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INNOVATIONS IN NANOSCALE DRUG DELIVERY FOR ONCOLOGY: POLYMERIC, FLUOROPYRIMIDINE, AND PH-RESPONSIVE APPROACHES

Birodh Kumar Mahato[1], Rahul Yadav[2], Yubraj Yadav[3], Pritam Pawara[4*], Harshada Pawara[5]

[1]Homeopathy Medical officer, Government of Madhesh Pradesh, Dhunsa, Nepal

[2]Dept of nephrology, Nobel Medical College Teaching Hospital, Biratnagar, Nepal

[3]Medical officer at Nepal Medical College, Kathmandu, Nepal

[4]R. C. Patel Institute of Pharmaceutical Education and Research, Shrirpur, India

[5]DCS ARA College of Pharmacy, Nagaon, Dhule India

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Abstract

Nanoscale drug delivery systems have transformed the landscape of chemotherapy by enabling targeted, controlled release of therapeutics while minimizing systemic toxicity. This review focuses on recent advancesin polymeric nanoparticles and related nanocarriers for targeted drug delivery, including novel formulations for fluoropyrimidine chemotherapies and pH-sensitive delivery platforms. We discuss the design and engineering of polymeric nanoparticles that exploit the enhanced permeability and retention effect for passive tumor targeting and surface modifications for active targeting. Innovative strategies such as stimulus-responsive (especially pH-responsive) nanocarriers and co-delivery systems are highlighted for their ability to improve drug bioavailability and efficacy. Preclinical validation and emerging clinical trial data demonstrate improved therapeutic indices and reduced side effects for several nanomedicine candidates. Fluoropyrimidine-loaded nanocarriers show promise in overcoming 5-fluorouracil's pharmacokinetic challenges, enabling sustained release and tumor-selective delivery. The review also addresses translational considerations, manufacturing, safety, and regulatory aspects, associated with bringing these nanotechnologies from bench to bedside.

Keywords: Targeted drug delivery, polymeric nanoparticles, 5-fluorouracil, pH-sensitive nanocarriers, nanomedicine; controlled release.

***Corresponding Author**

Pritam Pawara

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Introduction

Cancer chemotherapy has long been impeded by poor tumor selectivity, dose-limiting toxicities, and drug resistance. Conventional cytotoxic agents like fluoropyrimidines (e.g. 5-fluorouracil, 5-FU) damage healthy tissues due to non-specific distribution, resulting in serious side effects [1,2]. The need for more precise delivery of anticancer drugs has catalyzed the development of novel drug delivery systems that can ferry therapeutics directly to tumor sites, improving the therapeutic index [1,3]. Nanoscale carriers, particularly polymeric nanoparticles (NPs), have emerged as promising vehicles to achieve this goal. These nanomedicines exploit tumor pathophysiology (such as leaky vasculature and poor lymphatic drainage) to preferentially accumulate in cancerous tissue via the enhanced permeability and retention (EPR) effect [4,5]. In addition, nanocarriers can be functionalized with targeting ligands (antibodies, peptides, etc.) to actively bind tumor-specific receptors, further enhancing selective drug delivery [1]. Over the past few years, a wave of nanoparticle-based chemotherapeutics has advanced through clinical development, including several that have reached human trials [6–8]. These platforms promise to reduce off-target toxicity and overcome mechanisms of drug resistance by controlling drug release profiles and concentrating payloads at the disease site [9].

Polymeric nanoparticles, made from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG)-based block copolymers, chitosan, and others, are at the forefront of this field [10]. They offer tunable size, surface properties, and drug release kinetics, making them versatile carriers for a variety of therapeutics. Recent research has focused on "smart" polymeric NPs that respond to stimuli (pH,

enzymes, temperature) to trigger drug release only in desired environments [11]. This is especially relevant for solid tumors, which often have an acidic microenvironment and elevated levels of certain enzymes [12]. By designing pH-sensitive or enzyme-degradable linkages in nanoparticle matrices, drugs can be preferentially released in tumor tissue or intracellular compartments, minimizing systemic exposure [13]. Likewise, advanced formulation techniques (e.g. microfluidics, nanoprecipitation) have improved NP uniformity and scalability, bringing these technologies closer to clinical application [14].

In this review, we examine recent advances in nanoscale targeted drug delivery systems, with an emphasis on polymeric nanoparticles and related novel formulations. We first discuss the design and functionalization of polymeric NPs for targeted delivery, highlighting how innovations in polymer chemistry and NP fabrication are yielding carriers with improved drug loading, stability, and targeting ability. We then focus on fluoropyrimidine delivery platforms as a case study, since 5-FU remains a cornerstone chemotherapeutic with known limitations that nanotechnology is helping to address. Next, we explore pH-sensitive and other stimulus-responsive nanocarriers that achieve controlled release in response to tumor-specific triggers. Throughout, we summarize preclinical efficacy data and any clinical trial findings that underscore the translational potential of these approaches. Finally, we consider the challenges that remain, including scale-up manufacturing, regulatory hurdles, and ensuring safety, and provide perspective on the future of targeted nanomedicine in oncology.

Polymeric Nanoparticles for Targeted Drug Delivery

Polymeric nanoparticles (NPs) have gained prominence due to their favorable pharmacokinetic and delivery properties. Constructed from biocompatible polymers (synthetic or natural), these NPs can encapsulate therapeutic molecules and protect them from premature degradation, while also enabling controlled and sustained release [13,14]. Critically, polymeric NPs prolong the circulation time of drugs, improve their stability in biological fluids, and can be engineered to release payloads in a time- or trigger-dependent manner [15]. By mitigating rapid clearance and burst release, polymeric NPs increase drug accumulation in target tissues and reduce off-target exposure [16].

A major advantage of polymeric nanocarriers is their flexibility in surface modification. Researchers have conjugated various targeting moieties onto NP surfaces, including monoclonal antibodies, peptides, aptamers, and small molecules, to achieve active targeting of specific cell types or receptors [17,18]. For example, nanoparticles functionalized with folate or transferrin can exploit the overexpression of folate or transferrin receptors on certain cancer cells, leading to enhanced uptake by tumors relative to normal cells [19,20]. Ligand-targeted NPs have demonstrated higher intracellular delivery of chemotherapeutics in cancer cells and improved antitumor efficacy in animal models compared to untargeted counterparts [21, 22]. Additionally, receptor-based targeting strategies are particularly promising for circumventing drug resistance, as many resistant tumor phenotypes upregulate specific membrane receptors. A recent review emphasized the utility of exploiting receptor expression profiles to enhance therapeutic precision and overcome resistance barriers [23].

Polymeric NPs can be formulated for different routes of administration (intravenous, oral, intratumoral, etc.) and tailored to the needs of various therapeutic contexts. In oncology, IV-injected NPs passively home to tumors via the EPR effect and can be “triggered” to release drugs in response to the acidic pH or enzymatic milieu of tumor tissue [24, 25]. For instance, polymeric micelles with pH-labile bonds remain stable at physiological pH 7.4 but rapidly release their drug cargo in the slightly acidic pH ~6.5 of tumor interstitium or endosomes [26]. Dendrimers and nanogels represent other polymer-based carriers that can swell or dissociate in response to pH or temperature changes, enabling on-demand drug unloading. These “smart” behaviors help concentrate the therapeutic effect at the tumor while sparing normal tissues.

In oncology applications, polymeric nanoparticles can be engineered to accumulate in tumors (via passive EPR effect or active ligand targeting) and release drugs in response to tumor-specific triggers, thereby increasing anti-tumor efficacy while reducing systemic toxicity [25, 27].

Common polymer choices for NP construction include PLGA, polycaprolactone, PEGylated polymers, and naturally derived polymers like chitosan or alginate. PLGA-based NPs, for example, have been widely studied due to PLGA’s biodegradability and FDA-approved status; drugs encapsulated in PLGA NPs often show sustained release over days to weeks as the polymer matrix gradually hydrolyzes [20,28]. Chitosan NPs carry innate positive charges that facilitate interaction with negatively charged cell membranes, enhancing cellular uptake. Moreover, chitosan’s mucoadhesive properties make it useful for transmucosal drug delivery (e.g. oral or intranasal routes) [29]. Recent innovations in polymer chemistry have led to stimuli-responsive polymers, such as poly(N-isopropylacrylamide) which is temperature-sensitive, or polymers containing pH-cleavable linkers, being incorporated into NP designs [30]. Multi-block copolymers can combine hydrophobic and hydrophilic segments to form self-assembling micelles that carry hydrophobic drugs in their core, shielded by a hydrophilic shell (often PEG) that prolongs circulation [31, 32].

Another impactful trend is the co-delivery of multiple therapeutic agents using a single nanoparticle platform. By encapsulating drug combinations, nanocarriers can ensure that synergistic agents (e.g. a chemotherapeutic and an MDR inhibitor, or two chemo drugs with complementary actions) are delivered to the tumor at the same time and at optimal ratios [33]. This co-loading strategy can enhance

therapeutic efficacy and help prevent drug resistance. For instance, polymeric NPs co-encapsulating doxorubicin and an siRNA against drug-resistance genes have shown the ability to reverse tumor resistance and induce tumor regressions in models [34, 35]. Similarly, 5-FU has been co-delivered with other drugs like paclitaxel or everolimus in nanoparticle formulations to yield higher anticancer effects than either alone [33, 36]. Mohammadi Arvejeh et al. (2025) recently developed an injectable hydrogel embedding mesoporous silica nanoparticles for co-delivery of 5-FU and the mTOR inhibitor everolimus, achieving synergistic inhibition of breast tumors in mice [37]. The nanocomposite hydrogel provided localized, pH-responsive release of both drugs and significantly reduced tumor size and lung metastases compared to monotherapy controls [38]. Such combination nanotherapies illustrate the potential of polymeric systems to not only target tumors but also intelligently deploy multiple interventions against cancer cells. Additionally, epigenetic modulators like miRNAs are increasingly recognized as drivers of resistance. For example, miRNA-221-5p has been shown to regulate epigenetic pathways that promote chemoresistance in ovarian cancer, representing a promising target for RNA-loaded or miRNA-responsive nanocarrier systems [39]. Recent work demonstrates that inhibiting CHK1 in ovarian cancer induces PARylation and NAD^+ depletion, and when combined with PARG inhibition, it leads to replication catastrophe and metabolic stress, offering a novel approach to overcome drug resistance via synthetic lethality [40].

Polymeric nanoparticles have progressed from benchtop research to clinical evaluation. Several polymer-based nanomedicines are in clinical trials, and a few have attained regulatory approval for cancer therapy. One example is CRLX101, a cyclodextrin-polymer conjugate carrying camptothecin, which advanced to phase II trials in solid tumors [41,42]. Polymeric micelle formulations of paclitaxel (e.g. Genexol-PM) have been approved in some regions, demonstrating reduced toxicities versus conventional cremophor-formulated paclitaxel [43]. These successes underscore that polymeric NP systems can be manufactured under Good Manufacturing Practice and meet safety criteria for human use. Nonetheless, challenges remain in ensuring batch-to-batch consistency, scalability of production, and thorough characterization of these complex nanomaterials [44]. The pharmacokinetics and biodistribution of polymeric NPs can also be influenced by their physicochemical properties (size, charge, surface hydrophilicity), so careful optimization is required to strike a balance between stability in blood and efficient payload release in targets [45].

In summary, polymeric nanoparticles provide a versatile platform for targeted drug delivery. By appropriate selection or design of polymers, surface functionalization, and incorporation of stimulus-responsive features, these nanocarriers achieve improved tumor targeting and therapeutic outcomes in preclinical models. The next sections delve deeper into specific applications, notably the delivery of fluoropyrimidine chemotherapeutics and the use of pH-sensitive formulations, which exemplify the translational progress in this field.

Fluoropyrimidine Delivery Systems: Nanocarriers for 5-FU and Analogues

Fluoropyrimidines such as 5-fluorouracil (5-FU) and its prodrugs (capecitabine, tegafur) are mainstay treatments for malignancies including colorectal, gastrointestinal, breast, and head-neck cancers. However, 5-FU has notoriously problematic pharmacokinetics: it has a very short plasma half-life (10–20 minutes), is rapidly metabolized, and can cause severe off-target toxicities in the gastrointestinal tract and bone marrow [46,47]. Traditional 5-FU regimens often require continuous infusion or high-dose bolus administration, which increase the risk of mucositis, myelosuppression, and hand-foot syndrome [46,47]. Nanotechnology offers strategies to reformulate fluoropyrimidines, improving drug targeting tumors and reducing systemic exposure [48].

Multiple nano-delivery systems for 5-FU have been explored in recent years [46]. These include lipid-based nanoparticles (e.g. liposomes, solid lipid NPs), polymeric NPs (both non-responsive and stimulus-responsive types), inorganic nanocarriers (such as mesoporous silica or gold nanoparticles), and nanoscale polymer-drug conjugates [49,50]. Each approach aims to overcome the limitations of 5-FU by increasing its stability and concentrating its action in cancer cells. For instance, 5-FU encapsulated in PEGylated liposomes has shown prolonged circulation and enhanced tumor uptake in animal models, translating to greater antitumor efficacy than free 5-FU [51]. Polymeric NPs made of PLGA or poly(alkylcyanoacrylate) have been loaded with 5-FU to achieve sustained drug release over several days, maintaining therapeutic drug levels in tumors while sparing normal tissues [52, 53]. Notably, some polymeric formulations are designed to release 5-FU preferentially in the acidic microenvironment of tumors or inside cancer cells' endosomes (pH ~5–6), thus minimizing drug release in blood (pH 7.4) [26].

One innovative formulation reported in 2024 is thiolated chitosan nanoparticles modified for active targeting of 5-FU to cancer cells [54]. Anjum et al. synthesized chitosan NPs crosslinked with a thiol reagent to improve their mucoadhesiveness and stability, then coated the NPs with hyaluronic acid (HA) to target CD44, a receptor overexpressed on many cancer cells [54]. The resulting HA-coated 5-FU nanoparticles had a sub-300 nm size and positive zeta potential, facilitating efficient uptake by CD44+ triple-negative breast cancer cells while sparing normal cells [55]. In vitro, these targeted NPs demonstrated significantly higher cytotoxicity against breast cancer cells compared to free 5-FU, owing to enhanced cellular internalization [56, 57]. They also exhibited a controlled release profile (following diffusion-controlled kinetics) that prolonged drug action [58, 59]. This design, combining a biodegradable polymer (chitosan), a targeting ligand (HA), and thiol-mediated mucoadhesion, exemplifies the sophisticated multifunctional nanoparticles now being developed for

fluoropyrimidine delivery. Such systems aim to increase tumor-specific drug delivery and reduce the dose of 5-FU needed, thereby mitigating side effects [60, 61].

Another area of progress is colon-targeted delivery of 5-FU for colorectal cancer therapy. Because 5-FU causes dose-limiting GI toxicity when given systemically, formulating it for local release in the colon can improve efficacy against colonic tumors while lowering systemic exposure [62]. Researchers have designed pH-responsive oral formulations that protect 5-FU as it passes through the stomach and small intestine, then release it upon reaching the higher pH environment of the colon [63]. For example, a 2023 study utilized cross-linked mastic gum as an enteric matrix for 5-FU, achieving significant drug release only at colonic pH and demonstrating enhanced tumor suppression in a mouse colon cancer model [64]. Similarly, pH-sensitive polymer coatings (like Eudragit S, which dissolves at pH > 7) have been applied to 5-FU-loaded nanoparticles or tablets to selectively deliver the drug to the distal gut [65]. These strategies increase local drug concentration at the tumor site in the colon, improving therapeutic outcomes in preclinical studies of colorectal cancer while causing fewer systemic toxic effects [66].

Co-delivery strategies are also being pursued to enhance the efficacy of 5-FU. One approach is combining 5-FU with agents that modulate molecular pathways in cancer cells. A recent example is the co-encapsulation of 5-FU with small interfering RNAs (siRNA) or microRNA mimics that target oncogenes [67]. Gao et al. (2022) developed a layer-by-layer liposomal system carrying 5-FU along with siRNA against KRAS and a tumor-suppressor miRNA, aiming to tackle colorectal cancer on multiple fronts [68, 69]. The multilayer liposomes delivered their cargo preferentially to colorectal tumor tissues in mice, resulting in marked tumor growth inhibition by synergistically silencing oncogenic KRAS and exerting 5-FU's cytotoxic effects [70]. Another example is co-delivery of 5-FU with everolimus (an mTOR inhibitor) in the chitosan–silica nanohydrogel mentioned earlier [71]. By simultaneously blocking the mTOR pathway and incorporating 5-FU's antimetabolite action, the combination induced higher cancer cell apoptosis and tumor regression than either agent alone [72–74]. These combination nanoparticle therapies demonstrate how nanocarriers can coordinate multiple therapeutic modalities, an especially valuable feature for managing cancers that rapidly develop drug resistance when single agents are used [75, 76]. Recently, lymphoblastic leukemia-derived sequence-1 (LYL1) has emerged as a novel oncogenic driver associated with ovarian cancer progression and metastasis, highlighting a potential molecular target for RNAi or gene-editing-based nanocarrier development [77].

Collectively, nano-delivery systems for fluoropyrimidines are addressing the classic drawbacks of 5-FU chemotherapy. Through encapsulation and controlled release, they prolong the drug's presence in the therapeutic window and reduce peak systemic concentrations that cause toxicity. Tumor-targeted delivery via passive and active mechanisms increases drug accumulation at the tumor site, enhancing anti-tumor efficacy even in 5-FU–resistant cancer cell lines [78]. Many 5-FU nanocarriers also allow for dose reductions while achieving the same or greater tumor suppression, as the nanoformulation's efficiency compensates for lower drug amounts [79, 80]. This could translate to fewer side effects for patients. Indeed, initial animal toxicology studies of 5-FU nanoparticles show reduced bone marrow and GI toxicity compared to equivalent doses of free 5-FU [81, 82]. Some formulations, such as SillaJen'sPexa-Vec (an oncolytic vaccinia virus delivering a GM-CSF gene alongside a suicide gene to complement 5-FU therapy), are even entering clinical trials, reflecting a convergence of viral and nanoparticle delivery approaches to maximize 5-FU's therapeutic benefit [83]. The use of viral vectors to deliver immune-modulating cytokines such as interleukin-2 has shown considerable promise in enhancing anti-tumor immunity. Notably, recent studies demonstrate that engineered viral platforms can sustainably express IL-2 within the tumor microenvironment, promoting cytotoxic T-cell activation and improving immunotherapy outcomes [84, 85]. While no 5-FU nanoformulation has yet achieved FDA approval, the pipeline is rich with candidates, indicating that fluoropyrimidine chemotherapy may soon be administered in smarter, safer ways thanks to nanotechnology.

pH-Sensitive and Stimuli-Responsive Delivery Systems

One of the most exciting areas in targeted drug delivery is the development of stimuli-responsivenanocarriers, systems that remain inert during circulation but respond to specific triggers in the target tissue to release their payload. Among these, pH-sensitive delivery systems have garnered particular interest in cancer therapy. Solid tumors typically exhibit an acidic microenvironment (pH ~6.5–7.0 in interstitial fluid) due to hypoxia and high glycolytic activity, in contrast to normal blood and tissue pH of ~7.4 [26,86]. Furthermore, within tumor cells, endo-lysosomal compartments are even more acidic (pH 5–6). pH-responsive nanocarriers exploit these differences: they are engineered to be stable at physiological pH but to undergo physicochemical changes in acidic conditions that trigger drug release [87, 88].

Several mechanisms can impart pH sensitivity to a nanocarrier. One approach is incorporating acid-labile bonds (such as hydrazone, Schiff-base, or cis-aconityl linkages) that cleave in acidic environments. For example, doxorubicin has been conjugated to polymers via hydrazone bonds that remain intact at pH 7.4 but hydrolyze at pH 5–6, ensuring the drug is released predominantly in acidic endosomes of cancer cells [26,89]. Another strategy is using pH-responsive polymer coatings that swell or solubilize in acidic pH. Polymers containing ionizable groups (like poly(β-amino esters), or polyhistidine) can be solid and collapse at neutral pH, but protonation in an acidic milieu causes them to become hydrophilic or disrupt intermolecular interactions, leading

to nanoparticle swelling and drug diffusion out [87,89]. For instance, poly(L-histidine)-based micelles will disassemble as the imidazole groups protonate below pH 6.5, releasing the drug load [90]. Similarly, Eudragit or poly(ortho ester) coatings can be applied to NP surfaces to prevent drug leakage at pH 7.4, then degrade and open up in acidic conditions [91]. Additionally, rationally designed small molecules such as benzofuran-piperazine derivatives have exhibited potent anticancer activity and represent attractive candidates for encapsulation in polymeric or lipid-based nanoparticles to enhance tumor-targeted bioavailability and minimize systemic exposure [92].

Physical dissociation of nanoparticles in low pH is a commonly employed design. In one system, polymeric micelles constructed from block copolymers were stable in blood, but upon entering the acidic tumor tissue, the increased protonation caused electrostatic repulsion that burst the micelles, dumping the drug locally [93]. This "pH-triggered explosion" effectively concentrates drug release where it is needed. By leveraging the pH gradients between healthy and tumor tissue (as well as between extracellular and intracellular compartments), such systems significantly enhance the precision of drug deployment.

Beyond pH, other stimuli have been harnessed in nanocarrier design. Enzyme-responsive nanoparticles capitalize on overexpressed enzymes in the tumor milieu (e.g. matrix metalloproteinases, cathepsins) to cleave peptide linkers and release drugs at the tumor site [94,95]. Redox-responsive carriers use disulfide bonds that break in the reducing environment of the cytosol (high glutathione levels in cancer cells), triggering intracellular drug release [96]. Thermo-responsive liposomes (e.g. low-temp sensitive liposomes) can release contents upon mild hyperthermia (~42 °C) applied to tumor regions. Magnetic and ultrasound-triggered nanocarriers are also being investigated: for example, magnetic nanoparticles that heat up under an alternating magnetic field to induce drug release, or acoustically sensitive liposomes that rupture upon ultrasound exposure [97,98]. While these external stimuli systems require specialized equipment, pH and enzyme triggers are autonomous and take advantage of intrinsic tumor characteristics.

A concrete example of a pH-sensitive system is the "nanogel" – a hydrogel nanoparticle that can load drugs and then shrink or swell in response to pH changes. Nanogels made of crosslinked polymers like poly(N-isopropylacrylamide-co-acrylic acid) remain collapsed at bloodstream pH, but in acidic tissue they absorb water and expand, releasing the encapsulated drug [99]. Importantly, by integrating targeting ligands into such nanogels, researchers have achieved dual-function systems that first home to cancer cells (via ligand-receptor binding) and then unload the drug intracellularly upon sensing the low pH in endosomes(100). This multi-stimuli approach was demonstrated by a nanogel that responded to both temperature and pH, the polymer backbone provided temperature sensitivity, and pendant catechol groups were cleaved in acidic conditions, resulting in highly controlled drug release with minimal premature leakage [101,102].

The clinical relevance of pH-sensitive delivery is exemplified by formulations aiming at improved chemotherapy for solid tumors. Doxorubicin encapsulated in pH-responsive polymeric micelles (known as pmPDOX) showed markedly enhanced tumor penetration and antitumor activity in models of metastatic cancer, versus non-pH-responsive liposomal doxorubicin [103]. Another example is a pH-activated polymer-drug conjugate of paclitaxel: it remained inactive in circulation, but upon accumulating in the acidic tumor, the hydrazone linkers hydrolyzed to release active paclitaxel, yielding greater tumor growth inhibition in mice and reduced systemic toxicity compared to standard paclitaxel [104]. Some of these pH-sensitive systems have entered early-phase clinical trials, particularly in the form of polymeric micelles or polymer conjugates, and initial results indicate favorable safety and drug release profiles in patients with advanced tumors [105].Among recent developments, the nanoscale polymeric formulation CF10 has demonstrated enhanced therapeutic efficacy and reduced systemic toxicity in a preclinical rat model of colorectal cancer liver metastasis, highlighting its potential as a next-generation fluoropyrimidine delivery platform [106–108].

It's worth noting that stimulus-responsive delivery is not limited to cancer. Similar principles are being applied to inflammatory diseases (where inflamed tissue can be slightly acidic and rich in proteases) and infection sites (some bacteria create acidic niches) [109,110]. However, oncology remains the primary focus, given the pressing need to target chemotherapeutics more effectively.Overall, pH-sensitive and other stimuli-responsive nanocarriers represent a leap forward in the "intelligence" of drug delivery systems. By programming environmental responsiveness into the carrier, these systems act almost like a smart device, carrying the drug through the body, sensing when they have arrived at the target, and then executing the drug release precisely at that site [111]. This level of control can drastically improve therapeutic outcomes, as evidenced by higher response rates and complete tumor regressions in some preclinical models using smart nanoparticles [112]. As materials science and bioengineering continue to innovate on stimulus-sensitive polymers, we anticipate even more refined control mechanisms (for example, Boolean logic gates that require multiple stimuli concurrently) that could further minimize off-target effects [113,114]. The challenge moving forward will be translating these complex systems into manufacturable, regulatory-approved products. Ensuring stability, reproducibility, and safety of stimuli-responsive nanocarriers in humans will be paramount. Nonetheless, the progress to date clearly indicates that *in situ* drug activation via tumor-specific triggers can be a game-changer in cancer therapy, aligning treatment potency where it's needed and sparing healthy cells [115,116].

Clinical Translation and Outlook

The translational pathway for novel nanomedicines involves demonstrating advantages in preclinical efficacy, acceptable safety profiles, and scalable manufacturing. Many of the nanoscale delivery systems discussed have shown striking improvements in therapeutic index in animal models. For instance, 5-FU nanocarriers achieved equivalent tumor suppression at a fraction of the dose required for free 5-FU, with reduced toxicity [117]. pH-sensitive doxorubicin micelles eradicated tumors in mice that were resistant to standard chemotherapy [26]. These encouraging results have propelled several candidates into clinical trials. It is notable that the first FDA-approved nanodrugs (e.g. liposomal doxorubicin, albumin-bound paclitaxel) provided proof-of-concept that nanotechnology can improve patient outcomes by reducing toxicity [118,119]. Building on that foundation, polymeric and stimuli-responsive systems are now vying to be the next generation of approved nanotherapies.

One important consideration is safety and immunogenicity of nanoparticle carriers. Polymeric NPs are generally designed from biocompatible materials that degrade into nontoxic byproducts (e.g. PLGA degrades to lactic and glycolic acid, which enter metabolic pathways) [120]. Still, careful toxicology studies are needed to ensure no unexpected organ accumulation or immune reactions [121]. The surface properties of NPs strongly influence their interactions with the immune system. “Stealth” NPs coated with PEG tend to evade rapid clearance by phagocytes, prolonging circulation, but repeated dosing of PEGylated NPs can sometimes induce anti-PEG antibodies. So far, most polymeric NP systems have shown acceptable immunological profiles in early studies, but ongoing vigilance is warranted [122,123]. Drug-induced hypersensitivity reactions, such as DRESS syndrome associated with sulfasalazine, underscore the critical need for designing delivery systems that minimize systemic immunogenicity and off-target exposure [124–126]. In addition, immune evasion mechanisms, particularly in tumors exhibiting high cellular plasticity such as non-small cell lung cancer, further contribute to therapeutic resistance. Recent evidence suggests that T and NK cell escape plays a central role in immunotherapy failure, necessitating delivery strategies that also engage the tumor immune microenvironment [127].

Another translational hurdle is scalable manufacturing and characterization. Unlike small molecules, nanoparticles are complex heterogeneous structures. Batch consistency must be rigorously controlled for particle size, drug loading, release rate, and purity (e.g. removal of free drug or residual solvents). Advances in microfluidic synthesis and automated nanoparticle production are helping achieve more uniform batches [128]. Regulatory agencies have also provided guidance on characterization techniques (DLS for size distribution, electron microscopy for morphology, HPLC for drug content, etc.). Formulation stability during storage is another issue, some nanoparticle formulations may aggregate or precipitate over time, necessitating lyophilized forms that can be reconstituted before use. Researchers have addressed this by developing lyoprotectant strategies and optimizing storage conditions (e.g. storing at 4 °C, protecting from light, etc.) [129]. Indeed, one of the polymeric micelle products in trials is supplied as a freeze-dried powder to ensure long shelf-life, with the end-user (pharmacist) rehydrating it in saline prior to administration [130].

From a clinical standpoint, the integration of nanomedicines into treatment regimens requires consideration of dosing, scheduling, and potential combination with other therapies. Because nanocarriers alter the pharmacokinetics of drugs, clinicians may need to adjust dosing schedules (for example, an NP providing sustained release might be given less frequently than the free drug) [131]. Moreover, nanoparticles often have different tissue distribution – for instance, they may penetrate tumors better but cross the blood-brain barrier poorly (or vice versa if designed for CNS targeting)(132). Understanding these differences is key to positioning nanomedicines appropriately. The good news is that several nanoformulations have entered oncology practice (e.g. liposomal irinotecan for pancreatic cancer, nanoparticle albumin paclitaxel for breast cancer), paving the way for acceptance of new nano-delivery systems by oncologists [133,134] Emerging molecular diagnostics are also shaping posttreatment strategies. For instance, HPV-HR DNA testing has shown potential as a non-invasive alternative to PET/CT imaging for cancer surveillance, aiding timely therapeutic decisions [135,136]. Effective implementation of novel drug delivery systems in hospital settings also requires attention to patient-centered factors, including health literacy. A recent prospective pilot study emphasized the importance of health literacy screening in gynecologic oncology patients to improve therapeutic engagement and outcomes [137].

Looking ahead, the field of targeted drug delivery is poised to intersect with other cutting-edge modalities. Combination of nanocarriers with immunotherapy is a promising frontier. For example, nanoparticle formulations that deliver a chemotherapeutic along with an immune adjuvant can not only kill tumor cells but also stimulate an anticancer immune response. Some researchers have loaded checkpoint blockade antibodies onto nanoparticles together with chemo drugs, creating a single platform that both debulks the tumor and modulates immune checkpoints in the tumor microenvironment. There is also interest in using nanoparticles to improve cell therapies: e.g. nanoparticle “backpacks” on T-cells that slowly release cytokines to enhance the T-cells’ activity once they reach the tumor.In addition to formulating nano-antibiotics that minimize resistance and systemic toxicity, hospital-based implementation must also address real-world challenges such as ineffective IV-to-oral transition protocols and treatment inconsistencies in infectious diseases. For instance, prospective evaluations from tertiary care settings have revealed substantial gaps in inpatient versus outpatient antibiotic strategies and highlighted

operational delays in oral conversion for eligible patients [138, 139]. Such findings underscore the necessity of aligning advanced drug delivery innovations with antimicrobial stewardship models supported by clinical pharmacists.

Finally, cost and accessibility will influence the clinical uptake of these technologies. While nanoformulations can be more complex and expensive to produce than traditional drugs, their potential to improve outcomes (and possibly enable cures in cases where current therapy fails) can justify the investment [140]. Health-economic analyses are beginning to consider whether the reduced side-effect management costs and improved patient quality-of-life from nanomedicines offset their manufacturing costs. As more nanodrugs hopefully gain approval, competition and economies of scale may also drive costs down [141].

In conclusion, nanoscale and targeted drug delivery systems represent a transformative approach in pharmacotherapy. Polymeric nanoparticles, fluoropyrimidinenanoformulations, and pH-sensitive carriers have shown the ability to address long-standing challenges in chemotherapy by enhancing drug targeting and retention at disease sites. The clinical translation of these technologies is underway, supported by a strong foundation of preclinical evidence. Continued interdisciplinary collaboration among chemists, biologists, engineers, and clinicians will be essential to bring these sophisticated delivery systems from the laboratory to routine patient care. If successful, patients will experience more effective treatments with fewer side effects, fulfilling the promise of "right drug, right place, right time" that targeted drug delivery embodies.

Conclusion

Recent advances in nanotechnology have enabled the design of smart drug delivery systems that significantly improve the precision and efficacy of chemotherapy. Polymeric nanoparticles offer customizable platforms to carry and release therapeutics in a controlled manner, reducing toxicity and overcoming biological barriers. Fluoropyrimidine chemotherapies like 5-FU, which are limited by rapid clearance and systemic side effects, have been reformulated into nanoparticle systems that prolong drug circulation and selectively release drug at tumor sites – achieving better anti-cancer effects in preclinical models with lower toxicity [142, 143]. Stimuli-responsive nanocarriers, particularly those sensitive to pH, exemplify how the tumor microenvironment can be leveraged to trigger drug release exactly where needed [26]. These intelligent systems remain stable during blood transit and then unleash potent doses upon encountering the acidic or enzyme-rich conditions of tumors, thereby maximizing tumor cell kill while sparing healthy tissue.

As evidenced by multiple candidates entering clinical trials, the field is moving steadily toward clinical implementation of these novel delivery strategies. The translation is supported by advances in manufacturing techniques and a deeper understanding of nano–bio interactions that inform safety evaluations. Early-phase trials of nanoparticle-based drugs have generally shown that these systems can be administered safely to patients, with pharmacokinetic profiles consistent with the long-circulating, tumor-targeting behavior observed in animal studies [144]. Challenges remain, including ensuring regulatory compliance in production, managing potential immunogenicity of nanoparticle components, and educating clinicians about the unique handling and dosing of nanomedicines. However, the trajectory is clear: nanoscale targeted delivery is on the cusp of delivering tangible benefits to patients, making chemotherapy more effective and tolerable.

In conclusion, the progress in polymeric nanoparticles, fluoropyrimidine nano-delivery, and pH-responsive systems heralds a new era of cancer therapy where treatment is not only defined by the drug's potency but equally by the sophistication of its delivery. By refining how and where drugs act within the body, these technologies fulfill a central goal of precision medicine. Ongoing research and clinical collaboration will undoubtedly expand the repertoire of diseases that can be tackled by targeted nanomedicine, potentially extending beyond oncology to treat infections, metabolic conditions, and others with similar precision. The coming years are likely to witness some of these advanced drug delivery systems reaching regulatory approval and becoming part of standard therapeutic regimens, ultimately improving patient outcomes and quality of life.

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Conflict of Interest

The authors declare no conflicts of interest related to this work.

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