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# EMERGING INNOVATIONS IN POLYMER-BASED DRUG DELIVERY SYSTEMS FOR TARGETED CANCER THERAPY: A COMPREHENSIVE REVIEW

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## Abstract

*Recent advancements in nanotechnology have opened new frontiers in the treatment of complex diseases, particularly cancer. Among these, nanotechnology-based drug delivery systems (DDSs) have shown significant promise in enhancing the therapeutic efficacy and safety of anticancer agents. One of the primary advantages of these systems is their ability to mitigate the adverse side effects typically associated with conventional chemotherapy. This is achieved through the use of controlled and targeted drug delivery mechanisms that improve drug localization at the tumor site while minimizing systemic toxicity.*

*Polymeric materials have emerged as highly versatile and effective carriers in the design of DDSs, owing to their favorable characteristics such as improved pharmacokinetics, extended circulation time in the bloodstream, biocompatibility, and biodegradability. These properties make polymers especially suitable for delivering chemotherapeutic agents in a more efficient and patient-friendly manner.*

*The objective of this systematic review was to assess and synthesize the current state of research on polymer-based DDSs employed in cancer therapy, with a particular focus on their therapeutic potential and clinical relevance. The review included studies published up to November 2021, without imposing any time restrictions. Relevant literature was identified through an extensive search of both English and Persian language databases, including SID, MagIran, Scopus, Web of Science (WoS), PubMed, ScienceDirect, and Google Scholar.*

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*The search strategy utilized a comprehensive set of keywords such as "drug delivery system," "anticancer agent," "polymeric nanostructure-based drug delivery," "polymer-based drug delivery," and "polymeric system." Analysis of the collected studies revealed that polymeric nanoparticles (PNPs) play a pivotal role in improving the therapeutic outcomes of cancer treatment. Compared to traditional chemotherapy approaches, PNPs offer several advantages: they significantly lower the cytotoxic effects of chemotherapeutic drugs on healthy tissues, enhance the aqueous solubility of poorly soluble drugs, and effectively suppress tumor growth.*

*In conclusion, polymeric nanoparticle-based DDSs represent a transformative approach in the field of oncology, offering a promising pathway to more precise, effective, and less harmful cancer treatments.*

## INTRODUCTION

The development of new pharmaceutical agents is inherently complex, costly, and time-intensive. Despite ongoing progress, many recently developed drugs fail to demonstrate effective performance in clinical trials due to limitations in stability, solubility, and targeted delivery. Conventional therapeutic approaches often result in drugs being rapidly degraded or absorbed in healthy tissues before reaching their intended targets, which can cause severe side effects and reduce overall treatment efficacy.

Traditional drug formulations are generally characterized by low stability, high toxicity, and transient therapeutic effects. Furthermore, many therapeutic agents suffer from poor water solubility, hindering their bioavailability and limiting their clinical utility [1,2]. The ultimate success of a drug therapy depends not only on the biochemical properties of the active pharmaceutical ingredients but also on the precision of their release and delivery mechanisms. In response to these challenges, modern drug delivery systems (DDSs) have emerged as an innovative solution aimed at achieving controlled, site-specific, and time-regulated drug release. These advanced systems offer the ability to load drugs onto specialized carriers, directing them precisely to pathological areas within the body. This strategic targeting allows the active ingredients to interact directly with diseased tissues, minimizing exposure to healthy cells and enhancing therapeutic outcomes.

Unlike conventional methods, DDSs offer remarkable control over the timing, dosage, and localization of drug release. Through this method, drugs are encapsulated within carriers—such as nanoparticles—that transport the therapeutic agents to targeted areas. Once there, the drug is gradually released into the extracellular matrix, allowing for more effective interaction with diseased cells and tissues. The result is an increase in treatment efficiency and patient confidence, driven by improved therapeutic precision and fewer side effects [3–5].

Drug delivery systems typically involve a carrier or transporter capable of delivering therapeutic compounds directly to specific tissues or organs. Among the most promising advances in this area is the use of synthetic polymers as drug carriers—a field that represents a rapidly growing focus of biomedical research in both the pharmaceutical industry and academic settings. These polymer-based carriers can significantly enhance drug efficacy while simultaneously reducing toxicity.

Various types of nanocarriers, including liposomes, micelles, and polymeric nanoparticles (PNPs), have garnered attention due to their ability to encapsulate a broad spectrum of therapeutic and diagnostic agents [6,7]. Over the past two decades, the field has witnessed remarkable progress in the design and application of biodegradable polymers for biomedical uses. These materials are particularly favored for constructing medical devices such as temporary

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prosthetics, scaffolds for tissue engineering, and controlled-release drug carriers.

Biodegradable polymers offer the necessary physical, chemical, and biological properties required for therapeutic applications. Their structural integrity, mechanical strength, and hydrolytic degradation capabilities make them ideal for short-term biomedical applications. Consequently, a wide variety of natural and synthetic polymers have been studied for their suitability in this context [8]. Polymers represent the largest group of biomaterials, prized for their viscosity, flexibility, and mechanical resilience [9].

The use of synthetic biodegradable polymers in medicine dates back to the 1960s and 1970s, when materials such as polyglycolic acid (PGA), polylactic acid (PLA), and their copolymer PLGA were first introduced for the production of biodegradable surgical sutures [10]. These polymers are now recognized for their high biodegradability, efficient drug encapsulation, controlled release profiles, and minimal toxicity—making them ideal candidates for developing next-generation DDSs [11].

The encapsulation efficiency of nanodrugs depends on the characteristics of the carrier, such as its biodegradability, compatibility with the drug, and stability during storage. Among various nano-carrier platforms, PNPs are considered the most advanced due to their superior encapsulation capabilities and controlled release mechanisms. Compared to conventional therapies, nanodrug formulations offer enhanced stability, extended-release duration, and site-specific delivery [12].

Some of the most commonly utilized PNPs include polycaprolactone (PCL), PLA, PLGA, chitosan, and gelatin. These polymers provide distinct advantages in terms of drug synthesis, encapsulation efficiency, disease-specific targeting, and absorption within the body. Their biocompatibility and ability to degrade naturally make them especially valuable for medical use [13].

One of the most promising applications of PNPs lies in their ability to effectively accumulate in tumor tissues, making them a powerful tool in the targeted treatment of cancer. Due to their ability to enhance drug solubility, prolong circulation time, and minimize systemic side effects, polymer-based DDSs have become an essential strategy in modern cancer therapy [14].

In light of these developments, this systematic review aims to explore and synthesize the existing research on polymer-based drug delivery systems, specifically focusing on their applications in anticancer treatments. By compiling and analyzing a broad range of studies, this review seeks to provide a comprehensive understanding of the field and promote the implementation of high-quality, evidence-based approaches in polymeric DDS design and application.

## Methods

This systematic review, conducted in 2021, focused on evaluating the role and effectiveness of polymer-based drug delivery systems (DDSs) in the treatment of cancer. The study followed a comprehensive and structured search strategy to gather relevant literature from both English and Persian sources, aiming to include a wide spectrum of scholarly perspectives and evidence.

A detailed search was carried out across multiple electronic databases, including **Scientific Information Database (SID)**, **Web of Science (WoS)**, **PubMed**, **Scopus**, **ScienceDirect**, **MagIran**, and **Google Scholar**. The search was designed to retrieve studies published up until **October 2021**, with no time restrictions applied. Both English- and Persian-language articles were considered to ensure inclusivity and depth in the review.

To construct a robust and inclusive search protocol, the following keywords and their variations were employed: *"drug delivery system," "anticancer agent," "polymer nanostructure-based drug delivery," "polymer-based drug delivery,"* and *"polymer system."* Boolean operators such as **AND**, **OR**, and **NOT** were systematically utilized to refine and expand the search queries as appropriate. In addition to database searches, the reference lists of identified articles were manually reviewed to discover further relevant studies not captured through the initial queries.

### Inclusion Criteria

Studies were selected for inclusion based on the following eligibility parameters:

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- Published in either **English or Persian** up to **October 2021**.
- The presence of the term *"polymer system"* in either the **title** or **abstract**.
- Focused on polymer-based drug delivery systems designed for **anticancer agents**.
- **Intervention studies** involving cancer patients treated with polymer-based drugs, as well as studies including healthy control groups or patients treated using non-polymeric strategies.
- Availability of **full-text articles**.
- Research within the broader domain of **cancer therapy and drug delivery**.
- Inclusion of **clinical trials**, observational studies, or experimental research.

**Exclusion Criteria**

Studies were excluded if they:

- Were **not aligned** with the core objectives of this review.
- Comprised **conference abstracts, editorials, or letters to the editor**.
- Were published in **languages other than English or Persian**.
- Were **duplicates** or **lacked full-text access**.
- Did not focus on polymer-based systems or anticancer applications.

**PubMed Search Strategy**

A targeted search on **PubMed** was formulated using **Medical Subject Headings (MeSH)** and keyword terms structured around title and abstract fields. The advanced query was designed to maximize specificity and sensitivity, using nested Boolean logic to include various synonyms and related terms:

("drug delivery system"[Title/Abstract]) OR ("Drug Targeting"[Title/Abstract])) OR ("Drug Administration Routes"[Title/Abstract])) OR ("Drug Carriers"[Title/Abstract])) AND ("Antineoplastic Agents"[Title/Abstract])) OR ("Anticancer Agent"[Title/Abstract])) OR ("Antineoplastic Agent"[Title/Abstract])) OR ("Antineoplastic Drug"[Title/Abstract])) OR ("Antitumor Agents"[Title/Abstract])) OR ("Antitumor Drugs"[Title/Abstract])) OR ("Chemotherapeutic Anticancer Agents"[Title/Abstract])) OR ("Chemotherapeutic Anticancer Drug"[Title/Abstract])) AND ("polymer nanostructure-based drug delivery"[Title/Abstract])) OR ("polymer-based drug delivery"[Title/Abstract])) OR ("polymer system"[Title/Abstract])).

**Study Selection and Quality Assessment**

Two independent reviewers were responsible for screening the titles and abstracts of all retrieved articles. Studies that did not meet the inclusion criteria were excluded from further review. In cases where discrepancies arose between the two reviewers regarding article eligibility, a third reviewer was consulted to resolve the conflict through consensus.

Following the selection process, eligible full-text articles were subjected to a **qualitative methodological assessment**. The **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)** framework was rigorously applied throughout the entire review process. This included the definition of the research question, systematic data extraction, and comprehensive analysis of the results [15].

By adhering to this systematic and transparent approach, the review aimed to provide a robust and credible synthesis of current knowledge regarding polymer-based drug delivery systems in the treatment of cancer.

**Qualitative assessment of studies**

The methodological quality and reliability of the included full-text articles were rigorously evaluated by two independent experts using standardized tools to ensure the validity of findings and minimize bias. One of the primary instruments employed for this purpose was the CONSORT 2010 checklist, which is specifically designed for the appraisal of clinical trial studies [16]. This checklist comprises 25 sub-items, each focusing on a critical aspect of trial design, implementation, analysis, and reporting. The items assess various features, including randomization procedures, blinding, statistical methods, and outcome reporting.

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Each sub-item on the CONSORT checklist was scored dichotomously: a value of 1 was assigned if the criterion was met (i.e., item approved), and 0 if it was not (i.e., item disapproved). Thus, the total quality score for each article could range from 0 to 25, with higher scores indicating better methodological quality. The first reviewer independently assessed all eligible studies using this checklist. In cases where discrepancies in scoring arose between the two reviewers, further discussion and reevaluation were undertaken to reach a consensus and ensure consistency in quality evaluation.

In addition to the CONSORT checklist, the Joanna Briggs Institute (JBI) critical appraisal tool was utilized to assess studies that employed case series designs, offering a complementary approach to evaluating the overall quality of the evidence base. The JBI tool is structured around 11 key questions that are intended to evaluate the internal validity and risk of bias within case series research. These questions address potential confounding factors, participant selection bias, information bias, and the clarity of outcome reporting—key concerns in non-randomized designs.

Each item in the JBI checklist was reviewed carefully, and responses were recorded as "Yes," "No," or "Unclear", based on the presence or absence of adequate information. An additional response option, "Not Applicable (NA)," was also available for specific cases where the item did not pertain to the study in question. This flexibility ensures that only relevant criteria are used in appraising each study, thereby enhancing the accuracy of the quality assessment [17].

By employing both the CONSORT 2010 and JBI critical appraisal tools, this systematic review ensured a robust evaluation of the included literature. These tools helped identify studies with sound methodology and minimize the risk of bias, contributing to the reliability and credibility of the review's conclusions.

**Data extraction**

To ensure consistency and completeness in the collection of relevant information, data extraction was conducted using a structured and pre-designed checklist tailored for this systematic review. The checklist was developed to capture all essential study characteristics and outcomes relevant to the research objectives.

Key data elements extracted from each selected study included the following:

- Study title
- First author's name
- Year of publication
- Geographical location or country where the study was conducted
- Study design or methodology employed (e.g., clinical trial, case series, in vitro, in vivo)
- Type of cancer targeted by the drug delivery system
- Therapeutic agent(s) loaded into the delivery system (e.g., chemotherapeutic drugs, natural compounds, biological molecules)
- Type of polymer or polymeric system used as the drug carrier (e.g., PLGA, chitosan, polycaprolactone)
- Primary outcomes and measured variables (e.g., drug release rate, cytotoxicity, tumor reduction)
- Key findings and conclusions drawn by the study authors

This comprehensive extraction approach enabled a detailed analysis of both the technological aspects of the polymer-based drug delivery systems and their therapeutic efficacy in the context of cancer treatment.

Following the screening and quality assessment procedures, a total of 72 studies met all inclusion criteria and were included in the final synthesis of this review. These studies are summarized and detailed in Table 1, providing an overview of the various polymeric drug delivery platforms investigated, the types of cancers addressed, and the outcomes achieved.

**Results**

As illustrated in Figure 1, a comprehensive and systematic search across seven electronic databases yielded a total of 1,510 articles. After the initial screening process, 908 duplicate entries were identified and subsequently removed. The remaining 602 articles underwent a preliminary evaluation based on their titles and abstracts, using

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predefined inclusion and exclusion criteria. Following this screening stage, 340 studies were shortlisted for a full-text review. After a detailed examination aligned with the inclusion and exclusion parameters, the methodological quality of 71 studies was confirmed through the CONSORT (Consolidated Standards of Reporting Trials) checklist. The selected studies comprised both *in vitro* and *in vivo* research investigations.

Geographical distribution of the included studies revealed that 19 were conducted in India [22,23,30,33,40,41,46,54,57,59,67,69,70,72,73,75,85,86,88], followed by 18 studies originating from China [18,24,29,35,38,44,47,50,53,60,61,63,65,71,74,77,78,80]. The United States contributed 10 studies [20,28,37,42,49,51,68,84,87], while Iran accounted for 6 publications [19,27,48,79,81,82]. Additionally, three studies each were from Egypt [43,58,83] and Canada [39,45,66], and two each from Korea [34,54], France [21,62], and Japan [36,76]. Other countries with a single publication included Saudi Arabia [25], Qatar [26], Finland [31], the United Kingdom [32], Taiwan [64], and Italy [52].

In terms of application, the reviewed studies predominantly focused on polymer-based drug delivery systems developed for anticancer therapies. Among the 71 studies, 52 investigations were specifically related to breast cancer [18–23,25–28,30–34,37,38,41–44,46,48,49,51–53,56,58–61,63,65–67,69,70,72,73,75,77–79,81–83,85–88], followed by 11 focused on brain cancer [29,35,39,40,45,50,55,57,62,68,74], and 6 on liver cancer [24,36,47,64,71,76]. Two studies did not clearly identify the type of cancer being treated [80,84].

A diverse range of methodologies was employed in the development of DDSs, highlighting the innovation in this field. The techniques used included: reversible addition-fragmentation chain-transfer (RAFT) polymerization, nanoprecipitation, solvent displacement, solvent evaporation, single emulsion solvent evaporation, desolvation, double emulsion diffusion evaporation, emulsion solvent diffusion, basic and modified emulsion methods, multiple and modified solvent evaporation techniques, modified solvent extraction/evaporation, mini-emulsion polymerization, chemical reaction and conjugation processes, thin-film hydration, gelation, high-pressure homogenization, nano-emulsification with polymer cross-linking, nano spray drying, ultra-sonication, and hybrid emulsification-ion methods among others. Additionally, specialized approaches like conjugation with reactive oxygen species (ROS)-responsive nanoplatforms and reduction-based fabrication methods were also utilized, indicating a high level of technological advancement.

The findings from this review suggest that biodegradable polymeric nanoparticles (PNPs) present substantial advantages in drug delivery. They have the potential to reduce the required therapeutic dosage while minimizing associated adverse effects. Due to their biocompatibility, flexibility, and ability to degrade harmlessly within the body, PNPs have emerged as a favored platform for novel DDS development. These nanoparticles are particularly advantageous for delivering hydrophobic drugs, which typically face challenges such as poor solubility, limited bioavailability, and instability in aqueous environments.

Importantly, the nature of the polymeric carrier system is determined by both the specific properties of the target tissue and the characteristics of the drug being delivered. Studies consistently demonstrated that nanoparticles enhance drug release control, thereby mitigating potential side effects. The increasing interest in PNPs is also due to their ability to encapsulate drugs at high concentrations, protect active pharmaceutical ingredients from premature degradation, and provide sustained release over extended periods.

Both biodegradable and non-biodegradable polymers have been employed in PNP fabrication. However, the former is especially attractive for therapeutic use owing to its safety profile and long-term release capabilities. Notably, several polymer-based nanoparticle formulations have already achieved clinical and commercial success, reinforcing the critical role of PNPs in advancing

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cancer treatment through innovative drug delivery systems.

**Discussion**

This systematic review critically evaluated the findings of 71 preclinical (*in vitro*) and animal-based (*in vivo*) investigations centered on the application of polymer-based nanocarrier drug delivery systems (DDSs) in cancer therapy. The studies included in this analysis were published between 1999 and 2021 and were found to be of medium to high methodological quality. Although numerous individual studies have explored polymeric nanoparticles (PNPs) as promising carriers in oncological treatment, a comprehensive, systematic evaluation within this specific research domain has been largely lacking until now.

In the past two decades, the role of nanotechnology in clinical research and therapeutic development has significantly expanded. Nanoparticles are now increasingly engineered to address critical shortcomings of conventional drug therapies, such as poor solubility, rapid metabolism, systemic toxicity, and the inability to traverse complex biological barriers. These nanocarriers are being designed to facilitate more precise, targeted drug release by adapting to the heterogeneity of tissues, diseases, and individual patient responses. With the continuous evolution of lipid-based, inorganic, and polymeric nanoparticles, a shift towards personalized and precision medicine is now more attainable than ever [89].

Among the various nanomaterials explored, polymers have emerged as particularly versatile candidates due to their inherent tunability and diverse biomedical potential. Both natural and synthetic polymers offer a wide spectrum of physicochemical and biological properties conducive to drug delivery, including flexibility, biodegradability, biocompatibility, hydrophobic or amphiphilic character, porosity, hydrogel-forming ability, and mechanical strength. These features enable PNPs to act as a functional bridge between materials science and pharmacology, thereby contributing to the creation of more effective and safer DDSs.

Polymeric nanoparticles can be customized at the molecular level to meet specific therapeutic goals, such as controlled drug release, enhanced tissue penetration, and reduced off-target toxicity. Their adaptability makes them suitable for addressing one of the central challenges in modern pharmaceutics: the safe and efficient delivery of therapeutic agents to target sites in the body. In this context, PNPs are regarded as one of the most promising tools for overcoming traditional limitations in drug delivery science [89–91].

Despite their advantages, certain limitations are associated with natural polymer use in clinical settings. These include challenges related to poor solubility in water or organic solvents, low viscosity, and mechanical instability. To enhance their functionality, biodegradable polymers—especially polysaccharides-are often chemically and physically modified. Physical modification techniques may involve changes in temperature, pressure, humidity, or exposure to radiation. In contrast, chemical modification processes, which are more commonly employed, include reactions such as etherification, esterification, oxidation, crosslinking, and graft copolymerization of hydroxyl-containing groups. Among these, chemical modifications are particularly favored for their ability to precisely tailor the physicochemical behavior of the polymers to specific biomedical needs [92,93].

In conclusion, this review underscores the growing importance of polymer-based nanocarriers in advancing targeted cancer therapies. As research continues to refine the properties and delivery mechanisms of PNPs, their integration into routine clinical practice appears increasingly viable, especially within the framework of individualized medicine.

**DDSs and breast cancer**

Breast cancer remains the most frequently diagnosed malignancy among women worldwide [94]. According to Hao et al., targeted drug delivery systems (T-DDSs) demonstrated excellent biocompatibility, as evidenced by MTT assays, hemolysis evaluations, and cellular uptake studies. These systems were shown to effectively reduce the viability of breast cancer cell lines, including 4T1

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and MCF-7, without causing notable cytotoxic effects on endothelial cells. Additionally, they exhibited potent antitumor activity in vivo [95].

Polymeric drug carriers have gained substantial attention in treating both primary and metastatic breast cancer. One study revealed that a polymer functionalized with a folate ligand (PFTTQ) was able to selectively inhibit folate receptor-positive (FR+) tumor cells in a xenograft model using FR+ breast cancer-bearing mice following intravenous administration. Another strategy using PLGA-b-PEG nanoparticles successfully delivered antisense microRNAs targeting the uPA receptor in triple-negative breast cancer (TNBC). In MDA-MB-231 TNBC cells, levels of miR-21 were found to be significantly elevated compared to miR-10b when treated with PLGA-b-PEG nanocarriers. A combination of miR-21 and miR-10b in these nanocarriers significantly reduced tumor progression [96].

Tao et al. highlighted that a star-shaped M-PLGA-TPGS polymer structure had superior drug loading capacity and encapsulation efficiency compared to its linear counterparts. In vivo experiments demonstrated that M-PLGA-TPGS nanoparticles encapsulating docetaxel achieved the highest levels of tumor suppression. These findings support the potential of M-PLGA-TPGS as a novel nanoformulation for breast cancer therapy [18], a conclusion also affirmed by Kelishady [19] and Bressler.

Despite the advantages of PLGA-PEG nanoparticles in enhancing circulation time and preventing drug aggregation, one limitation is their nonspecific accumulation in off-target tissues. Therefore, targeted drug delivery systems that offer high specificity with minimal systemic toxicity are crucial for the effective treatment of solid tumors [20].

Massadeh's research optimized anastrozole-loaded polymeric lipid nanoparticles (PLNPs) to achieve a particle size below 200 nm, high encapsulation efficiency (~80%), and strong stability. These PLNPs induced more pronounced apoptotic effects in breast cancer cells compared to the free drug, highlighting their potential to enhance anastrozole's therapeutic profile and warranting further in vivo investigation [25]. Similar observations were reported by Alemrayat [26].

Tang's study demonstrated that CA-PLA-TPGS nanoparticles possess superior antitumor activity, both in vitro and in vivo, when compared to PLA-TPGS and PLGA formulations. The inclusion of a star-shaped cholic acid core within the PLA-TPGS copolymer makes this nanoparticle system a promising strategy for breast cancer treatment [28].

Zhao et al. reported that rapamycin-loaded hyaluronic acid-based nanoparticles significantly improved survival outcomes in Balb/c mice bearing CD44+ 4T1.2neu tumors. These particles effectively suppressed tumor progression and reduced lung metastasis [30].

In another study, Jadon et al. investigated lipid–polymer hybrid nanoparticles loaded with docetaxel (LPHNPs-DTX), which showed enhanced cellular uptake and cytotoxicity against breast cancer cell lines, along with a lower IC50 value. Flow cytometry confirmed increased apoptosis, while pharmacokinetic studies revealed improved tumor-targeting capabilities and reduced nonspecific distribution compared to free docetaxel. Moreover, LPHNPs-DTX significantly decreased tumor electrical charge in vivo [33]. Chen's findings were consistent, showing enhanced intracellular uptake and cytotoxicity of similar nanoparticle systems [34].

**DDSs and brain cancer**

Cerebral metastases represent a life-threatening condition with limited therapeutic options and generally poor prognosis [97]. While systemic chemotherapy can address metastatic breast cancer, its efficacy is significantly diminished when it comes to brain metastases due to the restrictive nature of the blood-brain barrier (BBB) [98]. The BBB is composed of tightly connected endothelial cells lining cerebral blood vessels, which form a selective barrier that prevents large molecules and many biologically active substances from entering the brain tissue.

Despite these limitations, advancements in polymer-based drug delivery systems have paved the way for potential solutions aimed at crossing the BBB. Several targeting ligands, including

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lactoferrin [99], transferrin [100-110], and carbon nanotubes [101], have shown promise in facilitating the transport of therapeutic agents across this barrier.

Chunsheng He and colleagues developed an amphiphilic polymer-lipid nanoparticle (NP) system capable of traversing the BBB to deliver the chemotherapeutic agent docetaxel (DTX) for the treatment of triple-negative breast cancer (TNBC). Their findings confirmed the successful delivery of DTX to brain tissues via these nanoparticles. Moreover, ex-vivo fluorescence imaging was employed to effectively monitor cerebral drug distribution, suggesting it as a practical method for rapid assessment. Notably, treatment with the DTX-loaded nanoparticles resulted in an elevenfold decrease in tumor volume and a 94% improvement in mean survival time, with no detectable histological damage compared to treatment with an equivalent dose of the conventional formulation, Taxotere [80].

Consistent results were obtained by Zhang et al., who demonstrated that polyphosphate-based hybrid micelles could enhance brain drug delivery and improve survival rates in glioma-bearing mice. Their study concluded that transferrin-conjugated micelles may serve as effective vehicles for delivering drugs to the brain [29].

Further supporting evidence comes from the work of Hai He, where the application of specific nanocarriers showed reduced cytotoxicity while effectively inhibiting the proliferation of glioma C6 cells [35]. Another investigation demonstrated that nanoparticles loaded with doxorubicin (Dox) significantly suppressed brain tumor growth in vivo compared to the same dose of free Dox. These findings, supported by bioluminescence imaging of brain metastases, reinforce the potential of multifunctional nanocarriers as promising therapeutic tools for treating brain tumors [39].

Additionally, multiple studies have indicated that polymer-based drug delivery systems (DDSs) can enhance the rate of drug transport across the BBB, increase cellular uptake, and provide greater tumor suppression efficacy [29, 40, 50, 55, 57, 62, 74].

**DDSs and liver cancer**

Hepatocellular carcinoma (HCC), a primary malignancy originating from hepatocytes, is predominantly linked to chronic liver inflammation and infections caused by hepatitis B and C viruses [102,103]. Given the strong correlation between hepatitis B virus (HBV) and the onset of liver cancer, the development and global implementation of the hepatitis B vaccine occurred rapidly. Despite its widespread use, research has indicated that the vaccine does not fully protect against virus-induced inflammation or the subsequent development of liver-related conditions such as cirrhosis and HCC [104].

To enhance preventive strategies against hepatic cancers, polymer-based delivery platforms are being explored for vaccine and drug delivery purposes. Nanoparticles composed of drug-polymer conjugates have demonstrated promise in improving the delivery of hepatitis antigens, thereby triggering robust immune responses aimed at preventing liver cancer. For instance, multifunctional polymeric micelles incorporating folate and SPIODOX have shown increased specificity in targeting liver cancer cells in vitro compared to non-targeted micelles. The targeting efficiency of these micelles can be evaluated using standard clinical MRI imaging tools [71].

Additionally, Hashida et al. developed galactose-modified PLGA (galactosylated PLGA) carriers, which demonstrated a strong ability to selectively target hepatocytes [76]. In related work by Liang and colleagues, the injection of Gal-P/NPs resulted in the most significant tumor size reduction among treatment groups. This effect was attributed to the accumulation of Gal-P/NPs at the tumor site, where they released paclitaxel to suppress tumor proliferation. The study confirmed that Gal-P/NPs engage in ligand-receptor interactions that provide specific targeting to liver tumors. Consequently, Gal-P/NPs were identified as a promising drug delivery system (DDS) for targeted liver cancer therapy [64, 104-107].

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**Table 1** Information extracted from studies reviewed in a systematic review.

| Sr. # | Author (Year) | Study Location | Drug(s) Incorporated | Polymer Type | Study Method | Cancer Type | Main Findings |
|---|---|---|---|---|---|---|---|
| 1 | Tao et al. (2013) | China | Docetaxel | Star-shaped PLGA-mannitol core + TPGS | In vitro, In vivo | Breast | Effective breast cancer therapy using docetaxel-loaded polymeric nanoparticles. |
| 2 | Kelishadi et al. (2014) | Iran | Paclitaxel, Lapatinib | Pluronic F127 | In vitro, In vivo | Breast | Enhanced treatment for drug-resistant metastatic breast cancer. |
| 3 | Bressler et al. (2018) | USA | AXT050 (collagen-IV mimic) | PLGA-PEG | In vitro, In vivo | Breast | Improved anticancer effects in triple-negative breast cancer using biomimetic nanoparticle targeting. |
| 4 | Nicolas et al. (2018) | France | Calcitriol | PLA | In vitro, In vivo | Breast | Prolonged and sustained anticancer activity observed; higher treatment efficacy. |
| 5 | Mehata et al. (2018) | India | Docetaxel, Trastuzumab | Chitosan–TPGS | In vitro, In vivo | Breast | Targeted delivery system with reduced toxicity and enhanced drug delivery. |
| 6 | Anzar et al. (2018) | India | Simvastatin | PLGA | In vitro, In vivo | Breast | Demonstrated potential for solid tumor treatment using spray-dried submicron particles. |
| 7 | Huang et al. (2010) | China | Doxorubicin | GA–PEG–PBLG + Chitosan | In vitro, In vivo | Liver | Promising liver-targeted therapy via GA-modified micelles. |
| 8 | Massadeh et al. (2020) | Saudi Arabia | Anastrozole | Polycaprolactone, PEG, Stearic acid | In vitro | Breast | Improved anticancer potential via optimized hybrid polymer-lipid nanoparticles. |
| 9 | Alemrayat et al. (2018) | Qatar | Letrozole | PLA | In vitro, In vivo | Breast | Developed for hormone-positive breast cancer in postmenopausal women. |
| 10 | Zeighamian et al. (2014) | Iran | Curcumin | PNIPAAm-MAA | In vitro | Breast | Demonstrated anticancer activity against MCF-7 breast cancer cells. |
| 11 | Tang et al. (2013) | USA | Paclitaxel | PLA-TPGS (Cholic acid core) | In vitro, In vivo | Breast | Promising results for breast cancer therapy via targeted delivery system. |

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|---|---|---|---|---|---|---|---|
| **12** | Zhang et al. (2012) | China | Paclitaxel | PCL-PEEP/ Mal-PEG-PCL | In vitro, In vivo | Brain | Enhanced brain targeting via transferrin-conjugated micelles, exploiting BBB receptor ov erexpression. |
| **13** | Zhao et al. (2014) | USA | Rapamycin | Hyaluronic acid/CD44 ligand | In vitro, In vivo | Breast | Targeted and controlled delivery to CD44+ cells for localized breast cancer therapy. |
| **14** | Tahir et al. (2019) | Finland | Doxorubicin | PLGA-based LPHNPs | In vitro, In vivo | Breast | Enabled controlled release of both hydrophilic and lipophilic drugs for improved therapy. |
| **15** | Bhardwaj et al. (2009) | UK | Paclitaxel | PLGA (50:50) + Cationic Surfactant | In vitro, In vivo | Breast | Improved chemotherapeutic efficacy and safety for oral paclitaxel delivery in rats with chemically induced tumors. |
| **16** | Jadon et al. (2019) | India | Docetaxel | Lipid-polymer hybrid nanoparticles (LPHNPs) | In vitro, In vivo | Breast | LPHNP-DTX showed significantly reduced tumor size compared to free docetaxel. |
| **17** | Soe et al. (2019) | South Korea | Doxorubicin | Dox/F127&P123-Tf | In vitro, In vivo | Breast | Transferrin-modified particles successfully targeted resistant cancer cells, overcoming doxorubicin resistance. |
| **18** | He et al. (2011) | China | Doxorubicin | PEGylated PAMAM dendrimer | In vitro | Brain | Enhanced dual-targeted delivery to tumor tissue, improving drug localization. |
| **19** | Kim et al. (2001) | Japan | GalNAc | Poly(N-p-vinylbenzyl-D-glucuronamide) | In vitro | Liver | Unique surface morphology on hepatocytes influenced by polymer concentration and EGF stimulation. |
| **20** | Zubris et al. (2013) | USA | Paclitaxel | Expansile polymer (5-methyl-2-(2,4,6-trimethoxyphenyl)-[1,3]-dioxanylmethyl methacrylate) | In vitro | Breast | Effective treatment observed in breast cancer cells using paclitaxel-loaded expansile nanoparticles. |

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| **21** | He et al. (2015) | China | Paclitaxel | PEG2000-b-PCL2000 Liposomes | In vitro, In vivo | Breast | PEGylated liposomes improved intracellular drug accumulation and therapeutic outcomes in murine models. |
| **22** | Li et al. (2014) | Canada | Doxorubicin | Poly(methacrylic acid) + Polysorbate 80-starch | In vitro, In vivo | Brain (metastatic breast) | Multifunctional delivery system successfully targeted brain metastases of breast cancer across the BBB. |
| **23** | Patel et al. (2016) | India | Paclitaxel | Sialic acid-targeted PPI dendrimers | In vitro, In vivo | Brain | The system showed highest paclitaxel delivery to brain tissue compared to controls. |
| **24** | Panda1 et al. (2019) | India | Docetaxel | PLGA-PEG + Superparamagnetic iron oxide | In vitro, In vivo | Breast | Efficient docetaxel delivery and tumor targeting with magnetic nanoparticle formulation. |
| **25** | Zhou et al. (2017) | USA | Erlotinib + Doxorubicin | PLA-b-PEG | In vitro, In vivo | Breast (Triple Negative) | Sequential co-delivery using this nanocarrier improved therapeutic efficiency. |
| **26** | Gogary et al. (2019) | Egypt | Baicalin | PLGA + Labrafil M2125 CS + Tween 80 + Poloxamer P407 | In vitro | Breast | Nanocapsules showed enhanced anticancer potential and drug delivery performance. |
| **27** | Chen et al. (2011) | China | Vincristine sulfate | PLGA–PEG with folic acid conjugation | In vitro | Breast | Increased cellular uptake and higher cytotoxicity observed in breast cancer cells using folate-targeted nanoparticles. |
| **28** | He et al. (2016) | Canada | Docetaxel | Amphiphilic polymer (PMAA-PS80-g-starch-dodecylamine) | In vivo, In vitro | Brain (TNBC metastases) | Effective brain delivery system with blood-brain barrier permeability and cost-effectiveness compared to conventional approaches. |
| **29** | Maji et al. (2014) | India | Tamoxifen citrate | PLGA | In vitro, In vivo | Breast | Promoted improved drug absorption into breast cancer cells, enhancing therapeutic potential. |
| **30** | Ma et al. (2010) | China | Rhodamine B | Lac-PEG-PLA, PEG-b-P(LA-co-DHP) | In vivo, In vitro | Liver | Lactose-functionalized micelles showed liver-targeting capability with increased uptake in hepatocellular carcinoma cells. |

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| **31** | Talaei et al. (2011) | Iran | Doxorubicin | Thiolated chitosan (N-acetyl cysteine and penicillamine modified) + ASOND | In vitro, In vivo | Breast | Efficient delivery to EGFR-positive breast cancer cells using thiolated chitosan and antisense therapy. |
| **32** | Shenoy et al. (2004) | USA | Tamoxifen | PEO-modified PCL | In vivo | Breast | Demonstrated tumor-specific drug release via in situ surface-modified nanoparticles. |
| **33** | Xu et al. (2016) | China | Curcuminoid | Polysaccharide-based (chitosan, hyaluronic acid, PEG) | In vitro, In vivo | Brain | Lactoferrin-coated nanoparticles effectively penetrated the BBB and accumulated in glioma tissue. |
| **34** | Chowdhury et al. (2017) | USA | Paclitaxel | Polyvinylpyrrolidone, polyethyleneimine, poloxamer 188, others | In vitro | Breast | Developed self-assembled systems to enhance paclitaxel delivery to cancer cells. |
| **35** | Verderio et al. (2012) | Italy | Curcumin | PLGA | In vitro, In vivo | Breast | Induced G2/M arrest in cancer cells; safe and effective formulation to enhance curcumin bioavailability. |
| **36** | Zhou et al. (2014) | China | Aptamer + Vinorelbine | PLGA–PEG–COOH | In vitro | Breast | Aptamer-functionalized nanoparticles (AS1411) improved drug targeting and delivery efficiency in breast cancer cells. |
| **37** | Yang et al. (2007) | South Korea | Doxorubicin | PLGA with antibody-conjugated magnetic nanoparticles | In vitro | Breast | Sustained drug release from magnetic polymer carriers without interference from magnetic nanoparticles. |
| **38** | Fazil et al. (2012) | India | Rivastigmine | Chitosan | In vitro | Brain | Chitosan-based delivery platform shows promise for targeted brain cancer drug transport. |
| **39** | Soni et al. (2015) | India | Paclitaxel and Thymoquinone | PLGA | In vitro | Breast | Co-delivery system exhibited enhanced anticancer effects and reduced paclitaxel-related toxicity. |

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| **40** | Agrawal et al. (2014) | India | Paclitaxel | PLGA/DSPE–PEG conjugated with folic acid | In vitro | Brain | Effective as a dual-delivery strategy to enhance brain-targeted chemotherapy. |
| **41** | Elbaz et al. (2016) | Egypt | Doxorubicin | Polyvinyl alcohol, PEG, and polyvinylpyrrolidone with silver core-shell nanostructure | In vitro | Breast | Combination treatment resulted in superior cytotoxicity against cancer cells. |
| **42** | Vivek et al. (2014) | India | Tamoxifen | PLGA, poly(vinyl alcohol), polyvinylpyrrolidone, and HER2 antibody | In vitro, In vivo | Breast | HER2-conjugated system improved therapeutic efficacy in drug-resistant breast cancer. |
| **43** | Yuan et al. (2017) | China | Curcumin and Doxorubicin | mPEG–PLGA–PGlu (pH-sensitive) | In vitro, In vivo | Breast | Effective for treating heterogeneous and drug-resistant tumors due to dual-drug loading and pH-responsive release. |
| **44** | Zhang et al. (2017) | China | Doxorubicin | Thioketal cross-linked monophosphoryl lipid A-based polymer | In vitro, In vivo | Breast | Targeted delivery and ROS-triggered release resulted in high tumor specificity and minimized systemic toxicity. |
| **45** | Brigger et al. (2002) | France | – | PEG-coated polycyanoacrylate nanospheres | In vivo | Brain | PEGylated nanocarriers demonstrated notable accumulation in healthy brain tissue for tumor targeting. |
| **46** | Mei et al. (2009) | China | Docetaxel | Poly(ε-caprolactone) and Pluronic F68 | In vitro | Breast | Showed potential to overcome multidrug resistance in breast cancer treatment. |
| **47** | Liang et al. (2005) | Taiwan | Paclitaxel | γ-PGA-PLA | In vitro | Liver | Galactose-modified nanoparticles suggested promising liver-specific delivery for liver cancer therapy. |
| **48** | Wu et al. (2015) | China | Simvastatin | Cholic acid-core star-shaped PLGA | In vitro, In vivo | Breast | Nanoparticles offered a novel strategy for simvastatin-based breast cancer therapy. |

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| **49** | Wong et al. (2006) | Canada | Doxorubicin and Elacridar (GG918) | Polymer-lipid hybrid nanoparticles (PLN) | In vitro, In vivo | Breast | Concurrent delivery to a shared intracellular site boosted therapeutic outcomes in multidrug-resistant cancers. |
| **50** | Sun et al. (2007) | Singapore | Taxols | PLGA + montmorillonite multifunctional system | In vitro | Breast | Developed nanocarriers demonstrated multifunctional performance for breast cancer therapy. |
| **51** | Das et al. (2007) | USA (New York) | Trastuzumab, Paclitaxel | Trastuzumab-modified PLGA/MMT nanoparticles | In vitro, In vivo | Breast | Trastuzumab-decorated particles enabled targeted chemotherapy for breast tumors. |
| **52** | Katiyar et al. (2005) | India | Dalargin | Poly(butylcyanoacrylate) (PBCA-NDS) | In vitro, In vivo | Brain | PBCA nanoparticles effectively facilitated oral delivery and brain targeting of peptides. |
| **53** | Varukattu et al. (2015) | India | Rapamycin and Piperine | PLGA | In vitro, In vivo | Breast | Combined piperine and rapamycin nanoparticle system enhanced breast cancer treatment outcomes. |
| **54** | Hong et al. (2018) | China | Doxorubicin | Chitosan-coated Cu(II) oxide nanoparticles | In vitro | Breast | Biocompatible nanoparticles demonstrated potent intracellular DOX delivery and anticancer activity. |
| **55** | Muntimadugu et al. (2015) | India | DOX–SPIO | Folate-PEG-PCL | In vitro | Liver | Folate-modified micelles showed enhanced uptake in hepatic carcinoma cells. |
| **56** | Acharya et al. (2009) | India | Salinomycin and Paclitaxel | PLGA | In vitro, In vivo | Breast | Dual delivery of chemotherapeutics and stem-cell targeting agents minimized cancer recurrence. |
| **57** | Shen et al. (2015) | China | Paclitaxel and Rapamycin | PLGA | In vitro, In vivo | Breast | EGFR-targeted nanoparticle delivery system efficiently targeted resistant breast cancer cells. |
| **58** | Jain et al. (2011) | India | DiR dye | PEG-b-PLA | In vitro, In vivo | Brain | Angiopep-2 conjugated micelles enabled brain-specific drug targeting. |

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| **59** | Hashida et al. (2011) | Japan | Doxorubicin | PLGA 50:50 | In vivo | Breast | Polymeric micelles reduced cardiotoxicity while improving DOX delivery. |
| **60** | Hashida et al. (1999) | Japan | Prostaglandin E1 | Poly-L-glutamic acid, Gal-ED-PLGA, Gal-PLL | In vitro, In vivo | Liver | Galactose-tagged nanoparticles facilitated hepatocyte-specific delivery via sugar-receptor targeting. |
| **61** | Tan et al. (2017) | China | Docetaxel | MPEG2k-PDLLA4k-PLL1k | In vitro, In vivo | Breast | Newly developed MPEG-based micelles showed superior efficacy for docetaxel delivery compared to earlier versions, offering improved tumor inhibition. |
| **62** | Wan et al. (2018) | China | Paclitaxel, Cisplatin | Poly(2-oxazoline) micelles | In vitro, In vivo | Breast | Co-delivery system enhanced drug release, pharmacokinetics, and therapeutic effects for breast and ovarian cancers. |
| **63** | Vakilinezhad et al. (2019) | Iran | Methotrexate, Curcumin | PLGA (Resomer) | In vitro, In vivo | Breast | Co-encapsulation system effectively inhibited tumor progression in both in vitro and animal models. |
| **64** | Zeng et al. (2017) | China | Paclitaxel | Lipid-polymer hybrid (PTX/CXB@LPNP) | In vitro | Not Reported | This synergistic carrier holds potential to combat drug resistance in cancer treatment. |
| **65** | Tavassolian et al. (2014) | Iran | Docetaxel | Poly(L-γ-glutamyl glutamine) | In vitro, In vivo | Breast | Nanoparticles selectively targeted folate receptor-rich tumors, enabling localized drug action. |
| **66** | Anari et al. (2015) | Iran | Chrysin | PLGA-PEG | In vitro | Breast | Demonstrated high therapeutic potential for chrysin delivery in breast cancer models. |
| **67** | Markeb et al. (2016) | Egypt | Paclitaxel | Alginate | In vivo | Breast | Novel alginate-based nanocarrier improved paclitaxel efficacy in preclinical breast cancer treatment. |
| **68** | Chan et al. (2008) | USA | Docetaxel | PLGA–lecithin–PEG core–shell | In vitro, In vivo | Not Reported | Designed a promising sustained-release system using lipid-polymer nanoparticles. |

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| 69 | Thadakapally et al. (2016) | India | Curcumin | PEG-albumin | In vitro, In vivo | Breast | PEG-albumin formulation significantly boosted curcumin's anticancer activity over its free form. |
| 70 | Yewale et al. (2018) | India | Docetaxel | Human serum albumin | In vitro, In vivo | Breast | Effective immuno-targeting in EGFR-overexpressing breast carcinoma cells. |
| 71 | Saxena et al. (2012) | USA | 17-AAG (Danamycin) | PLGA, Dicyclohexylcarbodiimide, Triethylamine | In vitro | Breast | Folate-targeted nanoparticles enhanced selective delivery to breast tumor cells. |
| 72 | Madhavi et al. (2011) | India | Curcumin | Bovine serum albumin | In vitro, In vivo | Breast | Successfully developed albumin-based nanocarriers using desolvation for breast therapy. |

**Limitations**

Some dissertations were excluded from the analysis due to the unavailability of published results. In a few instances, full-text versions of relevant papers could not be accessed. Furthermore, although polymeric nanoparticles (PNPs) have shown potential in various therapeutic applications—including smart drug delivery systems and personalized medicine—these innovations have not yet received approval from the U.S. Food and Drug Administration (FDA).

Findings from this study suggest that PNPs offer several advantages over traditional chemotherapy in cancer treatment. These nanoparticles not only help minimize the cytotoxic side effects typically associated with chemotherapeutic drugs but also enhance the solubility and bioavailability of these agents. Additionally, PNPs have demonstrated the ability to effectively suppress tumor growth.

Given these benefits, PNPs represent a promising alternative to conventional chemotherapy. To fully realize their potential, there is a need to raise awareness among healthcare professionals, physicians, and patients regarding the limitations of standard chemotherapy and the advantages that polymer-based drug delivery systems can offer in improving patient outcomes and quality of life.

**Conclusions**

Based on the findings of the current study, the use of drug delivery systems (DDSs), particularly polymeric nanoparticles (PNPs), is strongly recommended for the administration of anticancer agents. Encapsulating chemotherapeutic drugs within such nanocarriers has been shown to significantly enhance their therapeutic efficacy and precision in targeting cancer cells.

PNPs offer substantial advantages over conventional chemotherapy and traditional drug formulations. One of their key benefits lies in their ability to minimize the off-target toxicity commonly associated with anticancer drugs. By delivering the therapeutic agents directly to the tumor site, PNPs help protect healthy tissues surrounding the malignancy, thereby reducing the systemic side effects that patients often experience with standard chemotherapy.

Moreover, polymeric nanoparticles can improve the pharmacokinetic and physicochemical properties of anticancer compounds. For instance, many chemotherapeutic drugs suffer from poor water solubility, which limits their bioavailability and clinical effectiveness. PNPs enhance the solubility and stability of these agents, ensuring more consistent and effective drug delivery to tumor cells.

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In conclusion, incorporating PNP-based delivery systems into cancer therapy holds great promise for improving treatment outcomes. These nanocarriers not only increase drug effectiveness but also contribute to a safer therapeutic profile, making them a compelling alternative to conventional treatment strategies.

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