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POLYMERIC NANOPARTICLES AND FLUOROPYRIMIDINE PLATFORMS IN TARGETED CANCER THERAPY

Pritam I. Pawara[1], Md. Mojeeb G. Khan[1], Atul A. Shirkhedkar[1], Harshada P. Pawara[2]
[1]R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra, India
[2]DCS's ARA College of Pharmacy, Nagaon, Dhule, Maharashtra, India

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***Corresponding author**
Pritam I. Pawara

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Abstract
Targeted cancer therapy has been significantly advanced by the development of polymeric nanoparticles and novel fluoropyrimidine platforms. Polymeric carriers offer controlled release, biocompatibility, and surface modification capabilities that enhance tumor-specific drug delivery while minimizing systemic toxicity. Fluoropyrimidines such as 5-fluorouracil (5-FU) have long been central to chemotherapeutic regimens, yet their therapeutic window is often limited by metabolic instability and resistance. Recent innovations in nanoscale formulation, including the synthesis of polymer-conjugated fluoropyrimidines like CF10, demonstrate improved pharmacokinetics, tumor uptake, and anti-proliferative efficacy in preclinical models. This review summarizes current advancements in polymeric nanocarriers for delivering fluoropyrimidine derivatives, discusses formulation strategies to overcome drug resistance, and highlights translational applications in gastrointestinal and gynecologic malignancies. Together, these approaches represent a promising direction in the design of next-generation chemotherapeutic systems.

***Keywords*:** Polymeric nanoparticles, Fluoropyrimidines, Targeted cancer therapy, 5-fluorouracil (5-FU), Drug resistance, Nanocarriers.

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Introduction
Cancer chemotherapy efficacy is often limited by poor tumor selectivity and systemic toxicity. Conventional fluoropyrimidine drugs like 5-fluorouracil (5-FU) distribute non-specifically and damage healthy tissues, causing dose-limiting side effects [1]. These challenges have spurred the development of novel drug delivery systems to target chemotherapeutics more precisely to tumors. Nanoscale carriers, especially polymeric nanoparticles (NPs), have emerged as promising vehicles to ferry drugs directly to tumor sites and improve the therapeutic index [2]. By exploiting tumor pathophysiology, such as leaky vasculature and impaired lymphatics, polymeric NPs can preferentially accumulate in cancerous tissue via the enhanced permeability and retention (EPR) effect [3]. Moreover, these nanocarriers can be functionalized with targeting ligands (antibodies, peptides, etc.) for active targeting of tumor-cell receptors, further improving selective drug delivery [4]. In recent years, multiple NP-based chemotherapeutics have entered clinical development (and even trials), underscoring the potential of nanomedicine to reduce off-target toxicity and overcome drug resistance mechanisms by controlling drug release profiles and concentrating payloads at disease sites [5,6].

Among polymeric nanomedicines, fluoropyrimidine-loaded nanoparticles are a particularly compelling case study. Fluoropyrimidines (like 5-FU and prodrugs such as capecitabine) remain cornerstone chemotherapeutics for many cancers, yet 5-FU's pharmacokinetic drawbacks (rapid clearance, narrow therapeutic window) limit its efficacy [7]. Reformulating 5-FU into polymeric NPs or related nanocarriers offers a strategy to sustain drug release and improve tumor selectivity, potentially mitigating the severe gastrointestinal and bone marrow toxicities seen with free 5-FU [8,9]. This manuscript will focus on polymeric nanoparticles and fluoropyrimidine-based platforms in targeted cancer therapy, emphasizing

the chemistry of polymeric carriers, their fabrication and functionalization, and clinical relevancy of these systems.

We begin by discussing the design and synthesis of polymeric NPs for targeted delivery, highlighting how innovations in polymer chemistry and nanoparticle fabrication yield carriers with tunable drug release and targeting capabilities. Next, we examine fluoropyrimidine delivery platforms, nanocarriers engineered for 5-FU and its analogues, as an illustration of how nanotechnology is overcoming classic chemotherapy limitations. Throughout, we note preclinical efficacy data and emerging clinical trial results that demonstrate improved therapeutic indices. Finally, we consider the translational progress and challenges for bringing polymeric NP systems, including fluoropyrimidine monotherapy, into routine clinical use.

Polymeric nanoparticles for targeted drug delivery

Polymeric nanoparticles (PNPs) have gained prominence due to their favorable pharmacokinetic and drug delivery properties [10]. Constructed from biocompatible polymers (synthetic or natural), these NPs can encapsulate therapeutic molecules and protect them from premature degradation while enabling controlled, sustained release [11]. This encapsulation prolongs drug circulation time, improves stability in biological fluids, and mitigates the rapid clearance or "burst release" that plagues many free drugs [12]. By preventing immediate systemic exposure and dose spikes, polymeric NPs concentrate drugs in target tissues and reduce off-target toxicity [13].

A key advantage of polymeric nanocarriers is their surface modifiability and flexible chemistry. Researchers can conjugate various targeting moieties onto NP surfaces to achieve active targeting of specific cell types or receptors [14]. For example, decorating nanoparticles with folate or transferrin exploits the overexpression of folate or transferrin receptors on certain cancer cells, leading to enhanced uptake by tumors relative to normal cells [15]. Such ligand-targeted NPs have shown higher intracellular delivery of drugs in cancer cells and improved antitumor efficacy in animal models compared to untargeted NPs [16]. Active targeting can also help circumvent drug resistance, since resistant tumor phenotypes often upregulate specific surface receptors,a strategy to smuggle drugs into otherwise refractory cells [17].

Polymeric NPs can be formulated for various routes of administration (intravenous, oral, intratumoral, etc.) and tailored to different therapeutic contexts. Intravenously injected polymeric NPs tend to passively home to tumors via the EPR effect, but they can also be engineered to "trigger" release of drugs in response to tumor-specific cues such as acidic pH or enzyme-rich milieu [18]. For instance, polymeric micelles with pH-labile bonds can remain stable at blood pH 7.4 yet rapidly release their cargo in the mildly acidic tumor interstitium (pH ~6.5) or in endosomes [19]. Other polymer-based nanostructures like dendrimers and nanogels can swell or dissociate upon changes in pH or temperature, enabling on-demand drug unloading specifically at the tumor site [20]. These "smart" behaviors concentrate the therapeutic effect in tumors while sparing normal tissues.

Common polymers used for constructing nps include:

- **Poly(lactic-co-glycolic acid) (PLGA):** A biodegradable FDA-approved polymer. Drugs encapsulated in PLGA NPs often exhibit sustained release over days to weeks as the polymer matrix slowly hydrolyzes [21]. PLGA's biocompatibility and track record in humans make it a popular choice.
- **Poly(ethylene glycol) (PEG)-based copolymers:** Often used to form polymeric micelles or as a "stealth" coating. PEG provides a hydrophilic shell that prolongs circulation by reducing opsonization. PEGylated polymers can self-assemble into micelles that carry hydrophobic drugs in their core, improving solubility and half-life [22].
- **Chitosan:** A naturally derived polysaccharide polymer. Chitosan NPs are positively charged, which enhances interaction with negatively charged cell membranes and promotes uptake. Chitosan is also mucoadhesive, making it useful for oral or transmucosal drug delivery (it can stick to gastrointestinal mucosa for local release) [23]. Chemical modifications (e.g. thiolated chitosan) can improve its stability or targeting, as discussed later.
- **Stimuli-responsive polymers:** Advances in polymer chemistry have yielded novel copolymers that respond to stimuli. For example, poly(N-isopropylacrylamide) (PNIPAM) is temperature-sensitive (forming hydrogels at body temp but dissolves below a threshold), and polymers with pH-cleavable linkers (like hydrazone or Schiff-base bonds) are used in NP designs to achieve pH-triggered drug release [24,25]. These smart polymers impart environmental sensitivity to the nanoparticle.

Another important trend is co-formulation of multiple therapeutic agents within a single nanoparticle. By co-encapsulating synergistic drug combinations (e.g. a chemotherapy drug plus an inhibitor of a resistance pathway), nanocarriers can deliver both agents together to the tumor at optimal ratios. This ensures that combination therapy reaches the cancer cells simultaneously, which can enhance efficacy and help prevent or overcome drug resistance [26]. For example, polymeric NPs co-loaded with doxorubicin and an siRNA against a drug-resistance gene achieved tumor regressions in models that did not respond to doxorubicin alone [27]. Similarly, 5-FU has been successfully co-delivered with other agents (like the mTOR inhibitor everolimus or the chemotherapeutic paclitaxel) in nanoparticle formulations, yielding greater anticancer effects than

either drug alone. A recent 2025 study developed an injectable hydrogel embedding mesoporous silica nanoparticles for co-delivery of 5-FU and everolimus, achieving synergistic tumor inhibition in mice; the nanocomposite hydrogel provided localized, pH-responsive release of both drugs and significantly reduced tumor size and metastases compared to monotherapy controls [28]. These examples illustrate how polymeric systems can intelligently deploy multi-pronged therapies against cancer.

Polymeric nanoparticle platforms have progressed from the bench toward clinical translation. Several polymer-based nanomedicines are in clinical trials, and a few have attained regulatory approval. Notably, CRLX101, a cyclodextrin-based polymer conjugate carrying camptothecin, advanced to phase II trials in solid tumors [29]. Another success is a polymeric micelle formulation of paclitaxel (Genexol-PM), which has been approved in some regions and demonstrated reduced toxicities compared to conventional paclitaxel formulated with cremophor surfactant [30]. These cases prove that polymeric NP systems can be manufactured under Good Manufacturing Practice (GMP) conditions and meet safety criteria for human use. Nonetheless, challenges remain in ensuring batch-to-batch consistency, scalability of production, and rigorous characterization of these complex nanomaterials. The physicochemical properties of polymeric NPs (size, surface charge, hydrophilicity) strongly influence pharmacokinetics and biodistribution, so optimization is needed to balance stability in blood versus efficient release at the target [31].

In summary, polymeric nanoparticles provide a versatile platform for targeted drug delivery. Through appropriate polymer selection, surface functionalization, and incorporation of stimulus-responsive features, these carriers have achieved improved tumor targeting and therapeutic outcomes in preclinical models [32]. Next, we delve into a specific application: delivering fluoropyrimidine chemotherapies via polymeric and nanocarrier approaches, an area where nanotechnology is making significant inroads to enhance an old yet vital class of drugs.

Fluoropyrimidine Delivery Platforms: Nanocarriers for 5-FU and Analogues

Fluoropyrimidines such as 5-fluorouracil (5-FU) and its prodrugs (e.g. capecitabine, tegafur) are mainstay treatments for colorectal, gastrointestinal, breast, and head & neck cancers [33]. However, 5-FU's clinical use is hampered by problematic pharmacokinetics: it has an extremely short plasma half-life (~10–20 minutes) and is rapidly metabolized, requiring high or continuous dosing. Traditional 5-FU regimens (large bolus doses or prolonged infusions) lead to high peak systemic levels that can cause severe toxicities, notably mucositis, myelosuppression, and the hand-foot syndrome [34]. These toxic effects arise from non-specific distribution of 5-FU, damaging healthy proliferating cells in the GI tract and bone marrow. There is a pressing need to improve the delivery of 5-FU such that more of the drug goes to tumor tissue and less to normal tissue.

Nanotechnology offers multiple strategies to reformulate fluoropyrimidines and overcome these limitations. Over the past several years, a variety of 5-FU nano-delivery systems have been explored. These include lipid-based carriers (e.g. 5-FU encapsulated in liposomes or solid lipid nanoparticles), polymeric nanoparticles (both "standard" and stimulus-responsive types), inorganic nanocarriers (like mesoporous silica or gold nanoparticles), and even nanoscale polymer-drug conjugates Each approach aims to increase 5-FU's stability in circulation and concentrate its action in cancer cells, thereby improving efficacy and safety [35]. For example, 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. Similarly, polymeric NPs made of PLGA or poly(alkyl cyanoacrylate) have been loaded with 5-FU to achieve sustained drug release over several days, maintaining therapeutic drug levels in tumors while sparing normal tissues [36]. Notably, some polymeric formulations are designed to release 5-FU preferentially in the acidic microenvironment of tumors or within cancer cell endosomes (pH ~5–6), thus minimizing drug release in the neutral pH of blood [37].

A concrete example of an engineered 5-FU nanocarrier is the thiolated chitosan nanoparticle system reported in 2024. In this design, Anjumet al. synthesized chitosan NPs crosslinked with a thiol-containing reagent to improve NP stability and mucoadhesiveness, then coated the NPs with hyaluronic acid (HA) as a targeting ligand [38]. HA specifically binds CD44 receptors, which are overexpressed on many cancer cells (e.g. certain breast cancer subtypes). The resulting HA-coated 5-FU nanoparticles were around 200–300 nm in size with a positive surface charge, facilitating efficient uptake by CD44-expressing triple-negative breast cancer cells while sparing normal cells [39]. In vitro, these targeted NPs showed significantly higher cytotoxicity against breast cancer cells compared to free 5-FU, due to enhanced cellular internalization. They also exhibited a controlled, diffusion-driven release profile that prolonged the drug's action. This multifunctional NP design, combining a biodegradable polymer (chitosan), a targeting ligand (HA), and thiol-mediated stability, exemplifies the sophisticated "smart" fluoropyrimidinenanocarriers now being developed [38]. The outcome was improved tumor cell kill with potentially lower systemic exposure.

Another area of progress is colon-targeted delivery of 5-FU for colorectal cancer therapy. Systemic 5-FU causes dose-limiting GI toxicity; formulating it for localized release in the colon can boost efficacy against colonic tumors while reducing systemic side effects [40]. Researchers have created oral pH-responsive formulations that protect 5-FU as it transits the stomach

and small intestine, then release the drug upon reaching the higher pH environment of the colon. For example, a 2023 study used cross-linked mastic gum as an enteric matrix for 5-FU. This formulation remained intact through acidic gastric conditions but released 5-FU at colonic pH, achieving significant drug release only in the colon and demonstrating enhanced tumor suppression in a mouse colon cancer model [41]. 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. These colon-specific strategies increased the local drug concentration at the tumor site in the colon and improved therapeutic outcomes in preclinical colorectal cancer studies, while causing fewer systemic toxic effects [42,43]. Such approaches directly address the tumor microenvironment of colorectal cancer (where pH and transit time can be leveraged for site-specific release).

Beyond reformulating 5-FU alone, nanocarriers enable combination strategies to enhance fluoropyrimidine therapy. One strategy is co-delivery of 5-FU with agents that modulate oncogenic pathways or sensitize cells to chemotherapy. A notable example is the co-encapsulation of 5-FU with gene-silencing therapeutics like siRNAs or microRNA mimics against cancer-driving genes [44,45]. Researchers have developed a layer-by-layer liposomal system carrying 5-FU plus an siRNA against KRAS and a tumor-suppressor microRNA mimic; this multi-layer liposome preferentially delivered its cargo to colorectal tumors in mice and achieved markedly greater tumor growth inhibition by synergistically silencing mutant KRAS while 5-FU exerted its cytotoxic effect [46]. Another example is co-delivery of 5-FU with everolimus (an mTOR inhibitor) in the chitosan–silica nanohydrogel mentioned earlier. By simultaneously blocking the mTOR pathway and applying 5-FU's antimetabolite action, the combination induced higher cancer cell apoptosis and tumor regression than either agent alone [47]. These combination nanoparticle therapies show how co-loading fluoropyrimidines with complementary agents can overcome resistance and attack tumors on multiple fronts. This is especially valuable for cancers that rapidly develop resistance to single-agent chemotherapy Collectively, nano-delivery systems for fluoropyrimidines are addressing the classic drawbacks of 5-FU therapy. By encapsulating 5-FU in nanoparticles and achieving controlled release, they prolong the drug's presence within the therapeutic window and avoid the high peak concentrations that cause toxicity. Tumor-targeted delivery via passive EPR uptake and active ligand targeting increases drug accumulation at the tumor site, which can enhance antitumor efficacy even in 5-FU–resistant cancer cell lines. Many 5-FU nano-formulations also allow for dose reductions while still achieving equal or greater tumor suppression, because the improved delivery efficiency compensates for the lower drug amount [48]. In animal studies, 5-FU nanoparticles have demonstrated reduced bone marrow and GI toxicity compared to equivalent doses of free 5-FU. These findings suggest patients could experience fewer side effects for the same (or better) anticancer benefit. Indeed, initial toxicology studies in mice and rats show that nano-encapsulated 5-FU causes significantly less myelosuppression and gastrointestinal damage than traditional 5-FU, at therapeutic dose levels [49].

While no 5-FU nanomedicine has yet obtained FDA approval, the development pipeline is rich with candidates. One particularly promising example is a nanoscale fluoropyrimidine polymer called CF10. CF10 is a polymeric form of a fluoropyrimidine (a "polymer-drug conjugate") designed to overcome 5-FU resistance [9]. In 2024, Okechukwuet al. reported that CF10 significantly enhanced therapeutic efficacy and reduced toxicity in a rat model of colorectal cancer liver metastasis [7]. This polymer-drug conjugate remained in circulation longer and preferentially delivered the active drug to tumor sites, leading to improved survival in the animal model. Early-phase clinical trials of related polymeric 5-FU conjugates or nanoparticle formulations are anticipated, and some nanoparticle-based 5-FU therapies (or combinations like oncolytic virus plus 5-FU regimens) are under investigation [50,51]. The expectation is that fluoropyrimidine chemotherapy may soon be administered in "smarter" and safer ways thanks to nanotechnology.

Clinical Relevance and Outlook

Polymeric nanoparticles and fluoropyrimidinenano-platforms exemplify how nanomedicine can refine cancer therapy. Several nano-formulated chemotherapies have already proven their worth clinically (e.g. nanoparticle albumin-bound paclitaxel, liposomal doxorubicin), validating the concept that altering a drug's pharmacokinetics and biodistribution can reduce toxicity and improve outcomes. Building on that foundation, polymeric and stimulus-responsive systems are poised to become the next generation of approved nanotherapies [52]. For fluoropyrimidines specifically, the translation of 5-FU nanocarriers into the clinic could address a longstanding need in oncology for effective yet tolerable regimens. Early studies indicate that a 5-FU NP can achieve the same tumor suppression as free 5-FU at a fraction of the dose (with less toxicity), and that pH-sensitive doxorubicin micelles can even eradicate tumors resistant to standard therapy [53]. Such results are propelling several nanoparticle candidates into clinical trials.

Looking forward, safety and manufacturing considerations will be as crucial as efficacy. Polymeric carriers are generally made of biocompatible materials that degrade into non-toxic byproducts (for example, PLGA degrades into metabolic acids). Nevertheless, extensive toxicology studies in large animals and humans are needed to ensure no unexpected organ accumulation or immune reactions

occur [54]. Scalable manufacturing and quality control of polymeric NP drugs are also key hurdles, ensuring consistent particle size, drug loading, and release characteristics at large batch scales will require continued innovation in engineering and regulatory science. Regulatory guidelines for nanomedicines are evolving, and developers must demonstrate not only therapeutic benefit but also robust safety and quality attributes [55].

In conclusion, polymeric nanoparticles offer a powerful approach to targeted cancer therapy, and fluoropyrimidine-based nanocarriers serve as a vivid example of their potential. By improving drug targeting, sustaining release, and enabling combination therapies, these platforms aim to maximize tumor kill while minimizing collateral damage to healthy tissue. The progress to date – from smart polymer designs to positive preclinical results and early human trials, is highly encouraging. If ongoing trials confirm improved patient outcomes (higher response rates, longer survival, and lower toxicity), we can expect polymeric nanoparticle therapeutics, including next-generation 5-FU formulations, to become part of standard oncology practice. Ultimately, the integration of polymer chemistry and cancer pharmacotherapy exemplified by these systems could usher in safer and more effective chemotherapy protocols for patients worldwide.

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Conflict of Interest

The authors declare that they have no competing interests in relation to this work.

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