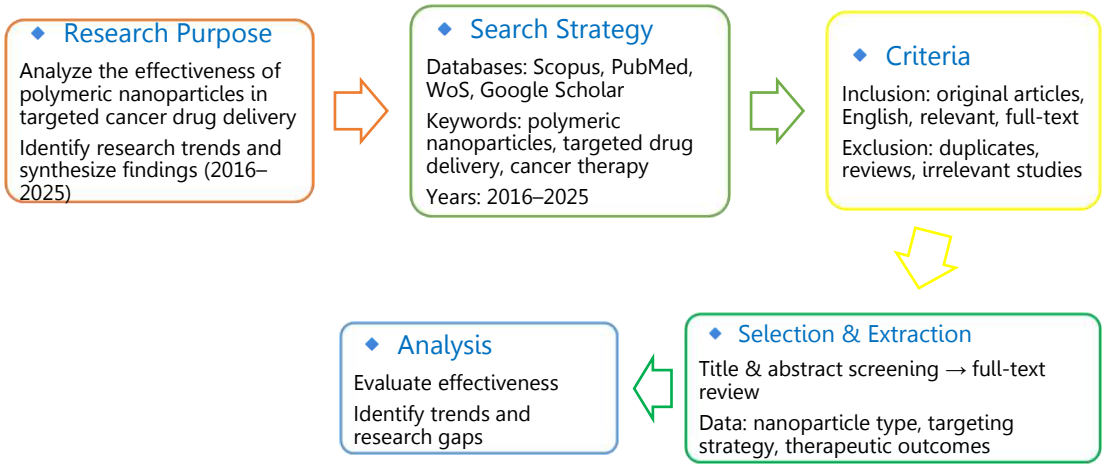

Figure 1. Steps in the systematic literature review method

3. RESULT AND DISCUSSION

Based on search results from the Dimensions database, 198,577 publications were initially identified using the defined keywords related to polymeric nanoparticles and targeted drug delivery in cancer therapy. Among these, 76,625 publications were categorised as open access (All OA), indicating a substantial proportion of studies that are freely accessible to the public. Furthermore, after limiting the document type to research articles, the number was refined to 70,302 publications, ensuring a focus on original scientific contributions. To enhance the relevance and recency of the analysis, an additional filter was applied to include only studies published within the last ten years (2016–2025), resulting in 59,964 publications. This progressive filtering process demonstrates a systematic approach to narrowing the literature to obtain a more focused, up-to-date body of evidence for subsequent analysis, as shown in Figure 2.

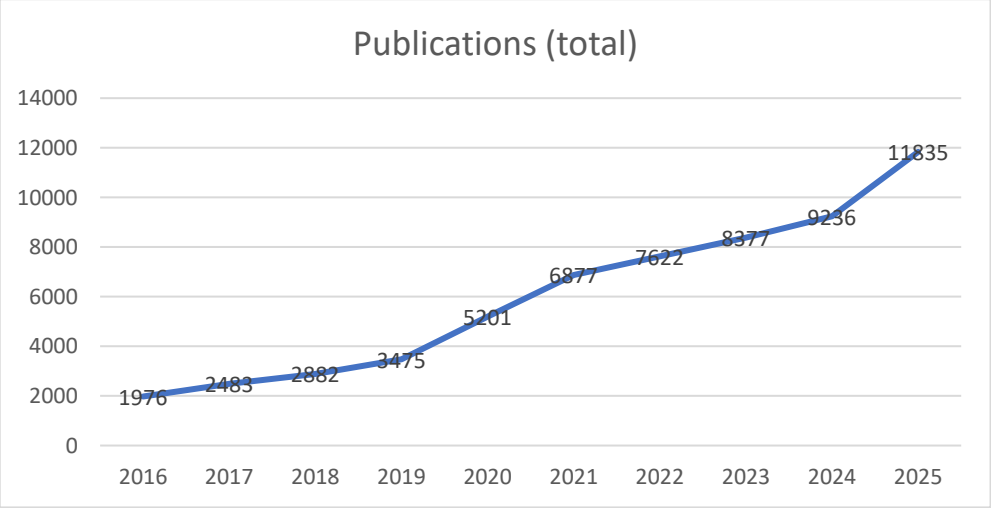

Figure 2. Annual Growth of Publications on Polymeric Nanoparticles and Targeted Drug Delivery in Cancer Therapy (2016–2025)

Figure 2 shows the trend in the number of publications from 2016 to 2025, indicating a consistent and significant year-over-year increase. In the initial phase, namely 2016–2018, the number of publications remained relatively limited, increasing from 1,976 to 2,882. This indicates that research on polymeric nanoparticles for targeted drug delivery was still in its exploratory stage and had not yet advanced significantly. Entering the 2019–2021 period, growth accelerated significantly, with the number of publications increasing from 3,475 to 6,877, reflecting the scientific community's growing attention to the potential of nanotechnology to enhance the effectiveness of cancer therapy. Furthermore, during the 2022–2025 period, this trend showed a significant surge, with the number of publications reaching 11,835 by 2025. This substantial increase indicates that the field of polymeric nanoparticles has become a primary

focus of global research, particularly in efforts to develop more selective, effective, and safe drug delivery systems for cancer therapy. This upward trend was further analysed using VOSviewer-based bibliometric analysis of keyword co-occurrences, revealing major clusters such as chemotherapy, immunotherapy, and radiotherapy, as well as material aspects such as nanocarriers and solubility, as shown in Figure 3.

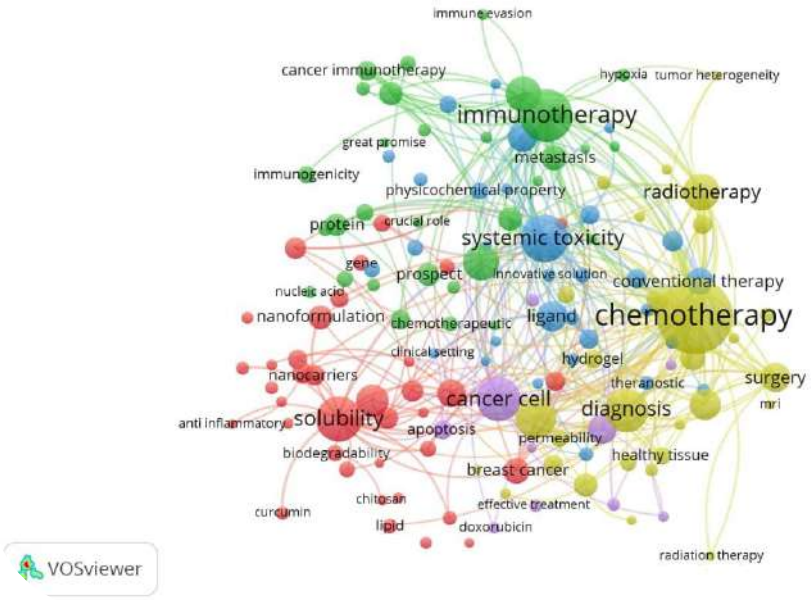

Figure 3. Visualisation of the Keyword Co-Occurrence Network in Research on Polymeric Nanoparticles for Targeted Drug Delivery in Cancer Therapy Using VOSviewer

- Red Cluster: Biomolecular Interactions and the Role of Proteins

The red cluster includes keywords such as 'protein' and 'crucial role,' highlighting the importance of biomolecular interactions in nanoparticle-based drug delivery systems. Conceptually, proteins form a protein corona on the surface of nanoparticles when introduced into biological environments. This phenomenon significantly influences nanoparticle stability, biodistribution, and cellular recognition. From a definitional perspective, these interactions determine how nanoparticles are identified and processed within biological systems. The interpretation suggests that the success of targeted drug delivery depends not only on nanoparticle design but also on complex interactions with biomolecules. Therefore, understanding protein–nanoparticle interactions is essential for improving therapeutic outcomes in cancer treatment.

- Blue Cluster: Physicochemical Properties of Nanoparticles

The blue cluster is dominated by keywords such as physicochemical property. These properties include particle size, surface charge, morphology, and stability, all of which play critical roles in determining nanoparticle behaviour in biological systems. In definitional terms, physicochemical characteristics govern circulation time, tissue penetration, and drug release profiles. The interpretation indicates that optimising these properties is fundamental to enhancing drug delivery efficiency, as they directly affect bioavailability and targeting precision toward tumour tissues.

- Green Cluster: Biological Systems and Targeting Mechanisms

The green cluster encompasses keywords related to biological systems and targeting processes. It includes mechanisms such as passive targeting via the enhanced permeability and retention (EPR) effect and active targeting using specific ligands. Conceptually, this cluster describes how nanoparticles interact with cancer cells, including cellular uptake and intracellular trafficking. The interpretation highlights that therapeutic success largely depends on nanoparticles' ability to selectively recognise and accumulate in cancer cells, thereby improving treatment efficacy while minimising off-target effects.

- Yellow Cluster: Clinical Applications and Combination Therapy

The yellow cluster includes keywords such as 'radiotherapy,' reflecting the clinical application of polymeric nanoparticles in cancer treatment. Radiotherapy is the use of ionising radiation to destroy cancer cells, and nanoparticles can act as radiosensitizers to enhance treatment effectiveness. The interpretation

reveals a growing trend toward integrating nanotechnology with conventional therapies such as chemotherapy and radiotherapy. This combination approach reflects a shift toward more comprehensive, synergistic, and precision-based cancer treatment strategies.

- Purple Cluster: Therapeutic Effectiveness and Cellular Response

The purple cluster includes keywords such as cancer cell, apoptosis, cell viability, and drug efficacy, representing the biological outcomes of nanoparticle-based therapies. Definitional aspects of therapeutic effectiveness include the ability to induce apoptosis, inhibit proliferation, and reduce cancer cell viability. The interpretation suggests that polymeric nanoparticles significantly enhance drug accumulation at target sites, thereby improving cytotoxicity against cancer cells while reducing damage to healthy tissues. This cluster represents the ultimate goal of targeted drug delivery systems.

To further elucidate the thematic mapping, this section outlines the classification of research domains, contributing authors, and key variables identified in the literature, as presented in Table 1.

Table 1. Summary of Key Research Focus, Authors, and Insights on Polymeric Nanoparticles for Drug Delivery and Cancer Therapy

No	Field / Focus	Authors	Key Insights / Research Variables
1	Physicochemical Characteristics and Nanoparticle Design	Ejigah et al., 2022; Guerrini et al., 2018; Li & Wang, 2018; Lu et al., 2023; Danaei et al., 2018; Kumari et al., 2016	Particle size, surface charge, morphology, surface modification (e.g., PEGylation), polymer composition (PLGA, pH-responsive copolymers), synthesis techniques (nanoprecipitation, emulsion), reproducibility, stability, drug release kinetics, bioavailability, off-target toxicity.
2	Biological Interactions and Targeting Mechanisms	Corbo et al., 2016; Bilardo et al., 2022; Taghavimandi et al., 2025; Behzadi et al., 2017; Shi et al., 2017a; Yin et al., 2020	Protein corona formation, modulation of immune recognition, opsonization, cellular uptake, endocytic pathways (clathrin-, caveolae-mediated, macropinocytosis), passive targeting (EPR effect), active targeting (ligand-mediated), dual-targeting strategies, specificity and penetration into tumor tissues.
3	Therapeutic Effectiveness and Multimodal Clinical Applications	Herdiana et al., 2023; Mengesha, 2024; Wang et al., 2018; Zhang et al., 2016; Rosa et al., 2017; Chen et al., 2017	Intratumoral drug accumulation, apoptosis induction, oxidative stress and caspase activation, controlled drug release kinetics, reduction of systemic toxicity, enhancement of therapeutic index, co-delivery of multiple drugs, radiosensitization, nanotheranostics, multimodal therapy integration, patient-specific adaptive strategies.

1. Physicochemical Characteristics and Design of Polymeric Nanoparticles

The physicochemical characteristics of polymeric nanoparticles critically determine drug delivery efficiency, as particle size, surface charge, and morphology significantly influence pharmacokinetic parameters and systemic biodistribution. Optimised nanoscale particles enhance tumour accumulation through the enhanced permeability and retention (EPR) effect while minimising rapid clearance by the mononuclear phagocyte system (Ejigah et al., 2022). Moreover, surface modifications, such as PEGylation, have been shown to increase circulation stability by reducing undesired plasma protein adsorption (Guerrini et al., 2018). Additionally, precise control of particle morphology and size distribution is essential to prevent aggregation and maintain consistent drug release kinetics (Li & Wang, 2018). Collectively, these parameters—size, surface properties, and morphology—fundamentally influence drug delivery performance and provide the foundation for the development of next-generation robust nanocarriers.

The design of polymeric nanoparticles must also integrate polymer composition, biological compatibility, and processing techniques to achieve optimal pharmacodynamic profiles. Selection of polymers, such as poly(lactic-co-glycolic acid) (PLGA) and pH-responsive copolymers, enables programmed drug release and predictable biodegradation in biological environments (Lu et al., 2023). Synthesis methods, including nanoprecipitation and emulsion techniques, are crucial to producing particles with uniform size and surface charge, thereby enhancing formulation reproducibility (Danaei et al., 2018). Systematic optimisation of these formulation parameters has been shown to improve drug bioavailability and reduce off-target tissue toxicity, which is critical for long-term clinical applications in cancer therapy

(Kumari et al., 2016). Therefore, a holistic physicochemical design is a prerequisite for developing effective and safe polymeric nanoparticle-based drug delivery systems.

The analysis of current studies indicates that the physicochemical characteristics of polymeric nanoparticles, such as particle size, surface charge, morphology, and surface modifications, are interdependent parameters that collectively govern their performance in drug delivery. Particle size critically influences tumour accumulation and systemic biodistribution, whereas surface charge modulates cellular interactions and clearance dynamics. Morphology and uniformity are central to maintaining controlled drug release kinetics, while surface modifications, such as PEGylation, reduce nonspecific protein adsorption and mitigate rapid opsonisation. In addition, the selection of polymer type and synthesis method significantly affects nanoparticle stability and reproducibility; for instance, PLGA provides predictable hydrolytic degradation and sustained release, and nanoprecipitation or emulsion techniques allow precise control over particle attributes, ensuring batch-to-batch consistency. Despite these advancements, most evidence is derived from in vitro or preclinical studies, limiting direct extrapolation to humans, and protein-nanoparticle interactions in vivo remain dynamic, with PEGylation not fully preventing opsonisation. Furthermore, current research predominantly focuses on spherical morphologies, whereas anisotropic geometries could potentially enhance targeting efficacy but are less explored. Collectively, these findings underscore the need for a multidimensional, integrative physicochemical design to achieve reproducible, predictable, and clinically translatable nanoparticle-based drug delivery systems, while highlighting the need for further in vivo validation and exploration of novel particle geometries.

2. Biological Interactions and Targeting Mechanisms

The initial interaction of polymeric nanoparticles with the biological environment begins with the formation of the protein corona, a layer of adsorbed plasma proteins that alters the nanoparticles' biological identity. The protein corona significantly affects biodistribution, immune response, and cellular internalisation, as its composition determines recognition by phagocytes and target cell receptors (Corbo et al., 2016). This corona formation is strongly influenced by nanoparticle surface properties such as charge and hydrophobicity, with neutral surfaces reducing opsonisation by undesired proteins (Bilardo et al., 2022). In the context of targeting, corona interactions can either facilitate or hinder active ligand-mediated targeting attached to the nanoparticle surface (Taghavimandi et al., 2025). Hence, effective surface engineering strategies must consider the composition of the protein corona to ensure successful in vivo therapeutic targeting.

Nanoparticle internalisation by target cells is highly dependent on both the nanoparticle's physicochemical properties and the targeting strategy used. Nanoparticles can enter cells via multiple endocytic pathways, including clathrin-mediated, caveolae-mediated, and macropinocytosis, all of which are influenced by particle size, shape, and surface charge (Behzadi et al., 2017). Passive targeting via the EPR effect enhances accumulation in tumour tissues, whereas active targeting with peptide or antibody ligands that bind specific receptors improves selective internalisation by tumour cells (Shi et al., 2017a). Dual-targeting approaches that combine both mechanisms demonstrate increased specificity and penetration into heterogeneous tumour tissues, thereby improving the therapeutic ratio while minimising off-target effects (Yin et al., 2020). These findings underscore the importance of a comprehensive understanding of biological interactions and appropriate targeting strategies for designing effective drug delivery systems.

The evidence underscores that biological interactions are fundamental, rather than peripheral, determinants of polymeric nanoparticle efficacy. The formation of the protein corona functions as a biological "mask," modulating recognition by phagocytes and target cells, thereby either facilitating or hindering intended targeting mechanisms. Consequently, precise surface engineering is essential to reduce nonspecific opsonisation while preserving the activity of targeting ligands. Cellular internalisation pathways are influenced by nanoparticle physicochemical properties, suggesting that design strategies must account for these biological preferences to optimise uptake. Complementary targeting strategies, combining passive EPR-mediated localisation with receptor-specific active targeting, enhance tumour accumulation and selective internalisation, thereby improving therapeutic specificity. While these studies convincingly demonstrate the critical role of the protein corona and dual-targeting approaches, limitations persist, particularly the dynamic and complex nature of corona formation in vivo, incomplete understanding of ligand-corona interactions, and the predominant focus on specific cell lines or tumour models, which may constrain the generalizability of findings across heterogeneous human tissues.

3. Therapeutic Effectiveness and Clinical Applications

The therapeutic effectiveness of polymeric nanoparticles in cancer therapy is largely determined by their ability to enhance drug accumulation in target cells and trigger desired apoptotic pathways, thereby inhibiting tumour cell proliferation more efficiently than free drug administration. Proper nanoparticle design enhances drug penetration into tumour tissues by increasing localised delivery and strengthening apoptosis induction via oxidative stress and caspase pathways (Herdiana et al., 2023). Controlled release kinetics within nanoparticle systems ensure prolonged therapeutic exposure, reducing dosing frequency without compromising efficacy (Mengesha, 2024). Preclinical studies indicate that such strategies reduce systemic toxicity while improving the therapeutic index of anticancer agents, particularly in intensive chemotherapy regimens (Wang et al., 2018). Therefore, the clinical effectiveness of polymeric nanoparticles in inducing cytotoxicity and apoptosis in cancer cells has become a critical validation of their role in modern oncology.

Integration of polymeric nanoparticles with other therapeutic modalities, such as chemotherapy and radiotherapy, can generate significant therapeutic synergy, thereby improving clinical outcomes for cancer patients. Co-delivery of multiple therapeutic agents within a single nanoparticle enables simultaneous targeting of distinct molecular pathways, enhancing treatment response and overcoming common drug resistance mechanisms (Zhang et al., 2016). Additionally, nanoparticles designed as radiosensitizers increase tumour cell sensitivity to radiation, allowing for dose reduction without sacrificing efficacy (Rosa et al., 2017). This approach also enables real-time monitoring of therapeutic responses through nanotheranostics, which combine diagnostic and therapeutic functions, thereby opening avenues for personalised and adaptive treatment strategies based on patient-specific responses (Chen et al., 2017). Collectively, these clinical applications highlight the substantial potential of polymeric nanoparticles to advance multimodal therapy strategies while improving patient outcomes and safety.

A critical synthesis of the current evidence indicates that the therapeutic efficacy of polymeric nanoparticles (PNPs) in oncology is inherently multifactorial. These nanocarriers enhance intratumoral drug accumulation and selectively trigger apoptosis, providing greater precision compared to conventional chemotherapeutics. Key design attributes, including controlled release kinetics, surface functionalization, and polymer composition, facilitate sustained drug exposure, optimise pharmacodynamic responses, and reduce off-target toxicity. Moreover, integration with multimodal treatment strategies, such as co-delivery of multiple agents, radiosensitisation, and nanotheranostic approaches, exploits synergistic mechanisms that improve tumour response, overcome drug resistance, and enable adaptive, patient-specific interventions. Notwithstanding these advantages, the majority of studies remain preclinical, and interspecies variations in tumour biology, pharmacokinetics, and nanoparticle biodistribution may constrain clinical translation. Additional concerns include potential long-term toxicity, immunogenicity, and variability in uptake due to tumour heterogeneity. Overall, while PNPs demonstrate substantial promise as active modulators of cancer therapy, further research is required to validate their safety, efficacy, and clinical applicability in human patients (Figure 4).

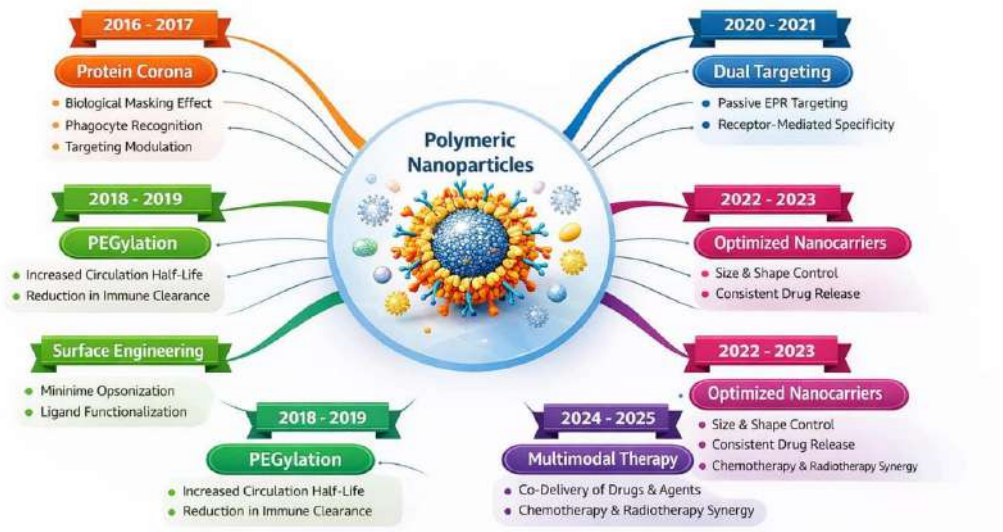

Figure 4. Evolution of Polymeric Nanoparticle Design and Therapeutic Strategies from 2016 to 2025

Since 2016–2017, research on polymeric nanoparticles has emphasized the importance of physicochemical properties such as particle size, surface charge, and morphology, which influence drug

delivery, tumor accumulation through the Enhanced Permeability and Retention (EPR) effect, and cellular internalization via clathrin-, caveolae-, and macropinocytosis-mediated pathways, with surface strategies such as PEGylation and passive or ligand-mediated active targeting to enhance therapeutic effects through apoptosis and cytotoxicity. During 2018–2019, the focus shifted to formulation reproducibility using nanoprecipitation and emulsion techniques, improving bioavailability, reducing off-target toxicity, and examining the impact of the protein corona on biodistribution and tumour specificity. In 2020–2021, studies implemented dual-targeting approaches, heterogeneous tumour tissue penetration, and the integration of synergistic multimodal therapies, while protein corona dynamics influenced targeting efficacy. Between 2022 and 2023, research focused on advanced physicochemical optimization, polymer selection (e.g., PLGA and pH-responsive copolymers), enhanced biological interactions (including immune modulation), and improved therapeutic outcomes through apoptosis pathways, oxidative stress, and caspase activation. By 2024–2025, the focus shifted to controlled drug release and pharmacodynamics, nanotheranostics for real-time monitoring and personalised therapy, and radiosensitisation to optimise radiation doses, collectively aiming to bridge preclinical findings to patient-specific clinical applications, reflecting the evolution of research from fundamental nanoparticle characteristics to therapeutic clinical relevance.

4. CONCLUSION AND RECOMMENDATION

Based on the analysis and evaluation of current studies, it can be concluded that polymeric nanoparticles (PNPs) hold significant potential in enhancing drug delivery efficiency and cancer therapy through multidimensional mechanisms, where physicochemical properties such as particle size, surface charge, morphology, and surface modifications collectively influence systemic biodistribution, tumour accumulation, and drug release kinetics. Biological interactions, including protein corona formation and passive/active targeting mechanisms, determine cellular internalization specificity and the therapeutic ratio. At the same time, integration of PNPs with multimodal therapies, such as combination chemotherapy, radiosensitization, and nanotheranostics, demonstrates synergistic effects that improve tumour response, overcome drug resistance, and enable adaptive, patient-specific treatment strategies. However, most studies remain in vitro or preclinical, limiting generalizability to humans; the dynamic nature of protein corona formation in vivo is not fully understood; the interplay between corona composition and targeting ligands affecting cellular uptake requires further exploration; and research has predominantly focused on spherical particles, leaving the potential of anisotropic geometries and tumour microenvironment heterogeneity largely unexplored. Therefore, urgent research directions include evaluating PNPs in more clinically relevant preclinical models, developing anisotropic nanoparticles to enhance specificity and tumour penetration, integrating PNPs with multimodal therapies in the context of real tumour heterogeneity, and investigating long-term safety and immunogenicity to support clinical translation, ultimately bridging the gap between preclinical evidence and human application and maximising the potential of PNPs in personalized and multimodal cancer therapy.

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